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Are gays and lesbians being unfairly excluded from your clinical trials?

IRBs should ask: Are there valid scientific reasons?

A recent analysis of clinical trials showing that gays and lesbians have been excluded from certain types of studies is causing reverberations within the research community — and beyond.

The analysis, whose results were recently published in a letter to *The New England Journal of Medicine*, has led to a call from five U.S. senators for an investigation by the U.S. Department of Health and Human Services.[1]

"This is more than an equality issue — it raises huge questions about the quality of medical information from flawed trials," Sen. John Kerry, D-Mass., said in a statement that accompanied an April letter to HHS Secretary Kathleen Sebelius.

Brian Egleston, PhD, a biostatistician at Fox Chase Cancer Center in Philadelphia, was the lead author of the letter. He said his interest in exclusions of gays and lesbians from trials was prompted by his service on Fox Chase's research review committee, a scientific review panel that looks at protocols prior to their submission to the institution's IRB.

"I saw a couple of protocols with language that studies were restricted to people in heterosexual relationships," Egleston says. He says one of the studies concerned couples counseling and the other was related to treatment for prostate cancer.

After he and another member raised questions about the two protocols, "it actually was something that research review asked the investigators to explain …before they approved the protocols."

This led Egleston and his colleagues to do searches of the ClinicalTrials.gov database looking for specific inclusion and exclusion criteria that limited participation in trials to heterosexuals.

When his group looked at studies containing the words "couples," "erectile dysfunction" or "hypoactive" (referring to hypoactive sexual disorder), they found 37 studies — 15% of all studies that included those words — that had language that in some way excluded gays

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and lesbians. For example, there might be a requirement that the participant "be in a reciprocal relationship with a person of the opposite sex."

Lack of validated measures

Egleston says the most common reason given by researchers for such exclusion criteria is a lack of validated measures of sexual functioning endpoints for gays and lesbians. He says commonly used surveys of sexual functioning have questions that are related to heterosexual relationships. But he says there are methods that can be used in both gay and straight populations, including the so-called "stamp" test, an older measure that is appropriate for men of any orientation, including men who are currently not in a sexual relationship.

Egleston says that the research community at Fox Chase has become educated about this issue and investigators are more often using study designs that can accommodate a diverse population.

Fox Chase's IRB now takes a close look at such exclusions as well, when they come up in review, says its vice-chairman, **Clifford Perlis**, MD, MBE.

"If there are compelling scientific reasons for excluding one group or another, that's reasonable, the same way you would deal with any other population," Perlis says. "But we basically put the burden on the principal investigator to justify any exclusions on a scientific basis, not just a convenience basis."

Perlis says that the exclusions he's seen don't seem to be caused by bias or malevolence against gays and lesbians.

"It's more often omission, rather than commission — assuming that someone is in a heterosexual relationship," he says. "Gradually, as times change, we're coming to the recognition that not only may someone's partner not be a spouse, it may be someone they just live with. And furthermore, it may not necessarily be someone of the opposite sex."

Egleston says he believes some of the trials simply use boilerplate language from previous trials on similar topics, perpetuating the exclusions.

Generalizability, equal access

Perlis and Egleston say there are instances when it's scientifically justified to focus on a targeted population — for example, an HIV prevention trial that Egleston found in his analysis.

"There, you can make a good case that the method of transmission of HIV is just so different between heterosexuals and gays and lesbians that you might need separate trials," he says.

But in many cases, he says, such separation isn't necessary. To focus only on heterosexual responses to sexual functioning raises two concerns, Egleston

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says — it may make the research less generalizable and creates an issue of unequal access to trials.

While the situation is similar to past concerns over exclusions of women and ethnic minorities from clinical studies, Perlis says he doesn't believe the scope of this problem is as large.

"I think Dr. Egleston's study shows that it is pervasive in certain types of studies," he says. "His letter is important because it highlights these differences and really forces the research community to ask important questions and say, 'Wait a minute — is it only heterosexual men who have erectile dysfunction? Or is this also a problem in some homosexual men?'"

He says the most important question an IRB should ask when presented with this kind of exclusion is: Is there a scientifically valid and meaningful reason for that exclusion?

Egleston expects more repercussions from his findings, based on what he's heard from gay and lesbian advocacy organizations.

"Some groups are trying to get the (National Institutes of Health) to put together some guidelines about this, as they did with women and ethnic minorities," he says.

But Perlis says his own IRB hasn't created any formal procedures for dealing with exclusions of gay and lesbian participants.

"It's been incorporated more under the general idea that we don't want to make a distinction unless there's a rational scientific basis for doing it," he says. "It's a little bit of common sense and a little bit of sensitivity and not necessarily a whole lot of new regulations."

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Health care reform law: Follow the money

Reporting pharma payments is biggest change

As sweeping as the 906-page health care reform bill is, it will have limited impact on human subjects research protection, experts say.

The Patient Protection and Affordable Care Act, signed March 23, 2010, by President Barack Obama, will put billions more dollars into research and pilot projects. Potentially this will increase volumes at some IRBs and research institutions.

Both the 2009 federal stimulus package and the new health care reform bill flood billions more into research, but the money has to be spent in the next few years, says **John Lewis**, vice president of public affairs for the Association of Clinical Research Organizations (ACRO) in Washington, DC.

Part of the new research money is designed to set up an infrastructure for the government to conduct the research, but the rest goes out in grants, Lewis says.

Much of this money is for comparative effectiveness research (CER), and while this will have a short-term bubble impact on boosting research projects nationwide, there are some long-term concerns, he says.

One of these concerns is whether the CER findings will result in choking off some of the research and development pipeline by creating a de facto higher standard for new drug approval by the Food and Drug Administration (FDA), Lewis explains.

"Or, what if you could bring a drug to approval, but it wouldn't be reimbursed by private insurers if there's research that says it won't be as good as what's on the market," he adds.

The bill's cuts in Medicare rates for specialists could have the positive repercussion of convincing more physicians to become researchers as a way to diversify their income and generate more revenue, suggests **David Vulcano**, LCSW, MBA, CIP, RAC, past-chair of the board of the Association of Clinical Research Professionals (ACRP) of Alexandria, VA. Vulcano is the assistant vice president for clinical research at the Hospital Corporation of America in Nashville, TN.

This could mean that research programs will need to train more new researchers in research ethics and human subjects protection, as well as good clinical practice guidelines.

'We didn't win that point'

Overall, it appears the biggest change from an IRB perspective is the bill's provision regarding financial relationships between physicians and pharmaceutical and device companies. This is section 1128G, Transparency reports and reporting of physician ownership or investment interests, in the bill.

"This is something where we had lobbied for a research exemption," Lewis says. "If a physician is paid for participating in a clinical trial, it should not be viewed as a conflict of interest. But we didn't win that point."

IRBs typically rely on investigators to disclose their own conflicts of interest and financial relationships with sponsors.

"We ask through the continuing review form about conflicts that would relate to the actual principal investigator or sub-investigators or coordinators directly participating in the research, and we include their spouse," says **John Isidor**, JD, chief executive officer of Schulman Associates IRB in Cincinnati, OH.

"We ask if they have received money outside of the trial in excess of $10,000, and that's where I see a potential impact with IRBs," Isidor says.

The federal government and IRBs seem to be more interested in these physician/investigator conflicts of interest (COIs) than are research participants, says **Alan M. Sugar**, MD, former chairman of the New England Institutional Review Board, and professor of medicine at Boston University School of Medicine in Boston, MA.

"There have been several studies that look at a subject's perception of these COIs," Sugar says. "The overall conclusion is that study participants really don't care at all whether there is a financial interest by the investigator or not."

IRBs need to determine what constitutes a significant COI and proceed accordingly, he adds.

"Of course, if the law requires specific disclosures then the IRB must comply," Sugar says.

Both burden and opportunity

The new bill's disclosure provision will create both an opportunity and a burden for IRBs, Isidor notes.

IRBs might move toward having a zero dollar threshold to be better aligned with the health care bill's very low threshold. The bill says any transfer of more than $10 or an aggregate of $100 in one calendar year will need to be reported.

If an investigator were to report receiving a certain amount of money from a sponsor, then the IRB could check the government's online information to see if what the PI reported to the IRB matches what the sponsor reported to the government, he adds.

"Either the institutional conflicts of interest (COI) committee and/or the IRB can say, 'Look, we reserve the right to cross-check your disclosures against publicly-available databases for researchers and physicians,'" Isidor says.

Basically, the new bill says that on March 31, 2013, any manufacturer who provides a payment to a physician or other provider must report this to the U.S. Department of Health and Human Services (HHS).

These payments could be for research work. Consulting fees, honoraria, gifts, entertainment, food, travel, education, charitable contribution, royalty, investment interest, direct compensation, grants, and other payments also have to be reported. The bill states that if the payment or other transfer of value is related to marketing, education, or research specific to a covered drug, device, biological, or medical supply, the name of that covered drug, device, biological, or medical supply have to be included in the report.

This type of public disclosure could create a disincentive for physicians to get involved in research, Lewis says.

"We understand the concern over conflicts of interest, and there are clear cases that everyone can agree are conflicts of interest," Lewis says. "But when a physician is paid for conducting a clinical trial and is gathering data or health outcomes, then that's not a conflict and should be encouraged."

A number of pharmaceutical companies voluntarily have released this information, although it hasn't been done in a comprehensive way, Lewis notes.

"Now it will be a requirement," he says. ■

Explain research, give kids greater role

Children may not be aware they're in research

Despite efforts by IRBs and investigators to improve pediatric assent, a survey of children with cancer who have been enrolled in clinical trials showed they often don't understand that what they're involved in is research and that they wanted more of a say in making the decision to participate.

The survey of children ages 7 to 19 who had participated in oncology research through the Children's Oncology Group/Pediatric Brain Tumor Consortium was published in a recent issue of the journal *Pediatrics*.[1]

Investigator **Yoram Unguru**, MD, MS, MA, a pediatric oncologist at Herman and Walter Samuelson Children's Hospital at Sinai in Baltimore, MD, says it is the first study to examine younger and older children's understanding of the oncology research in which they were enrolled, as well as their decision-making preferences.

Unguru's group interviewed 37 children who

had previously been enrolled in trials — some very recently, some months earlier — using a Quality of Assent (QuAs) instrument created by Unguru and modeled on an adult quality-of-consent tool.

Children were asked about their familiarity with research (whether they remembered hearing a research term such as "study," "research," "protocol," etc.), their knowledge of what research was, whether they understood its goals and about their own role in the decision to participate in a trial.

Unguru says he wasn't greatly surprised by results in the understanding portion of the study:

- Nineteen respondents (51%) didn't know or remember that their treatment was considered to be research;
- Asked whether they were able to understand the information given to them about the trial at enrollment, 26 (70%) indicated that it was "a little hard" or "very hard" to understand.
- Most of the children understood that the purpose of research was to increase generalizable knowledge and the most common reason they gave for participating (27 children or 73%) was to "help other children." But the same number of children incorrectly thought that the research intervention was not more risky than other interventions and that the medicines they were given were proven to be the best treatment for their illness.

Kids want greater role

Unguru says this level of understanding actually compares pretty well to groups of adult research participants surveyed in other studies.

"Adult responses aren't all that different — you'd be shocked," he says. "While the majority of the kids didn't understand things like randomization or risk/benefit or that the intervention of the experimental arm may not be as effective as the standard arm, they did get certain aspects of it. The vast majority knew that the reason they were enrolled in the trial was to help kids who have cancer in the future."

He says he was intrigued by the results of the decision-making portion of the study.

While all of the children wanted to have a role in the research decision, nearly half reported that they had little or no role in their enrollment decision and 14 of the children (38%) said they didn't feel free to dissent to enrolling in the trial. Older children tended to want greater levels of involvement and all but one said they wanted to make the decision jointly with their parents.

Unguru says those results should cause investigators and IRBs to think about how children can participate better in those decisions.

"A fair number of the kids told me that while they felt they may have had a little role in deciding to participate in their clinical trials, the main reason they enrolled was because they were told to, either by their parents or their doctor," he says.

It's a tricky issue — Unguru says there are times when it's appropriate for a parent to overrule a child's wishes and enroll him or her in a trial.

"But I do think that at an individual level, we need to, as much as possible, try to figure out what these kids are able to do," he says. "This is where it gets difficult — to what extent do we need to listen to kids and allow their decisions to carry the day? We always need to listen and we always need to offer them the ability to participate, but there are different levels of participation."

Talk about research

To improve the understanding of pediatric participants, Unguru says the kids themselves had some good recommendations.

He says the overwhelming majority of the children (32, or 87%) said they would have wanted someone to explain research to them better before they were asked to enroll in a study. Often, he says, children come in with a cancer diagnosis and in the urgency to act quickly, consent and assent are rushed so that the intervention can start.

"The kids told me they really would have liked it if someone would have told them what this whole research thing is and why it's done, as part of the (assent) conversation," Unguru says. He says that preference held even when he pointed out that time can be of the essence in starting a treatment.

"Still, half of that 87% wanted that explanation, even if it meant delaying the start of treatment — and they were aware of the consequences of that. I found that very interesting."

He says children also suggested that they would have liked to talk to other kids involved in research, to get a better understanding of what it means to be a research participant. He says some of these conversations likely are going on informally now.

"If you go into a waiting room of any pediatric oncology unit, kids talk all the time," Unguru says. "They talk, they share, they learn from one another.

"I would argue as a parent that I would like to make sure the information kids are getting is appropriate information," especially given results on the knowledge portion of this survey, he says.

Unguru says that IRBs handling pediatric stud-

ies should make sure that investigators are taking steps to ensure that kids understand what their participation means. He's currently refining his QuAs tool to shorten the time it takes to administer it and he plans to use it in larger-scale trials to gather more data.

"A pediatric oncologist or research nurse can use an instrument similar to the one that I came up with to ascertain that kids understand what they're agreeing to when they assent to research," he says. "And the kids will be able to clarify what topics they don't understand as well.

"I'm trying to shorten this tool so that it will only take 15 minutes. Because time is a problem. We're all busy, we don't have a lot of time, but 15 minutes I think we can squeeze in."

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Building trust in the research partnership

Overcoming obstacles to minority enrollment

Improving the participation of minority populations in research has been a holy grail for researchers and IRBs.

Now a team from the University of Pittsburgh has begun an ambitious project to delve more deeply into the reasons that representation of minorities in research still lags behind that of whites — as well as developing and disseminating best practices that might finally help overcome this problem.

Sandra Crouse Quinn, PhD, associate dean for student affairs and education at the university, is a principal investigator for the "Building Trust Between Minorities and Researchers" project, which has received a $4 million grant from the National Center on Minority Health and Health Disparities, a part of the National Institutes of Health.

Quinn says one novel element of this effort is an emphasis on IRBs — surveying them to determine their role in the process and working with Public Responsibility in Medicine and Research (PRIM&R) to develop a curriculum for IRB members geared toward supporting recruitment and community engagement.

"IRBs have a unique perspective on this," Quinn says. "IRB members and IRB staff have a role to play in informed consent and often in monitoring enrollment. To the best of our knowledge there has not been a lot of work done on what their observations are about the process."

She says that despite numerous studies showing minority distrust of research and researchers, there are significant gaps in knowledge that she hopes to address with her study.

"What do people actually know about research — not just are they willing to participate, but what is their level of knowledge? What factors would contribute to their willingness to participate?"

She says there also has been much more work done on the attitudes of African-Americans than on those of Hispanics. And Quinn wants to hear from researchers, research staff and IRBs about their perceptions.

Surveys and interviews

The data collection for the project will have three parts:

• An online survey launched in conjunction with PRIM&R for investigators, research staff, IRB members and IRB staff. Questions will differ depending upon the participant's role in research.

Quinn says there will be some specific questions for community IRB members.

"We really do want to hear their perspectives," she says. "Because what we hear from talking to folks at PRIM&R is that community members, while they are valuable, often feel like they don't have the gravitas perhaps to be as effective on the IRB."

• A series of longer qualitative interviews with investigators who conduct different types of research, from clinical trials to community-based behavioral research.

"Those interviews are really aimed at what are the lessons they've learned, what are the best practices, what are the mistakes they've made," Quinn says. "So we can pull out of that some things that are really teachable to other investigators and research staff."

• A national telephone survey of about 3,700 African-Americans and Hispanics looking at their attitudes about and knowledge of research.

Information gleaned from these surveys and interviews will be used to come up with a curriculum for engaging minority communities in research.

"How might you engage people from your community that's being targeted for participation — maybe in a community advisory board, maybe in other ways," Quinn says.

CBPR not only answer

Quinn expects her group's recommendations to expand well beyond the community-based participatory research (CBPR) model that's often used in public health and environmental health research.

"CBPR has its place and it's valuable," she says. "But particularly when you're talking clinical trials, the fit is not good. True community-based participatory research, where the community helps develop the questions, etc., isn't a model that's applicable across all kinds of research questions."

Quinn's group will develop workshops and webinars in coordination with PRIM&R. Some of this work already has begun; she says they did a workshop last year on community research advisory boards. They plan to have several sessions at PRIM&R's December conference.

"Our goal is that we leave not just PRIM&R but the NIH Office of Bioethics and our (Clinical and Translational Science Institute) partners with a curriculum that they could use as a whole, or that they could use in pieces with investigators, research staff and IRB members," Quinn says.

In the meantime, she is hoping for a large response from IRBs during the data collection phase of the project. Interested IRB members and staff can visit the project's website http://www.healthdisparity.pitt.edu/buildingtrust.asp

"We would love to have a flood of IRB people involved in this process," she says.

The survey will be available online until June 14. ■

EUA or eIND? Testing drugs in an emergency

Concerns about H1N1 emergency use authorizations

With the end of the 2009-2010 flu season, it's easy to get complacent about the threat of pandemic flu. After all, the much-feared H1N1 virus appears to be on the wane in the United States, and total deaths here didn't reach some dire predictions made last summer.

But the World Health Organization has warned that the H1N1 virus could continue to mutate and may not be fully conquered until 2011.

And some argue that the health research community so far hasn't taken sufficient advantage of this flu strain to study the effectiveness of drugs used to treat it.

"I feel like there's a real ethical imperative for us, when we do see these outbreaks, to collect data as best we can," says **Andrea Meyerhoff**, MD, MSC, DTMH, an adjunct associate professor and infectious disease specialist at Johns Hopkins School of Medicine in Baltimore, MD. "The public expects us as a medical and public health community to hold to certain scientific standards."

Meyerhoff is concerned that with the advent of the Food and Drug Administration's Emergency Use Authorization (EUA) process, drugs that might have been given to research participants as part of a clinical trial are instead being distributed under EUAs with less oversight and insufficient data collection afterward.

The EUA was introduced in 2004 as a way to allow the use of unapproved drugs or devices without IRB approval in emergency infection situations when there are no adequate approved and available alternatives. The FDA may issue an EUA when it concludes, based on existing evidence, that it is reasonable to believe that an intervention may be effective at diagnosing, treating or controlling a serious or life-threatening disease or condition.

No IRB, informed consent

But Meyerhoff says the use of EUAs — which lack not just IRB approval but detailed informed consent and may not require extensive data collection — bleeds away potential patients from clinical trials that could give officials better information about the drugs.

During the H1N1 emergency, the FDA has issued three EUAs for antiviral drugs. In a recent letter to the Journal of the American Medical Association, Meyerhoff looks at one of them, peramivir.[1] Meyerhoff says the October 2009 EUA issued for peramivir marked the first time that an EUA had been issued for an unapproved drug.

She notes that the FDA fact sheet for peramivir cites results from four clinical trials. Only one was a multi-dose study and that one did not include the dosage that FDA eventually authorized in its EUA. At the time the EUA was issued, only 33 patients had ever received this authorized dose. And Meyerhoff says that because reporting requirements for EUAs are limited, important questions

about the drug's safety and effectiveness may not be answered.

She says clinical trials planned by peramivir's manufacturer hoped to enroll 300-400 patients by spring 2011.

"What we saw was that as soon as the EUA was issued, about 500 patients lined up to get the drug, with relatively little oversight," Meyerhoff says. "I see a sort of race between actually enrolling patients in clinical trials vs. doling out the drug without a whole lot of mechanisms in place to see how well it works or what kind of safety profile eventually evolves."

Using an eIND

Meyerhoff says she would prefer to see such drugs distributed in these types of situations through another FDA mechanism, the emergency Investigational New Drug (eIND) regulation. That mechanism also allows for quick turnaround in urgent situations, but still requires IRB oversight.

"(Under the eIND provision,) an individual patient can get access to an investigational drug just as an individual — not enrolled in a clinical trial," she says. "The physician who wants to use the drug can access the drug and the IRB oversight requirement can actually kick in once they're using the drug. So there's still IRB oversight, but there's still a little bit of adjustment so that the drug can get to the patient as quickly as possible."

Meyerhoff says that when she was a medical officer at the FDA, she handled many emergency use INDs for individual patients, and could usually turn them around in a day.

She says IRBs could help encourage the use of this mechanism by having a procedure in place to act quickly as well.

"IRBs may have a provision for some kind of fairly quick convening," she says. "Sometimes the institution has a standing IRB that has some kind of emergency provisions available. Certainly if we're envisioning an outbreak of influenza where there were new agents needed, an institution would want to look at how quickly they can get their IRB together."

Meyerhoff says IRBs should let researchers know that this method of approving drugs for emergency use is available.

"Clinicians don't always understand that they can get an individual patient use IND," she says. "That's something I think would be very important to make sure is known up front."

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Who's on first? Time for an IRB member roster

An efficient way to track IRB data

If your IRB office is well-organized, but IRB member information is dated and difficult to track, then it's time for a simple electronic solution: an IRB member roster.

The Office for Human Research Protection (OHRP) requires IRBs to file an electronic IRB member roster file, but one research institution has found that it's also helpful to have your own electronic roster.

An electronic IRB roster can reduce IRB staff work by making some information available on the IRB's Web site and by keeping updates simple and fast.

The OHRP roster requests some basic IRB member information, while an internal board roster can be expanded to include additional data, such as updated curriculum vitae, IRB position, meeting availability, contact information, and more, says **Charlotte H. Coley**, MACT, CIP, director of the IRB educational programs at Duke University in Durham, NC.

"We have a memo field where we can put in miscellaneous information," Coley adds. "Our staff uses this to put in that an IRB member is trading meeting dates with someone else and other news about members."

Duke University has grown to include more than 200 IRB members on nine boards, including one rapid response board that meets only when there's an emergency need.

The electronic roster uses Microsoft Access software for its database, which tracks all necessary IRB member information, Coley says.

"We grew from 50 IRB members to 240 over the last 10 years, and it gets mind-boggling," she says. "It became more than a fulltime job just to keep up with the board members' activities."

The database makes much of that work automatic and more efficient.

Here are some of the advantages and ways it

works:

• **Collect all necessary information about each board member:** The database includes each board member's curriculum vitae, along with the date the CV was submitted.

This way if it's been two years since a board member has updated his or her CV, the database will generate a report, and an IRB staff member can send out an email to IRB members as reminders about updating their CVs, Coley says.

The database also includes each board member's telephone numbers, emails, professional positions, assigned IRB, credentials, date joined the IRB, degree, department, appointment, designations, orientation and training status, etc., she adds.

• **Create master membership list:** "The database generates a list of orientation reports, showing me for each month who joined an IRB," Coley says. "It's a rolling report so I can quickly add up how many people have been through orientation."

From this, Coley makes a master membership list that can be converted to a PDF format and posted on the IRB Web page.

"So if anyone gets a request from a sponsor for the IRB list, then they can download this PDF," she adds. "This cuts down on the phone calls coming into the IRB requesting the information."

The master list also can be used to track the members' years of service on boards.

Duke University uses this information to provide members with service awards for one year, three years, five years, and multiples of five years, Coley says.

"Each month we give out certificates stating their (milestone) year of service and thanking them," she says. "We also give them a little brass lapel pin."

This makes it easy to track those milestone events and manage a recognition program that is aimed at encouraging IRB members to continue serving, she adds.

"It's a very inexpensive way to generate a lot of good will," Coley says.

• **Keep data at fingertips in event of audits or other needs:** "As new members start on an IRB, we put their information in the database," Coley says. "If an auditor comes in we can access an IRB member report with the push of a button."

• **Generate reports on voting and attendance:** IRB staff keeps a voting log at each IRB meeting, and this information can be accessed easily.

"It generates a lovely spreadsheet that lists everybody, the agenda number, items on the agenda, and how members voted for these," Coley says.

The database also can generate a "will attend" sheet that is circulated at each meeting. When members answer with their plans to attend or not to attend, the IRB staff can check the attendance roster to make certain they have a quorum and the right mix of board members.

"You need to know who is coming to the meeting so you can make assignments to them to be primary reviewers for that meeting," Coley explains. "Also, if you need a pediatrician for a particular protocol, and the board's pediatrician member isn't planning to be present, then you can find an alternate IRB pediatrician or assign that protocol to another board."

• **Use internal roster to update OHRP roster:** "Unfortunately, we couldn't link our database to OHRP's because it created security risks," Coley says. "So now we have to manually create a roster for each of our boards and make changes to the OHRP roster."

The university's own IRB member roster is treated as the master list, and it's used when updating OHRP's information.

"We submit to OHRP monthly," Coley says. "We tried to submit quarterly to OHRP but we found it took us two weeks to collect the information and to make sure all the changes were done correctly."

The IRB office now generates a paper IRB member report that lists all board members by the board to which they are assigned, and this is compared with OHRP's roster list, she explains.

"We go into OHRP's list to make changes and double check that we've caught everything that has happened since the last update," she adds. ■

COMPLIANCE CORNER

IRB effectively handles research concerns

Compliance tools help with success

Human subjects research organizations need a thorough, fair, and effective way of handling complaints and concerns about research trial ethical and regulatory violations.

The key is to investigate potential noncompli-

ance issues with integrity so that the process will be as fair as possible.

"The key philosophy for an effective compliance program is to have the intent to improve the quality and ethical conduct of research," says **George Gasparis**, executive director of the Columbia Human Research Protection Program at Columbia University in New York, NY.

"You work with those for whom you received allegations of noncompliance to strengthen their research programs," he adds.

Once an investigation is complete, it's important to assist research sites with implementing corrective action plans to prevent future noncompliance.

"It's key that compliance efforts are not seen as punitive or as a policing of researchers," Gasparis says.

The goal for the compliance program is to work with investigators as a team to improve the quality of investigators' research, ethical conduct, and protection of subjects, he adds.

The first step is to recognize noncompliance, and this entails staff education via the organization's website and other mediums. There are several other key steps to achieving this goal. They are as follows:

Separate minor incidents from serious ones: The noncompliance policy makes it clear when an incident is minor and therefore unlikely to impact human subjects. The policy directs the IRB to consider minor noncompliance cases within the review, rather than sending them to the compliance team for action, Gasparis says.

An example of a noncompliance incident would be the investigator whose study has expired prior to his submitting a renewal application to the IRB. If the study had actively enrolled subjects during this lapsed period, then that would be considered serious noncompliance. If data analysis occurred during the lapsed period after all subject activity had stopped, then it would be considered a minor noncompliance, Gasparis explains.

Serious noncompliance issues are reported to the appropriate regulatory agency, including the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA), he notes.

"We explain to researchers that it's essential that we have an effective compliance program that identifies noncompliance and corrects it," Gasparis says.

Regulators want to know these main points:

- What did an institution do to prevent it from happening?
- If the noncompliance impacted subjects, how was the study changed or how did they work with subjects to resolve the concerns that were raised?

Audit studies both proactively and when noncompliance is alleged: Compliance audits serve as educational vehicles and can be used to identify noncompliance risk in cases of study sites that have not had noncompliance complaints.

These audits also can serve as a way to correct problems when noncompliance is identified.

The Columbia IRB uses compliance audit worksheets that help keep auditors focused and thorough.

Research institutions that are just beginning compliance and auditing programs should consult with institutions and individuals that have experience in this area, Gasparis suggests.

Also, national human subjects research conferences are a good resource for training on how to conduct compliance oversight activities, he adds.

The Columbia University IRB's not-for-cause audit and quality assurance visit regulatory worksheet contains nine pages. Among its audit questions are the following:

- Are all regulatory documents available and in order?
- For investigator-initiated studies, is there an investigational plan available?
- Have all unanticipated problems involving risks been reported to the IRB?
- Have all amendments/protocol modifications been submitted to the IRB and approved prior to implementation?
- Have all advertisement/announcements been approved by the IRB?
- Are subjects randomized correctly, according to the randomization plan?
- Is subject enrollment within the agreed upon numbers?
- Is the initial protocol approval letter on file?
- Is the current IRB protocol approval letter on file?
- Are there any lapses between approval dates?
- Was any research-related activity conducted during any lapsed period?

Provide follow-up to audit and reported results: "Once our findings are reviewed, we create a summary of how we conducted the investigation, our findings, and our recommendations for corrective actions," Gasparis says.

"We report our findings and develop a report that is reviewed by me and the IRB. Serious noncompliance also is reported to the IRB executive committee, which includes the chair of each of our IRBs, the associate director of the IRB, and the vice president for research operations," Gasparis says.

Corrective actions always include a recommendation for education and training.

If a research site's noncompliance is serious and appears to be part of a trend, then the audit can be repeated or extended to other studies with the potential to have similar problems.

The compliance office can put research sites on a cycle of monthly records review where compliance officers assess whether the site has effectively implemented the corrective action plan, Gasparis says.

"We have had situations where there was noncompliance found in one study, and then we found it in three or four other studies," he explains. "We put the site on a monitoring program, and now they're a model research team."

The site had to hire additional staff because the chief cause of their problems was a lack of resources, he adds.

"If something went wrong, we conduct a root-cause analysis and then apply appropriate corrective actions," Gasparis says.

"There has to be an awareness of what was wrong and how to do it right," he notes. "We need to have confidence that there is a change in the process that likely will prevent the noncompliance from occurring again." ■

IOM: Cancer research needs new focus

Improved treatments for cancer will be delayed and patient lives will be lost unnecessarily unless the efficiency and effectiveness of the clinical trials system improves, a new report from the Institute of Medicine (IOM) concludes.

The National Cancer Institute's (NCI) Clinical Trials Cooperative Group Program asked the IOM to assess the state of cancer clinical trials and provide advice on improvements. The IOM recommends changes to transform the Cooperative Group Program into a dynamic system that efficiently responds to emerging scientific knowledge; involves broad cooperation of stakeholders; and leverages evolving technologies to provide high-quality, practice-changing research. Four overarching goals should guide improvement efforts:

• Improving the speed and efficiency of the design, launch, and conduct of clinical trials

• Making optimal use of scientific innovations

• Improving selection, prioritization, support, and completion of clinical trials

• Fostering expanded participation of both patients and physicians

For more on the report go to: http://www.iom.edu/Reports/2010/A-National-Cancer-Clinical-Trials-System-for-the-21st-Century-Reinvigorating-the-NCI-Cooperative.aspx. ■

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

■ Protecting the identities of individuals in genome studies

■ What it means to take the community into account in research

■ Survivor of unethical research discusses ethics, IRBs today

■ Learn more about expert unanticipated events policies

■ Biological samples court finding could change IRB review

CNE/CME QUESTIONS

21. The 2010 Patient Protection and Affordable Care Act, requires pharmaceutical and device and other companies to report all payments or gifts to physicians in excess of what amount of money?
A. $10 or aggregate of $100
B. $200
C. $1000
D. $10,000

22. In a survey of pediatric oncology research participants, what percentage of children understood that the intervention they were receiving was considered to be research?
A. 11%
B. 49%
C. 87%
D. 100%

23. Which of the following uses of an investigational drug does NOT require IRB oversight?
A. A formal clinical trial
B. An Emergency Use Authorization (EUA)
C. An emergency Investigational New Drug use (eIND)
D. None of the above; all require IRB oversight

24. The Columbia University IRB's not-for-cause audit and quality assurance visit regulatory worksheet contains which of the following questions?
A. Are all regulatory documents available and in order?
B. For investigator-initiated studies, is there an investigational plan available?
C. Have all amendments/protocol modifications been submitted to the IRB and approved prior to implementation?
D. All of the above

Answers: 21. A; 22. B ; 23. B; 24. D.