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Recent problems with Vioxx highlight need for post-marketing changes

Experts discuss fallout from most recent controversies

The clinical trial industry watched with concern late last year as the national media drew attention to the problems with some painkillers — COX-2 inhibitors, including rofecoxib (Vioxx) and celecoxib (Celebrex) — which were linked to increased risk for heart disease. Two days before Christmas, the FDA issued a public health advisory recommending limited use of COX-2 inhibitors.[1]

Last year's controversy over the COX-2 inhibitors falls on the heels of the ongoing controversy over the use of selective serotonin reuptake inhibitors (SSRIs) in adolescents. In recent years, some parents have attributed their teenagers' suicides to the youths being prescribed paroxetine (Paxil) for depression.[2]

"The most important lessons from this are that the system we've had in place and relied upon for a long time now is really not accomplishing what it was intended to do," says **Greg Koski**, PhD, MD, CPI, senior scientist for the Institute for Health Policy and an associate professor of anesthesia for Massachusetts General Hospital, Partners HealthCare System, Harvard Medical School in Boston.

"It's clear that although the FDA has the primary responsibility for ensuring safety of all of the new drugs and devices and biologics that come out, they simply can't do that job unless they have all of the necessary information," he says. "And we've no system to ensure that they, in fact, get all of the information."

Some news reports said that earlier clinical trials involving rofecoxib had noted increased heart disease risk, and these findings also may give clinical trial professionals cause for concern, Koski notes.

"We learned that the [pharmaceutical] industry often is in possession of information that they'd just as soon neither the FDA nor public have access to because it might have adverse consequences for marketing and sales of their product," he says. "And that's — in my mind — an unacceptable situation."

The immediate impact of the problems involving COX-2 inhibitors will be changes in post-marketing studies, says **LaDale George**, JD, senior counsel in the health law department/health care business counseling

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Editorial Questions

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practicing group of Foley & Lardner in Chicago.

"Right now, I'm seeing a lot of impact planning by the industry where they are evaluating the placement of post-marketing studies in their marketing departments rather than in their R&D departments," he says.

"Typically, post-marketing, post-regulatory approval studies have more often than not been conducted or overseen by the marketing department of large pharmaceutical companies rather than by the research department," George explains. "In many ways, this has given those post-marketing studies less of a view toward scientific merit and more of an expression of expanding market opportunity for the product."

By re-housing the research post-approval research in the research department, investigators will have a better opportunity to connect statistical data to earlier trial adverse events, he adds. **(See story on related changes that need to be made in clinical trial industry, p. 15.)**

A big lesson to be learned from the rofecoxib experience is the research industry needs a more careful review of clinical trials while they are ongoing, says **Elizabeth E. Hill**, RN, MS, DNSc, assistant professor and director of clinical research management program at the Duke University School of Nursing in Durham, NC.

"I'm concerned because I feel like there's not anyone who has the big picture with all of the adverse events," Hill says. "Who knows whether they are being reported accurately and whether the right judgments are being made of them."

Return to drug safety

The FDA also will need to make changes, particularly by returning its focus to drug safety, say **Anthony T. Dren**, PhD, consulting professor and **George "Trey" Turner**, BScPharm, MA, RAC, assistant clinical professor in clinical research management program at Duke University School of Nursing.

"It's a very difficult situation because a few years ago the FDA really was being faulted for not approving new drugs, and there was a shortage of new products coming on the market in the U.S. vs. Europe," Dren says. "So the funding has gone to the new drug approval area and not on the drug safety area."

This shift has resulted in some slack in the evaluation of long-term safety and a shortage of personnel in that area of the FDA, Dren adds.

After the Prescription Drug User Fee Act,

which gave the FDA fees from drug companies to help expedite the review process, was passed in 1992, Congress cut back FDA funding, which shifted resources away from the area that conducts post-market surveillance, Turner says.

"Drug companies point to the $800 million cost of bringing a new drug to market," he adds. "What I'd like to see is some commitment by the people profiting from the drug to support an agency that would do long-term follow-up."

One way to do this is through long-term clinical trials, but they're large and expensive and include multisites that are costly to track, evaluate, and record, Turner says.

However, if the FDA was given adequate funding for post-market surveillance and long-term tracking, some of the current problems might be avoided, he notes.

"Ongoing monitoring is more important now than ever before because of the direct-to-consumer marketing [by drug companies] that in the past didn't exist," says **Ellen Hyman-Browne**, JD, MPH, director of research compliance at the New York University School of Medicine in New York City.

"I'm not a physician, but I assume that doctors feel under some degree of pressure to satisfy the request of their patient for a particular drug," she says.

Also, there is a growing public sentiment that the FDA and its mission have been adversely influenced by the pharmaceutical industry, Koski says.

"There have been concerns raised about the FDA advisory committees that are an important part of overall safety and efficacy reviews," Koski notes. "And the industry seems to have a strong influence within those committees by virtue of the fact they often have consulting relationships and other types of financial or nonfinancial relationships with actual members of those committees."

While these relationships are not necessarily evil and while there are many individuals involved who have a high degree of integrity, the problem is the system, which needs a greater measure of accountability, Koski adds.

Will database improve safety?

One way to restore accountability is through the use of a clinical trials database, Koski and Dren say.

"This will help alert practicing clinicians that there are studies that have been done and they should at least ask about the outcome," Dren adds.

With such a register or database, then no one would be able to hide the existence of clinical trials in which the outcomes were unfavorable, Koski says.

Medical journal editors have begun to push the clinical trial industry for a public register, and in early January 2005, the pharmaceutical industry announced its plans to publish detailed information about all clinical trials, except for Phase I trials.[3]

The exact form, location, and management of a clinical trial database are big issues, Koski says.

"There are tens of thousands of clinical trials going on around the world and how you actually coordinate the collection and review and deposition and processing of that information is not a trivial problem at all," he says. "It's easy to say, 'Let's have a database,' but to have a properly constructed database that would have data available in a way that's meaningful and not have it misused is a very large logistical problem, and we're not there yet."

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Industry in need of major improvements

Best solution? More clinical trials

At the very least, pharmaceutical companies and other sponsors who rely on the clinical trial industry need to evaluate how they conduct post-marketing studies and make improvements that will increase public safety, a health law expert says.

For instance, there is a need for an increase in post-marketing studies to be conducted in a manner that is more consistent with the level of regulatory oversight given to Phase III-B studies, says **LaDale George**, JD, senior counsel in the health law department/health care business counseling practicing group of Chicago-based Foley & Lardner.

"I believe there's going to be an increase in Phase IV studies and an expansion of the requirement for diversity of subjects in participating trials," he says.

"We've seen two connecting regulatory events lately," George explains. "One is the post-market rejection of products, which is Vioxx."

The other is a heavy enforcement by the FDA of off-label marketing of products, he notes.

Off-label marketing by pharmaceutical companies is the result of pharmaceutical companies learning about positive results from the use of their product in a manner that is different from how it was labeled, George explains.

"But the company has never gone back to test or run a trial to validate that information that would support a change in the labeling," he says. "If they would have run a trial to support a change in the labeling it would be considered a Phase IV trial because of post-regulatory approval, and it would likely support the off-label activity that is being marketed by the company inappropriately."

Instead, the companies at times have spread the word to physicians that an off-label use might work, and the FDA has cracked down heavily on this activity as illegal marketing, charging some drug companies with millions of dollars in fines, George says.

"So what I see is the industry is getting two simultaneous messages: if you're going to market off-label, you will be punished; so therefore, run a real trial to support what your claims are," he says. "And secondly, I'm seeing the industry being informed that it needs to run stronger, more accurate, and appropriate Phase IV trials in order to not have products pulled from the marketplace."

The FDA should refocus its energies on safety as opposed to effectiveness, George suggests.

"The marketplace will determine whether or not a product is more effective than another," he says. "The FDA's concern should be on safety because the marketplace is not the testing ground for safety."

While many in the clinical trial industry fear that further FDA scrutiny for safety could result in even more expensive clinical trials and longer delays in getting a new product to market, George disputes that contention.

If the FDA would spend its time looking at safety and not at whether or not it's putting another me-too product on the marketplace, it won't take longer, he says.

Let the marketplace and corporate advertising determine which of the hundreds of statin drugs will be used by consumers, but have the FDA charged with the responsibility of putting safety first, George says.

With regard to the ongoing issue of whether selective serotonin reuptake inhibitors (SSRIs) should be prescribed for children and teenagers, he says that is a problem with a lack of diversity in clinical trials.

"To some extent with SSRIs, there was limited testing on suicidality in adolescents, and that's where things went awry," George says. "That's an issue of diversity and special population testing."

Diversity and special populations

The need for greater diversity in clinical trials also was highlighted in 2003 by the safety alert issued by GlaxoSmithKline, based in Middlesex, England, regarding the use of salmeterol xinafoate (Serevent), George notes.

GlaxoSmithKline's letter to the health care community says one study [post-regulatory approval] found that among African Americans taking salmeterol xinafoate, an asthma inhalant medication, there was a statistically significant greater number of primary events and asthma-related events, including death, compared with those taking placebo.[1]

"As a result, there has been some re-labeling and indication changes for the product to address the impact on a special population," George says.

The same problems have been found in pediatrics medicine where drugs approved for adults have proved problematic for children, he notes.

These issues likely will result in an expansion of trials and a push for greater diversity among clinical trial subjects, George reports.

"You will need to learn if the pharmacokinetics of your product are the same or different based on ethnicity, and that's significant," he says.

Although this issue is treated as new, it's based on old facts and common knowledge of health-related differences between people of different ethnic groups, he says.

"For example, Native Americans don't metabolize grain alcohol the way many non-native American populations do," George says. "And for Hispanics, some diabetes medications on the market are not as effective in many Hispanic populations."

The FDA does not mandate proportionality testing, even in areas of high prevalence, and that's a mistake, he says.

"If you know that African Americans have a higher incidence of high blood pressure, then before you bring a blood pressure medication to that market, you need to test a higher proportion of that population," George explains.

This philosophy seems to be catching on with pharmaceutical companies, who are increasing their level of diversity, he adds.

One special population for which there are no easy solutions is children, George notes.

Testing children is a public policy problem because it will continue to be difficult to convince parents to have a healthy child used as a volunteer to test a product that would provide a minor health solution, he says.

"This is something we as a community of patients and providers need to come to terms with how we're going to test better in those populations to assure more accurate and effective treatment of our patients," George says. "Until patient-specific targeted therapies are developed, all medicine still is trial and error."

Reference

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Risk management starts with contract

Think of contracts as fluid documents

Research institution administrators could more easily protect their clinical trials against legal risks and other problems if they began the risk management process at the bargaining table when the research organization staff and for-profit pharmaceutical company staff hammer out the clinical trial agreement.

For example, it takes vigilant clinical trial and institutional monitoring to make certain that common procedures, such as blood draws, that subjects undergo as part of a clinical trial are not mistakenly billed to Medicare, which would consider it double billing and could result in a hospital system paying thousands of dollars or more in fines.

However, if the research administrators first had negotiated a contract with the research sponsor that specifically omits language that suggests the sponsor will reimburse for blood draws and other procedures, then there's no danger that Medicare will consider the incident a double billing and fraud, explains **Michael Slocum**, JD, president of Slocum & Boddie located in Springfield, VA. Slocum spoke about negotiating clinical trial agreements at the Society of Research Administrators (SRA) International Annual Meeting, held Oct. 23-27, 2004, in Salt Lake City. The Slocum & Boddie firm conducts business law, including representing research institutions in clinical trial negotiations.

What can happen if the contract contains the pharmaceutical company's detailed cost budget list is that Medicare will find one case in which a nurse charged Medicare for a blood draw that was used, at least partially, for a clinical trial, Slocum says.

Because of the clinical trial contract, Medicare officials say that this constitutes double billing, which is fraud, he adds.

"The way they work is [fraud inspectors] don't have to go out and prove you did this every time — they only have to prove you did it once," Slocum tells *Clinical Trials Administrator.* "Then they use statistical sampling to show how many other times you must have done it, and that's why hospitals end up paying these incredible settlements, like $90 million, because of picky charges picked up by auditors and extended out on a statistical basis."

The simple solution is to keep the detailed cost analysis out of the contract and use language that only refers to a fixed fee for the clinical trial, he adds.

The problem is that pharmaceutical companies often use boilerplate contract language drawn from different industries, and the lawyers sent to discuss the contracts typically are young and have no courtroom experience, Slocum says.

That's why it's important that research administrators recognize that these agreements are negotiable, he notes.

"The other purpose of a contract is to give you a road map on how to work together," Slocum says. "If you approach it from that direction, most of the issues do fall out in a way that's acceptable to a vast majority of research institutions and a vast majority of drug companies."

Slocum says there are six areas in a clinical trial agreement that cause the most problems. **(See story on six contract problems and their solutions, p. 18.)** The six areas include the following:

- HIPAA and confidentiality;
- publication restrictions;

- payment details;
- indemnification;
- choice of law clause;
- patent rights.

Don't just sign on the dotted line

The reason standard clinical trial contracts continue to include phrasing that is problematic is because research institutions do not engage the help of knowledgeable people who can fight the pharmaceutical company lawyers on these details, Slocum notes.

"It's my impression that most of the drug company lawyers you deal with are reasonably junior in the organization, and most clinical trial negotiators have to fight to get through to a lawyer," he says.

It's like the philosophy of Tom Wolfe's term the "flak catchers," Slocum says, referring to Wolfe's 1971 book, *Radical Chic & Mau-Mauing the Flak Catchers,* which details the frustrations of people trying to get through government bureaucracy where gatekeepers are there simply to say, "No."

"Corporations put front people out to be flak catchers, to tell you 'No' at the first level you deal with," Slocum says. "It's their job to say, 'We can't do that; it's not our policy.'"

The key is to force them to bump you past that level, and hiring someone who is knowledgeable about clinical trial contracts is the best way to get that boost up, he notes.

Always negotiate, Slocum advises.

"You can negotiate over e-mail; and 90% of the time if you just ask for these changes, you will get them," he says.

Strategies for research contract negotiations can be found on Slocum's web site at www.slocum boddie.com.

An example of some of the questions that need to be considered prior to contract negotiation, include these listed by Slocum in his speech at the SRA 2004 Annual Meeting:

- Can the sponsor approve the principal investigator (PI)?
- What is the PI's commitment to conduct the study?
- If the PI becomes unable to complete the study, must the sponsor consent to a new PI?
- Can the sponsor follow the PI?
- Are there multiple PIs?
- How long will records be held?
- What's the time frame for completion of the study, the marketing application approval, discontinuation of the IND?
- How will study records be maintained?
- How will the transfer of study records be handled?
- Who owns the documents and how are things kept in accordance with HIPAA and state laws?
- What information will be disclosed by the sponsor to the institution?
- What information will be disclosed by the institution to the sponsor?
- How will confidentiality be maintained with regard to third-party information?
- How will confidentiality be maintained with regard to patients/subjects?
- What are the obligations regarding confidentiality on the part of the investigator, staff, and students?

Research institutions also could learn more about how their own contracts can be changed by checking out some examples offered on the web sites of major research institutions, including the University of Texas' at: http://www3.utsystem.edu/ogc/IntellectualProperty/clinical%20trials.htm. ■

Six prime areas for potential problems

Expert provides possible solutions to each

Standard pharmaceutical company contracts for clinical trials typically include some less than desirable details, which research and institutional administrators may overlook if they are unfamiliar with contract language, a national clinical trial contract expert says.

For instance, clinical trials usually are fixed price contracts, but the terminology that's used in the contracts tends to be about cost reimbursement, says **Michael Slocum**, JD, president of Slocum & Boddie in Springfield, VA.

Why should that concern a research institution? Because the federal government does care about the wording of these contracts, since that's what the government uses to make its case for fraud and abuse, he says.

Slocum outlines the six areas that pose the most problems for research institutions and what can be done about them:

1. Confidentiality: Pharmaceutical companies often leave it up to research institutions to adhere

to state privacy laws and HIPAA, Slocum says.

"Usually, you can satisfy the drug company's needs by getting the data de-identified or by using limited data sets," Slocum notes.

However, the clinical trial contract may include language that permits the pharmaceutical company to pick up every piece of data the clinical trials office develops, so it's important that the contract be negotiated to provide for exceptions that are necessary for the research institution, he says.

For example, information should be made available in the event a patient/subject needs emergency medical care, Slocum says.

"A lot of drug company lawyers will agree to this once they understand what you're talking about," he says. "Say you are giving subjects XYZ heart drug, and then one person is out on the highway and gets crunched by an 18-wheeler, ending up in someone else's ER."

The patient or family or an ID bracelet lets the hospital's physicians know the patient is involved in a clinical trial, so the ER doctor calls the clinical trial investigator to find out more about the patient's medical history, Slocum says.

"The PI doctor can't ask someone else's lawyers at 2 a.m. for permission, and he needs to be able to provide whatever information the other doctor needs without worrying about whether it is confidential or not," he says. "So we want an exception for information that's necessary for emergency medical care information."

Also, a research institution should seek an exception for information that is needed to properly defend itself legally, Slocum adds.

"A lot of drug company lawyers say, 'You can subpoena that,'" he says. "But we want to provide information to insurance underwriters and to law firms that might be the institution's litigation firm or not, and we maybe even want to provide the information in a mediation situation to the opposite side so we can get out of having a claim from a patient."

And finally, a research institution might need to be able to bring up that information in its own defense if the drug company sues the research institution, Slocum says.

2. Publication rights: Research administrators should not assume that the contract will permit them to publish the study's findings or publish the findings regardless of whether they support the sponsor's interests, he says.

"Some naïve biotech companies use the same clause [prohibiting publication] they might use with a for-profit testing lab, and it's absolutely not acceptable," Slocum explains. "Everyone needs to understand that no matter how small your hospital is, you should take time to negotiate."

More commonly, drug companies will include language in the contract that requires the research institution to agree to not publish until all of the clinical trial sites are finished, he says.

"How will you ever know if all of the sites are finished," Slocum says. "The drug company could be slick and keep one trial going."

That type of contract language harkens back to the construction trade contract language, he adds.

The solution would be to have one drop-dead date included in the clause, so that the research institution could publish by that date regardless of the clinical trials status at other sites, Slocum advises.

"Secondly, I don't agree to coordination of publication, where it has to go to a committee, unless the committee is independent of the drug company," he says. "I have to know the committee has independent doctors who are not beholden to the drug company to decide whether or not the publication goes out."

It's a mistake for institutions to automatically give up the right to publish because the publication clause also covers any type of public disclosure, Slocum explains.

"So if a doctor finds out that patients are being killed on the trial and wants to bring this up, then the only way he can is through a publication clause," he says. "Even if he wants to talk about it with *The Wall Street Journal* or on his own web site, he can't without the publication clause."

Also, a major publication change these days involves what medical journal editors have begun to require as additional criteria for publication, Slocum adds.

The International Committee of Medical Journal Editors has decided that studies will not be published unless drug companies agree to list clinical trials in a register, so Slocum advises research institutions to include a requirement that the trials be listed in a register.

Last fall, pharmaceutical companies balked at this contract change; but more recently, they've become more flexible and are permitting the contract change, he says.

Sponsors have realized that if their clinical trials are turned down for publication because there isn't a register then the test product probably would not be approved by the FDA, Slocum says.

"Unless research can be published, the FDA

doesn't accept it as legitimate research," he says. "That's a blanket generalization, but essentially that's true — the research has to be publishable."

Typically, Slocum advises research institutions to make agreements that the sponsor lists all phases of clinical trials, he adds.

A last note on this part of the contract involves what principle investigators often do routinely and that is to sign a personal confidentiality agreement, that may be more strict than the clinical trial agreement, Slocum says.

This can be a big mistake that is avoided by simply having the institution's or a personal attorney review the confidentiality agreement before it is signed, Slocum adds.

3. Payment details: Another pointless part to most pharmaceutical company contracts is a detailed cost list of clinical trials procedures and budget line items, Slocum says.

These itemized lists are pointless because the contracts typically are fixed price deals or at least fixed price per subject, he explains.

So while the sponsor might have used its own itemized list to determine what that fixed price would be, there is no reason to include the itemized breakdown of costs in the contract itself, Slocum says.

"Don't accept super detailed cost budget documents," he states. "Instead, accept a document that says you'll do the work in accordance with the protocol and will be paid a fixed price of X for the whole trial or a per patient price of X, but that you will not be paid for individual procedures."

Or if the pharmaceutical company balks at removing the budget details because they say it's part of their template, then language should be put into the contract that essentially states, "We're charging you a fixed price at bottom and whether it's for standard of care or for other reasons, it's this fixed amount," Slocum says.

Medicare and other government auditors accept this type of language as a disclosure that means the sponsor is not paying for specific clinical trials procedures, he says.

4. Indemnification: "This is probably the most negotiated clause for the least probable reason," Slocum says. "I would love to see an actual court case between a drug company and research organization related to indemnification or driven by indemnification, where it was a crucial issue, but I cannot find one," Slocum says.

Basically, indemnification means that the contractor assumes all liability from the contractor's own negligence arising out of the contract.

While this is pretty standard and straight-forward in the contract world, some sponsors will want to add more confusion by cross-indemnification for their own negligence, which is not allowed in nearly all states, Slocum says.

"It's against public policy, and even if you say, 'I won't be responsible for my own negligence, state law would not enforce that," he says.

The other reason why it's pointless to carve up too many points on this clause is because when patients/subjects are hurt and sue, they almost never sue just one party, Slocum says. "They sue everybody and let them sort it out."

Another clause to add to the contract is one that requires the pharmaceutical company to provide the defense on such lawsuits because one firm should take the lead and they typically have handled similar cases made at other research institutions and have all of the necessary data and information readily available, he says.

5. Choice of law clause: Clinical trial contracts typically list a state where the laws would apply to this agreement, but it's better to leave out any mention of a state, Slocum says.

"If they take the state's name out completely, then the contract is performed in your state; and state laws say the law applied to the contract is the law of the place of performance," he explains. "In absence of an agreement otherwise, that's the rule."

6. Patent rights: "This is the least important issue in clinical trials because unlike normal basic research that an academic institution will do, a drug company has already done the basic research and has patents on all of the drugs and devices," Slocum says. "All they need from you is the testing."

So this part of the contract would not be a problem at all except that some pharmaceutical companies have gotten overreaching and demand all of the copyrights, which a research institution cannot give them, he says.

For example, a research institution may not give a sponsor the rights to all of the patient records or to reprints of published articles because the research institution doesn't own those rights, Slocum adds.

"Publishers take copyrights on the articles, and doctors don't have the right to say they can give away a reprint because it doesn't belong to doctors anymore," he says.

These sort of changes to a clinical trial contract may seem intuitive, but the reason they are necessary is because pharmaceutical companies continue to use contract language that is written purely from

a lawyer's point of view and not from a risk management point of view, Slocum notes.

"The folks who should be driving these agreements are risk managers," Slocum says. "It's not just how do we paper the case enough so it looks like we did it, but what are the risks?" ■

Accreditation of PIs may be the answer

Soon certification exams may be required

Clinical research experts say the industry is beginning to recognize the need to hold clinical investigators to similar standards for practice and accreditation as physician specialists by requiring them to become certified in the practice of clinical research.

Within the past few years, research organizations have initiated or expanded clinical trial certification to include principal investigators (PIs).

The organizations that offer certification programs for PIs include the Drug Information Association of Horsham, PA; the American Academy of Pharmaceutical Physicians (AAPP) of Apex, NC; and the Association of Clinical Research Professionals (ACRP) of Alexandria, VA. Also, several other organizations offer certification for clinical research professionals or associates.

Clinical trial administrators and research managers should embrace the certification trend because it ultimately will mean more knowledgeable investigators and improved safety for clinical trials, experts say.

For example, a worst-case scenario in the clinical research field involves the all-too-common scene in which physicians get involved with clinical trials only to decide after finishing one or two trials that this is not them, says **Greg Koski**, PhD, MD, CPI, senior scientist for the Institute for Health Policy and an associate professor of anesthesia at Massachusetts General Hospital, Partners HealthCare System of Harvard Medical School in Boston.

"They suddenly realize this is hard work and so they do one trial and say, 'That's it for me,'" Koski says. "That means people who have perhaps the least level of training experience and commitment are doing a large number of trials."

Requiring clinical investigators to become certified would be a good first step in the direction of weeding out the dabblers and improving the skills level among the remaining clinical researchers, he notes.

Certification is a positive move to enhance the conduct of clinical studies and further safeguard the protection of individuals participating in clinical studies, say **Jeffrey W. Sherman**, MD, FACP, chief medical officer and executive vice president of NeoPharm Inc. of Lake Forest, IL, and **Irwin G. Martin**, PhD, acting executive director of the Drug Information Association.

The driving concern behind certification is subject/patient safety, says **Joan L. Drucker**, MD, CPI, medical director of AAPP.

"We consider an adequate education ultimately is what's best for patients and subjects in clinical trials," she says.

AAPP started its certified physician investigator program (CPI) in 2003 in response to the nation's need for training of clinical investigators, Drucker notes.

"In the late 1990s, the Institute of Medicine was holding a number of clinical research roundtables to see what were the needs of clinical investigation in the United States, and they developed a number of recommendations, and some are similar to what you see in the National Institutes of Health research road map," she explains. "But one area that caught our attention was a sense that there is a greater need for training of clinical investigators in the future."

The AAPP certification program offers only one designation, the CPI, and it's available only to MDs or the equivalent, Drucker says. **(See chart on researcher certification programs, p. 22.)**

ACRP, which began certifying clinical research coordinators (CRCs) in 1992 and clinical research associates (CRAs) in 1995, first offered a certifying exam for investigators in North America in 2002, says **Carol D. McCullough**, RN, MBA, director of certification, credentialing & accreditation of ACRP.

"To date, ACRP has certified almost 15,000 clinical research professionals, including 245 investigators worldwide, with 206 from the U.S. and Canada," she reports.

All three PI certification programs require successful completion of an examination that demonstrates mastery of good clinical research practices, research ethics, regulatory affairs, study design, and other areas that a clinical investigator should know, says Koski, who helped write the exam for AAPP and was involved in the early stages of developing the ACRP's examination process.

Researcher Certification Programs

Drug Information Association

Offers: Certified Clinical Investigator (CCI)

Qualification criteria: MD, PhD, DrPH, PharmD, DMD, DO, NP, or PA; plus must be a principal investigator or sub-PI on Form FDA 1572 within past 24 months

Recertification requirements: Three years; re-examination or 30 hours of CE credits

American Academy of Pharmaceutical Physicians

Offers: Certified Physician Investigator (CPI)

Qualification criteria: MD or equivalent; plus must be a PI, sub-PI, Co-PI within past 2 years

Recertification requirements: Five years; re-examination and continuing education

Association of Clinical Research Professionals

Offers: Certified Clinical Research Associate (CCRA), Certified Clinical Research Coordinate (CCRC), Certified Clinical Trial Investigator (CCTI)

Qualification criteria: For CCTIs: Valid doctorate-level degree in medical field or licensure in recognized medical specialty in which clinical trials are conducted; plus clinical trial experience and education

Recertification requirements: Two years; 24 hours of approved CE credits

Source: Association of Clinical Research Professionals, Alexandria, VA (www.acrpnet.org); Drug Information Association, Horsham, PA (www.diahome.org); American Academy of Pharmaceutical Physicians, Apex, NC (www.aapp.org).

Physician investigators who are actively involved in clinical research would probably be able to pass the exam with 30 hours or fewer of study, Koski estimates.

There are several courses offered on-line and also by these various organizations to prepare people, particularly in good clinical practices and regulatory affairs, he says.

"One of the great benefits of an examination and certification process like this is it gets people to take the time to look at things they might not otherwise have looked at," Koski says. "They may come across new information they didn't know, and just preparing for the exam helps to improve the knowledge base for those involved in the clinical trials process."

National standard on the horizon?

As momentum builds for research physician certification, there has been some discussion about creating a national certification standard, and, eventually, moving toward one certification process, Koski says.

"There have been some very early discussions among representatives from the three organizations to explore various ideas and opportunities," Koski says. "We're moving in that direction, and my personal view is that a failure to do so would potentially undermine the acceptance of the investigator certification because people will be less likely to know what it means."

"ACRP does favor having one investigator designation that would become a standard for the clinical trials industry," McCullough says.

"Historically, ACRP had discussions with several organizations prior to anyone having an investigator certification program for just that reason," she adds. "Just recently, we have participated in a conversation with other organizations and agreed that we would begin to explore the possibility of moving toward a single investigator certification."

From the perspective of investigator training, it really should be a national standard, Drucker says. "We support the idea that there should be a common standard for everyone to be measured against. We're having some very preliminary discussions with the other organizations we know of and some outside third parties to see what it would take."

DIA has not endorsed nor dismissed the idea of a single designation for clinical investigators, Sherman and Martin say.

However, they note that a single standard already is in place for physician specialty areas, such as internal medicine, for certification, which is done by the American Board of Medical Specialties, and for other areas, such as drug approvals by the FDA.

"Why is this area of medicine, such as this clinical investigation, the only one that doesn't require separate training?" Drucker says. "Any other practice of medicine requires specialty training and licensing before you can see patients, and somehow there's a feeling that if we're experts in our specialties then we ought to be able to sit down and read

the regulations and know what to do, and most of us do."

However, when national headlines highlight the deaths of patients participating in clinical trials and other problems, then it requires the research industry to take a look at the whole process and think about making it better, Drucker adds.

"We think having investigators trained specifically in requirements of how to do a trial and patient safety would ultimately lead to a safer end result," she says.

Certification programs provide a way to demonstrate compliance with standards of professional practice in the conduct of clinical trials, McCullough says.

"The certification of investigators and the whole clinical research team helps ensure that they have a well-versed knowledge of good clinical practice requirements for the conduct of high-quality clinical trials and are able to assess their application in practical situational scenarios," she adds. ■

New bioterror vaccines are getting in the pipeline

The federal government has awarded $232 million to fund research and development of new vaccines against three potential agents of bioterrorism: smallpox, plague, and tularemia. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), will administer the contracts.

The funding responds to a key objective of the NIAID biodefense research agenda, which emphasizes the development of new and improved medical products against "Category A" agents — those considered by the Centers for Disease Control and Prevention (CDC) to pose the greatest threat to national security.

The smallpox awards continue advanced development work that began in 2003 on two modified vaccinia Ankara (MVA) vaccine candidates. These contracts will support larger scale manufacturing of the vaccines as well as further safety and effectiveness studies in animals and humans. The tularemia and plague awards will fund early-stage product development of the respective vaccines, which will include dosage formulation, pilot batch production, and initial clinical assessment. All four contracts are for purchases of vaccine lots intended for research use. Any future purchases of additional vaccines for stockpiling in the event of an emergency will depend on the results of the research currently under way.

CE/CME instructions

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 certificate of completion. When your evaluation is received, a certificate will be mailed to you. ■

COMING IN FUTURE MONTHS

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- Follow these tips to handling international trial sites
- Improve communication between partners in multisite trials
- Revamp compliance program following these guidelines
- Use this strategy to design a drug supplies accountability log

NIAID awarded two contracts totaling up to $177 million for advanced development of MVA vaccines against smallpox. MVA is a highly weakened form of the vaccinia virus that cannot replicate in human cells.

Previous NIAID research has demonstrated that MVA nearly is as effective as the standard smallpox vaccine, making it a promising candidate for use in children and pregnant women as well as people with weakened immune systems or skin conditions such as eczema. The new contracts will allow the companies to continue the work they began under contracts awarded in 2003. ■

CE/CME objectives

The CE/CME objectives for *Clinical Trials Administrator* are to help physicians and nurses be able to:

- review pertinent regulatory mandates;
- develop practical clinical trial oversight strategies;
- review best practices shared by facilities that successfully conduct clinical trials. ■

CE/CME *questions*

5. In 2004, the manufacturer of Vioxx pulled the popular painkiller off the market because of what adverse event?
A. It was linked to Crohn's disease.
B. Post-marketing research of rofecoxib showed that clinical trial subjects were at greater risk for liver disease when taking the painkiller than were subjects taking a placebo.
C. Post-marketing research of rofecoxib showed that patients were at greater risk of heart disease when taking the medication than were patients who were taking a placebo.
D. It was linked to a greater risk for Type 2 diabetes.

6. From a risk management perspective, why is it important to negotiate a clinical trial contract that does not have a detailed budget template?
A. Since the budget template no doubt includes average costs, it serves the research institution's interests better if it is not included in a contract and these costs are instead negotiated on an ongoing basis.
B. Actually, the reverse is true: It's important to include a budget template, even when the contract involves a fixed price.
C. Because this places a research hospital at greater risk of a Medicare fraud finding.
D. Because this may result in a sponsor asking for a refund if the listed number of procedures in the budget template are greater than the number of procedures actually performed.

7. When negotiating a clinical trial contract, it's important to put a drop-dead date included in the clause relating to when the study can be published. Why?
A. If the sponsor requires publication to wait until all trials are complete, it is possible that one trial will never be formally closed out and investigators at other sites will be unable to publish their data.
B. Without a drop-dead date, an investigator who notes an unusually high number of deaths in a trial will be unable to inform the public about those adverse events.
C. Without the drop-dead date included in the contract, the contract's language will prohibit all publication, including disclosure to the media.
D. None of the above.

8. Which of the following is not one of the new certification programs offered for clinical trial investigators?
A. Certified Clinical Investigator (CCI)
B. Certified Research Investigator (CRI)
C. Certified Physician Investigator (CPI)
D. Certified Clinical Trial Investigator (CCTI)

Answers: 5-C; 6-C; 7-A; 8-B.