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ADMINISTRATOR
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IN THIS ISSUE

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Adaptive protocol design challenges researchers to think outside the box

New generation of clinical trials on horizon

Imagine conducting clinical trials that provide a greater possibility of personal benefit to participants and reach conclusions in a faster and more efficient manner.

Thanks to technological advances and the efforts of investigators who made an effort to think outside the box, such a possibility can be a reality today. The only thing holding it back is the research industry's reluctance to change the old methods and processes, says **Donald Berry**, PhD, a professor and chair of the department of biostatistics and applied mathematics at the University of Texas M.D. Anderson Cancer Center in Houston.

"There are conflicts here with people who have been doing something this way all of their lives and to say that what they're doing is not the best way is a hard sell," Berry says.

Sometimes radical new changes only come about when someone new enters the field and looks at the old process in a different way. That's what happened when Berry entered medical research from a statistician background.

Berry wanted to come up with a way to improve clinical trial research and improve patient care, but his ideas quickly met resistance. "It was like I was from Mars," Berry says. "They thought I was naïve and didn't have an appreciation for what clinical research was about."

So Berry began working on clinical trials, following convention until he was well-enough established to discuss the possibility of change. A funny thing happened when he began to discuss changing the trial process: other people also began to discuss change, and more people began to listen.

"Other people have had these kinds of notions, these revolutionary ideas like we ought to be looking at the data that we collect during the course of the trial to understand where we're going and to try to modify where we're going based on what we see," Berry says. "In the past five to 10 years, these ideas have started to gather momentum in the pharmaceutical industry, and certainly in the medical device industry, and within some institutions."

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Bayesian method vs. frequentist approach

Essentially, Berry promotes what he calls Bayesian statistical methods in clinical trials, which allow investigators to know the research answer much earlier than the standard approach. "If you know the answer you can stop the trial," Berry says. "Or if the answer is looking interesting you can modify the trial, and in some cases you might have to make the trial bigger because you are on the cusp."

The chief objection in the clinical trial industry is the fear of bias, Berry notes. "There are potentials for bias, but it is possible to accommodate that and get over those biases," he says. "Sometimes you have to view it as a cost benefit where the benefits are so great that you might have to sacrifice a bit of bias now and then."

This approach also could be called adaptive designs, says **Jane Perlmutter**, PhD, a breast cancer survivor who is on the national board of the Y-ME National Breast Cancer Organization in Chicago.

"The Bayesian approach and adaptive designs are all things that I think can help us more efficiently and effectively speed up the process of clinical trials," Perlmutter says.

"Adaptive designs modify the proportion of patients getting one treatment versus another as the treatment progresses," Perlmutter says. "I think that is advantageous to patients."

Traditional clinical trials are designed in the frequentist approach which expects a single experiment to lead to an answer, although in practice it typically will take converging evidence from a number of trials before an answer is considered complete, Perlmutter says. "In Bayesian statistics, the basic premise is we have a lot of knowledge and any experiences we have change our beliefs, and these have to be taken in the context of previous beliefs," Perlmutter says.

Perlmutter uses the analogy of an eye exam to explain how adaptive design works: "When you go to get glasses, it's always frustrating when the optometrist says, 'Which is better: A or B?' and you don't know," she says. "But what the optometrist does is give you two extremes, and he rapidly realizes where your problem area is, and then he can adapt the eye test until you're clearly within this small range."

In Bayesian statistics, clinical trials are put into that small range and kept there until there's a clear conclusion, Perlmutter explains.

"Sometimes there will be a short test because it's clear where the problems are," she says. "And sometimes you'll keep testing because you're not sure which the right one is."

Berry published a paper about Bayesian clinical trials in *Nature Reviews* journal, and it was accompanied by an editorial that called for further investigation of the method in order to solve

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Editorial Questions

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the problems of long lag time in studying and approving new molecular entities (NMEs).1,2

Berry has been involved in clinical trials that use the Bayesian design approach, and he explains how the process works, using examples from his own work.

For instance, this approach was used in a three-arm trial in acute myeloid leukaemia. The study involved using troxacitabine (T) combined with standard therapies: first with idarubicin and separately with cytarabine. These arms were compared with an arm that used the two standard therapies in combination.[1]

"I said to the investigator, 'Let's not randomize patients equally; let's assign patients according to how they do on the various drugs and drug combinations, so if one arm was doing better we'll assign patients to it with a higher probability, and if it is doing badly then we'll drop the arm,'" Berry recalls.

In the study's final results, the troxacitabine and idarubicin arm was dropped after it had 24 patients, and the troxacitabine and cytarabine arm was dropped after 34 patients, because both of the experimental arms had a lower complete remission rate than did the standard treatment, Berry says.

"Ten out of 18 patients had a complete remission in the standard arm, which is similar to historical results," Berry says. "In the troxacitabine/cytarabine arm there were only three out of 11 remissions, and in the other arm there were zero complete remissions."

When Berry and co-investigators sent an article about the trial to one journal, the response was that it was a lousy trial because an arm with complete data from only five patients does not have enough information to draw any conclusions, Berry says.

The second journal where the article was submitted loved the design and published it, Berry notes. "We've gotten really quite positive reactions," Berry says. "There are still some people who say, 'Maybe you made a mistake,' and I say, 'Maybe we did, but if we made a mistake we didn't make much of one because the Bayesian probability of benefit from the troxacitabine/idarubicin arm is quite small.'"

Berry asks people who question the trial's design whether they would want to try troxacitabine/idarubicin if they got the disease.

One area of clinical research that has used the Bayesian statistical method more than others is the medical device field, Berry notes.

"They do the adaptive kinds of design we're talking about," he says.

Also, drug companies are beginning to use adaptive design in dose-finding trials, Berry says.

"The standard dose-finding trial has you assigning the drug equally to a number of doses," Berry says. "So you close your eyes and then open them a year or two later and say, 'Oh rats! I wish I would have done something else.'"

With adaptive design, investigators look at data as the trial continues and fine tune the trial to where the dose response curve seems the most interesting, Berry says.

This may result in the trial being stopped or a particular dose arm being dropped.

With some trials already moving into the direction of adaptive design, this type of clinical trial design is the wave of the future, Berry says.

Pharmaceutical companies and the FDA are changing, partly due to necessity, he notes.

"It's a novel kind of idea, and there's no question that it will have to come, and it will come faster in AIDS than say in heart disease," Berry says. "It ties efficiency to treating patients better, and it saves patients on average and it saves time, which is something very important to pharmaceutical companies."

With the Bayesian approach, clinical trials can reach a conclusion more rapidly, and they have the potential of coming up with a better solution and giving more trial participants a better treatment, Perlmutter says.

"The Bayesian theory says, 'If while I'm running the trial I look at the data and see that most patients are doing better with one drug, then I should change the odds," Perlmutter explains. "If I give more patients that apparently better treatment than one of two things will happen: either I'm helping the patient and I more rapidly run to the conclusion that this is the better drug, or the arms will start to converge again and look alike."

Either way, the patients are treated better or no worse than they would be under the clinical trial with a traditional design, Perlmutter adds.

"But I think people are very skeptical and are concerned that the FDA won't approve things that use those approaches, and so drug companies that would like to get their studies out faster and less expensively are saying, 'It's no good if the FDA will send it back,' and scientists are saying, 'I'm not sure this is rigorous,'" Perlmutter says.

Critics of the change might question why the Bayesian design hasn't been used for decades if it

indeed provides all of the reported benefits, Perlmutter says.

"The answer is we didn't have the tools years ago to do the Bayesian statistical method because we didn't have computational power," Perlmutter explains. "Traditional statistics can be solved by purely mathematical techniques, but with the Bayesian method, the mathematics is beyond computational approaches, so you have to use a simulation approach."

Perlmutter recalls her graduate school years pre-desktop computers when running a simulation would take all night. "Now a desktop computer can do the same thing in 30 seconds," she says. ■

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Special Coverage: AAHRPP conference 2006

Stanford's COI policy covers gray areas

Fictitious vaccine scenario illustrates complexity

Stanford University (Stanford, CA) has an extensive human subjects research conflict of interest (COI) policy that covers details that sometimes are overlooked at research institutions. Despite having strong COI policies and procedures, the institution's research programs have remained strong.

"We have an amazingly entrepreneurial faculty," says **Harry B. Greenberg**, MD, a Joseph D. Grant professor in the Stanford University School of Medicine. Greenberg was scheduled speaker about conflict of interest and research at the Association for the Accreditation of Human Research Protection Programs (AAHRPP) 2006 conference on Quality Human Research Protection Programs, held Feb. 26-28 in Phoenix.

"Though we're trying to exercise rigor in following our COI principles, we haven't stopped any good science from getting translated into the commercial realm," Greenberg says. "Stanford prides itself on being a great translating university."

Managing conflicts of interest is very important in human subjects research because of the great concern that problems can lead to direct problems with research subjects, Greenberg notes.

Greenberg illustrates the complexity of ironing out conflicts of interests with this fictitious scenario: "Supervax is a company involved in a late-stage, phase III, multi-site study of a vaccine, and a two-month-old child develops hives and wheezing right after getting the vaccine," Greenberg says.

The child is brought to the emergency department and is treated and gets better. Assistant professor Dr. Brill is the principal investigator of the study. Dr. Brill needs publications in order to receive a promotion, and 10 percent of her salary is paid through the vaccine study, he adds.

Dr. Brill wants to classify the baby's reaction as a serious adverse event (SAE), and she asks her department chair Dr. Roberts about the case. Dr. Roberts correctly points out that the event must be life-threatening and not potentially life-threatening in order to be a serious adverse event. Dr. Roberts has stock options in the company conducting the study, and he had agreed prior to the study's initiation to not be involved in subject recruitment or treatment. But Dr. Roberts was involved in lab analyses for the study, Greenberg says.

The question Greenberg asks research audiences is whether Dr. Brill and/or Dr. Roberts have conflicts of interest.

The answer is that Dr. Brill does have a conflict of interest, although it's not a traditional COI from a financial perspective, he says. "Dr. Brill has no direct personal financial relationship with the company, but since part of her salary is being paid by the company and through the university to her, she has some form of conflict of interest. Nobody addresses that issue, but it's still a conflict of interest."

Also, and probably, more importantly, Dr. Brill needs publications in order to be promoted, so she also has a non-financial conflict of interest that almost all academic faculty have, and this is another area of conflict of interest that is sometimes overlooked, Greenberg says.

Dr. Roberts, on the other hand, has a direct financial conflict of interest, and he should not have been involved at all with the clinical part of the study, and he certainly should not have given advice to Dr. Brill, he says.

"Dr. Roberts gave accurate advice about SAEs, but that involvement pollutes the study," Greenberg says. "We would not have permitted him to make a response to Dr. Brill at Stanford."

"Would you allow this study to occur at Stanford Medical School?" Greenberg says. "Probably not; we might allow a human study where there's a significant financial involvement by a principal

investigator when there's a compelling reason to justify the PI's involvement." For instance, if a study was unique and it might not happen elsewhere, and there was a chance it could help people, then the institution might find a way to enable the study to occur, Greenberg says.

But in the case of a multi-site, phase III study, there is nothing unique about it, and so it could have easily been done at another clinical trial site where there was no financial COI, he says.

Stanford University sets an example in its COI policies pertaining to the institution itself with its policy of relinquishing all equity that the university has in start-up companies when there's any likelihood that a human subjects clinical trial, sponsored by the start-up company, might occur at Stanford, Greenberg says.

"In the first couple of cases after initiating this policy we had to simply give away the equity," Greenberg notes. "Now we build it into our licensing agreements with buy-back clauses that say the company will buy back the equity at whatever price is fair if there's a desire to do the clinical trial of that product at Stanford."

For staff, Stanford's COI policy prohibits Stanford faculty from holding titles that are managerial titles in outside companies while the faculty members are Stanford employees, Greenberg says.

"This policy even pertains to start-up companies that the employee has initiated as well as for any other for-profit entity," Greenberg adds.

"And we have a zero dollar reporting requirement," he says. "We ask people to report conflicts of interest at the zero dollar level."

Although the university generally will permit conflicts of interest to occur at a higher dollar threshold, the faculty and staff are required to report all COIs under the threshold, as well, Greenberg explains.

"Another area where Stanford is different from other institutions is we have a very strong disinclination to permitting students to be involved in start-ups initiated by their faculty mentor," Greenberg says.

"This policy came after some issues that have been reported in the press in the past where there was concern by students about their involvement in start-up companies," he says. "Involvement of students seems so inherently full of potential conflict that we strongly discourage it."

The university's philosophy is that the student's primary role at Stanford is to get an education, and it would be difficult to decipher what a faculty mentor's motivation is when the students are working for a mentor in a start-up, Greenberg adds.

"The other thing we have done that many other universities have not done as frequently is we basically disallowed, in almost all cases, the funding of research in the laboratories of people who are the sponsoring company's founder," he says. "So say I founded a company, and the company says 'We want to give Harry Greenberg's lab a gift or a grant to do research.'"

This type of relationship is very difficult to manage because of the inherent conflict of interest, Greenberg says.

"When you give that grant are you using Stanford labs and university to advance your company for personal gain, or is this work directed at your academic mission?" Greenberg says. "It's better not to let it happen." ■

Special Coverage: AAHRPP conference 2006

Getting through the accrediting process

Select a point person and anticipate corrections

Seeking accreditation for research institutions' human subjects research protection programs is becoming an increasingly popular choice. The Association for the Accreditation of Human Research Protection Programs (AAHRPP) of Washington, DC, now lists more than 30 accredited institutions, and another 200 are undergoing the accreditation process.

Once an organization commits to seeking accreditation, the process is arduous but rewarding when an institution succeeds, says **Larry D. Milne**, PhD, vice chancellor for academic affairs and research administration at the University of Arkansas for Medical Sciences (UAMS) in Little Rock. The institution has had full AAHRPP accreditation since June 2005.

"AAHRPP's original comment to us was 'We want you to be accredited, and we'll help you in any way we can,' and they delivered on that," Milne says. Milne offers these suggestions for how to achieve accreditation:

- **Conduct a self-study.** The first step in seeking accreditation is to conduct a self-assessment that will help an institution highlight weaknesses and strengths, Milne suggests. "We pulled together a lot of our policies and procedures, and it amounted to 4,600 pages," Milne says.

The AAHRPP application includes a two-page form, a program overview, copies of documents used by the organization, and an index. The institution decides whether to apply as a preliminary applicant or as a formal applicant.

• **Prepare for a site visit.** "After you've done your self-study, they set you up with a site visit, Milne says. "We had a team from AAHRPP come in to look at our whole program."

The institution's human subjects protection program had grown from one IRB and no staff to three medical IRBs and one behavioral IRB, and the institution had 10 people on staff in the research compliance group, Milne recalls.

Then the initial report arrived on Jan. 10, 2005, and it listed observations and recommendations for each of 77 elements that AAHRPP feels are important for accreditation, Milne recalls. "Many are minor, but others we found needed to be completely overhauled or new," he says.

• **Assign tasks.** One way to tackle accreditation findings is to form a committee and assign tasks to different people, but it's a good idea to have one person in charge, Milne says.

"We actually decided we needed one person to be responsible and take charge," Milne says. "We have one individual who was knowledgeable of the IRB process, and she was the best person to do this."

An executive committee, consisting of IRB chairs, the chief administrator for the IRB, the head of research compliance, the director of sponsored programs, and Milne, worked with the woman who had been put in charge of accreditation efforts. "So there were six of us, and we told everybody, 'You block out from 9 to 10 a.m. every Thursday," Milne says.

The idea was to expedite the process because institution officials wanted to get a report back to AAHRPP within one month, Milne notes.

Many decisions were made by e-mail ballots in which committee members voted either "I agree," "I disagree," or "Let's discuss." Milne says. "We discussed it one time and then a policy was written," Milne says.

• **Take advantage of available resources.** Accreditation officials encourage institutions to use what works at other research sites, Milne says.

The visitation team included people who came from accredited sites, and they would say, "Don't re-invent the wheel — our policies and procedures are on our web site, so take anything you want," Milne recalls.

Now that the UAMS is accredited, Milne and colleagues also share material and offer advice to those who call them.

• **Do not give up when first you don't succeed.** After many hours of working on correcting problems, including having the IRB director take off time to devote to the process, the institution received an "accreditation pending" status, Milne says.

"We were thrown out there in never-never land," Milne says. "AAHRPP called and said, 'You have a lot of stuff to do, but we don't know if you can do it by the next council meeting in June."

The institution had to make changes to the accreditation report and form another IRB, as well as hire additional staff, Milne notes. "They reviewed our updated report and felt we had made changes according to their suggestions and that we had a program that merited full accreditation," Milne says.

• **Maintain accreditation.** The institution's full accreditation will last three years, and then it's time to return to the process. However, there still is a lot of work to do in the interim, Milne says.

"The next self study should not be nearly as difficult," he says. "But I think the other thing that happens is you're constantly changing." For instance, AAHRPP changes its policies and standards, and then an institution will have to respond to these changes. The executive committee has to continue to meet to discuss changes and decisions, Milne says. ■

International sites must pay attention to detail

Audit readiness depends on it

[Editor's note: In the second part of a two-part Q&A interview, ***Anatoly Gorkoun****, MD, PhD, project manager of clinical operations of PSI Pharma Support International in Saint Petersburg, Russia, discusses how international sites and audits and regulatory factors.]*

CTA: How should a site be prepared to maintain a trial audit capability, and what are some details on how these audits should take place?

Gorkoun: It is a good clinical practice (GCP) requirement to keep an audit trail. It's covered at general GCP and/or study specific training

sessions, such as a session on "Requirements re source documents maintenance." All international auditors mentioned that Russian sites maintain source documents very carefully. Normally, all sites maintain comprehensive patient charts, including the hospital chart or outpatient chart. All ancillary documents are enclosed in these charts, including lab reports, X-rays, ultrasound, computer tomography, position emission tomography, films, files, and descriptions, etc.

The sites are audited by internal quality assurance auditors, sponsors' auditors, independent auditors, and Food and Drug Administration (FDA) auditors. The audit process in Russia doesn't differ much from the audits done in the U.S. The only difference is that a translator is needed to assist auditors since the local source documents are written in the Russian language.

As part of GCP training, the investigators need to be taught about monitoring and audit. The investigators work with monitors on a regular basis, so the monitoring process is not an issue in most cases. Audits happen less frequently than monitoring visits, and the audit is an important event for each study. The investigators should be aware of it. So they need to be trained how to prepare the site for an audit. At the beginning of the study, the investigators should be provided with general knowledge about monitoring and the audit, but for in-depth preparations, it's better to start doing it after the site receives audit notification.

When sites anticipate an audit, the best approach is to keep the site ready for the audit throughout the entire study.

There is no way to make corrections in the source documents before the audit, and there is no way to re-write any data. The auditors need to see a natural state of the site. When sites try to improve quality in a hurry, there is a very good chance they'll make an even bigger mess or demonstrate noncompliance. We need to wait until the audit report is issued and then improve quality based on the audit report findings and recommendations.

Investigators need to understand the importance of accurately maintaining documents. Auditors say that if a monitor describes in monitoring reports a persistent absence of some documents at the site, such as screening logs and distribution of responsibilities list, and all of those documents appear in a nice order a day before the audit, then it might be reported as a finding. The auditors might state that the site does not maintain the documents throughout the study, putting together the on-site study file specifically for auditors before the audit. If the investigators think that it's enough just to show documents during the audit, they are wrong. They need to realize that those documents must be maintained throughout the entire study, and it will be specifically checked by the auditors.

Keeping in mind the presentation on training issues for the SoCRA conference in Orlando, I had been asking auditors from different companies: "How do you see the preparation process? Do you have any specific message to deliver to investigators?"

What they said, and it was the same message with different wording, was, "Ask the investigators not to be scared by the audit. There is no need for specific preparations. Just ask the investigators to be available, to keep their facilities available, and to keep all source documents available. These are the best things they can do for us."

So, in preparing a site for an audit, it's a good idea to instruct the investigators about the audit structure and the type of auditor's activities. It's a good idea for investigators to learn about any frequently asked questions, such as these:

- What is the distribution of responsibilities at the site?
- What is the process of patient identification?
- What is the informed consent process?
- How is the site's work organized?

Investigators will need to think about these questions in order to provide the most complete responses.

Also, the investigators need to know how auditors evaluate quality, so it's a good idea to explain to them the definitions of observations and the respective consequences (observations, major observations, critical observations).

CTA: What regulatory considerations in working with Russia are there, above and beyond what is already required in the United States?

Gorkoun: The Russian regulatory authority accepted the ICH GCP guidelines, and thus, it's the main document, regulating clinical trial conduct in Russia.

CTA: Please describe how the monitoring process might differ for an international site?

Gorkoun: The monitoring process is regulated by Standard Operating Procedures (SOPs). I would not say that the monitoring process differs a lot in different countries. If the sites in different countries are involved in a global study, maximum

uniformity will be applied to the monitoring process, and it's the reason why the same monitoring procedures are applied for a global study in all countries. If several CROs are responsible for site management and monitoring in different countries, they will accept the same the same sponsor's SOPs to provide uniformity of the monitoring process.

One difference can be noticed though—since in Russian and Eastern European countries most of the monitors are MDs, if there are any medical questions, these are discussed at the monitoring visit with an investigator by the monitor.

CTA: Is there anything else that American clinical trial sites need to know about working with Russian sites and other international clinical trial locations?

Gorkoun: Actually, American clinical trial sites, or Canadian or Australian, etc., don't work directly with Russian sites. There are a lot of country-specific issues in each country, and, even if American or Australian sites know why enrollment is higher in Russia, it might be useless experience for other countries in some cases.

But knowledge of all those features can be helpful for American and other pharmaceutical companies who are running global clinical trials in Russia and Eastern Europe.

First of all, Russian sites are not overloaded with clinical trials, so there is a potential.

The Russian investigators believe that it's prestigious to run global trials at their sites, and so some of the motivation factors are international involvement, experience, publications, and recognition.

An investigator's grant is another of the motivation factors.

Among the important things to take into account is the medical insurance system, which is different in different countries. It's obvious that if the patient has the most complete medical insurance it will lead to his/her reluctance to be involved in most clinical trials. If the patient expects more benefits from the trial due to availability of free sophisticated medical procedures/examinations and the best treatments, which are better than what can be provided by the patient's basic medical insurance, then such a patient will agree to become a clinical trial subject more willingly.

In different countries, we can face different medical systems. They can be centralized, decentralized, private, or mixed. For instance, if we need to train the investigators in enrollment issues, it might be different for sites in countries with different systems. In some countries, especially those with a centralized medical system, it's much easier to organize patient referral networks to enroll more patients, while for sites in other countries it might be a very difficult task to have patients referred to a clinical trial site. As for Russian sites, the establishment of referral networks is a routine practice and usually contributes to a high enrollment rate. ■

Compliance Corner

Follow an expert's advice in reporting to regulators

A clearly defined process is place to start

Clinical trial sites and institutions could improve compliance if they have a clearly defined process for reporting to regulatory authorities, an expert says.

"It sounds simple and obvious, but it's not always simple and obvious," says **David L. Wynes**, PhD, an associate vice president for research and an institutional official for Federal Wide Assurance for the university's human subjects program at the University of Iowa in Iowa City.

"Many institutions spend a great amount of time working out the standard operating procedures (SOP) on how an IRB reviews protocols," Wynes notes. "But they need to think about the back end of the process and recognize that, inevitably, there are going to be unanticipated problems that occur, including new adverse events, previously unreported, and there may be situations of noncompliance."

Since institutions are becoming more active in post-approval monitoring and, as a result, they are more likely to find any existing noncompliance, it's extremely important to have a well-documented process on how to handle these situations, Wynes says. Wynes offers these suggestions for details to include in the process:

- **Know what to report.**

"While there's some guidance in the regulations, there also has to be some determination within the institution and IRB of what constitutes a reportable incident," Wynes says.

For example, the University of Iowa defines serious adverse events in an 89-page "Investigator's Guide to Human Subjects Research," which is available on the institution's Web site. The institution's definition is as follows:

"A serious adverse drug event is any adverse drug experience (associated with the use of the drug), occurring at any dose that results in any of the following outcomes:

— death,

— life-threatening adverse drug experience,

— inpatient hospitalization or prolongation of existing hospitalization,

— a persistent or significant disability/incapacity,

— a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above."

Among the other terms that the institution will need to define include the following:

— unanticipated problems,

— unexpected adverse events,

— noncompliance.

"It's my experience in talking with colleagues at other institutions that when you're confronted with a situation or problem, and you're engaging in a dialogue with a regulatory agency, you have a much stronger basis for your actions if you're operating off clear definitions and clear procedures," Wynes says. "You and the agency may disagree slightly on how you define serious adverse event, for example, but it's clear that you have a definition and are applying the definition and using it consistently."

The institution that does not have a definition may find that the regulatory agency contends that they are reporting SAEs inconsistently and without established criteria, he notes.

"Something else to remember is that in many cases where you have an unanticipated problem, adverse event, or something, the institution or IRB can get caught up in addressing the problem," Wynes says. "And if you don't have a clear process for reporting as you are required to under regulations, then that piece can get lost because you're so focused on a resolution."

So part of any compliance policy should include a process that describes how and to whom reports are made, he adds.

• **Know the best approach for reporting.**

Institutions may not have a written policy or procedure for this aspect of reporting, but it's important to also know the best approach for reporting and making initial contact with a regulatory agency, Wynes says.

"In many ways that changes depending on the circumstances," Wynes says.

For instance, some regulations use the term of reporting in a timely manner. An institution will need to define "timely manner" and stay consistent within that definition, he says.

Besides reporting in a timely manner, an institution may need to take the report from the investigator or IRB monitor and review and resolve it, Wynes says.

Also, if a site has a serious adverse event that results in serious injury or death to a participant or involves a grievous case of noncompliance then it may be wise to make a verbal report to the regulatory agency, Wynes suggests.

"You might go on an accelerated time frame to give initial notification, saying, 'We don't have any more details, but we wanted to let you know that something serious has occurred at our institution,' and then you start a dialogue on what the process will be," Wynes says.

If the initial report is made verbally, then perhaps the site could follow up with an email, he notes.

"What's important is that you give the information they need when they need it," Wynes says. "In a worst-case scenario, the regulator will hear of the incident from a third party, whether it's the news media or another research institution, and the agency would know nothing about it."

This prompt verbal notice helps with the partnership that is formed between regulators and research sites, Wynes says. "Recognize that regulators are a partner in this process and make sure you're working with them in that way," Wynes says.

At the University of Iowa, the standard operating procedures (SOPs) say the IRB chair will do the formal notification and provide a copy to an institutional official, Wynes says. The chair is notified by principal investigators, research participants, or others.

"We have a post-approval monitoring program where monitors meet with investigators to review procedures and ensure compliance," Wynes says. "And in that process, something could be identified."

At the University of Iowa, the IRB's standard operating procedures require the human subjects office to compile a monthly report of all unanticipated problems involving risks to subjects or others and to forward the report to the Office of Human Subjects Protection (OHRP) and the Food and Drug Administration (FDA).

• Have a process for evaluating the report.

It's important for an institution to have definitions and processes for reporting to an IRB and providing evaluations by the IRB, Wynes says.

Definitions should include the significance of the information, as well whether the incident meets the institution's reporting criteria, he adds.

Every aspect of reporting an incident should be spelled out in the policy, and the reporting process will need a paper trail, Wynes says.

"In the end everything should be in writing," he says. "Whether you make the call and follow-up five minutes later with an email or with a FedEx delivery, you need to make those kinds of decisions and have them in the policy."

• Know how to make a corrective action plan.

"I like to be an optimist and hope that most of what we're encountering can be resolved through some sort of corrective action," Wynes says. "If there has been some serious experience or unanticipated problem in research that has to be reported, the question is, 'Can that be corrected?'"

For example, if there's a problem with a device, the institution will look to the principal investigator, the manufacturer, and others to tell the IRB what can be changed to ensure this sort of thing doesn't happen again, Wynes explains.

Or if it's the type of incident that likely will happen again, then the site needs to factor that possibility into the risk-benefit analysis reported to the IRB and decide how to describe this risk to research participants, he adds.

"Can we minimize it? And what kind of information do we need to provide to participants so they can recognize that there's a new risk, previously undetermined?" Wynes says.

This type of response is one kind of corrective action, he says.

"A different response might be where you find some sort of noncompliance by a research team," Wynes says. "Depending on the nature of the noncompliance, the response might be better education."

In most cases, noncompliance is a paperwork problem, and a corrective action plan could improve the situation with better education and, possibly, additional monitoring, he notes.

"Once you know employees have additional information, then make sure they're complying with expectations," Wynes says. "You could evaluate the department to make sure resources are adequate for that clinical research program." ■

Going beyond reporting adverse events to IRBs

ORIO system is explained

Investigators often find it difficult determining what types of information should be reported to an IRB, and they may report too many incidents or omit important information.

At the University of Michigan in Ann Arbor, MI, IRB officials have developed a new methodology that assists investigators in screening for the correct reportable events, whether they are adverse events or other occurrences.

"We wanted to develop a methodology for other things IRBs are responsible for keeping track of," says **JuneAnne Insco**, CIP, IRBMED coordinator at the Medical School Institutional Review Board at the University of Michigan. The new system is called Other Reportable Information or Occurrences (ORIO).

"We didn't want to change what the regulators wanted us to monitor, but there are other types of things that need to be reported," Insco says.

The system captures information about unanticipated problems, protocol deviations, and serious noncompliance issues, even when these do not harm subjects, Insco says.

For example, a drug included in the study might have been mislabeled or not handled appropriately, Insco says. "Even if the drug is not administered to subjects in the study and the subjects don't have an adverse reaction and are not hospitalized, this still could pose a risk on another day, so it's a situation that needs to be addressed," Insco explains.

The acronym ORIO was designed to be familiar and easy to understand, and its name is general enough to include every reportable incident of interest to the IRB, she says.

For instance, an ORIO might include a situation in which one subject involved in a study is arrested and incarcerated, she says. When this happens the investigator will need to complete additional paperwork in order to keep the subject in the study, and the IRB would need to be notified, Insco says.

It may be in the best interest of the person to stay on the study drug, but the prison is not able to administer it, and so other arrangements would have to be made, Insco says. "There are other research-impacting events that don't involve adverse events per se, and these are always the ones that you want to hear about," Insco says.

Sometimes it's unclear whether the incident is related to the study, but investigators should report the possibility. "Perhaps someone has an auto accident and no one is hurt in it, but you had taken blood from that person for eight hours all day, and it was a fasting study," Insco says. "And so there's a reasonable idea that the person might have passed out behind the wheel from fasting, and that could have caused the accident."

Since the subject wasn't hurt in the auto accident, there wouldn't be an adverse event report, but it would require an ORIO report, Insco says. "Given the nature of the research and the fact that the person had just left the clinic, it could be considered a causal relationship," Insco says.

Here's how the electronic AE/ORIO reporting system, called eResearch, works:

• Investigators/clinical trials staff select the study name. The person filing the report first clicks on the link for "approved studies," then click on the name of their own study, entering the study work-space to view more details.

• They follow instructions for new adverse event/ORIO reporting. From a line below the AE/ORIO prompt, the person filing the report selects whether the reportable event is an AE or an ORIO, and then he or she completes the title information with a reference identifier, such as Subject #2, SAE 3-25-06.

For AE submissions, the questions asked include the date of the event, the responsible site for the event, the grade of event according to the FDA's definition of serious, whether the event is related to the intervention, and whether the event was expected, Insco says.

The interactive electronic form then asks that, if applicable, the person completing the report notify the principal investigator that the report is ready to be reviewed and submitted, by posting correspondence and checking the "PI box" in the study team member list. This will trigger an e-mail.

• IRB staff review AE/ORIO reports. The AE/ORIO reports are automatically routed to the IRB office for immediate review by IRB staff, Insco says. When IRB staff receives a new AE they will automatically see all of the AEs that the study team previously has submitted for the study.

"In the old system we would require investigators to submit AEs in summary format with their continuation of review, but this way the system is doing the decision-making triage for them," Insco says. "And when we do the scheduled continuing review, our reviewer will automatically see all the AEs the study team has submitted for the year."

Since switching to the new reporting system, the IRB has received more reports of protocol deviations than it had in the past, Insco notes.

The system also has reduced some unnecessary reporting and provided a better awareness of tracking protocol deviations, Insco says.

"Our AE reporting is a little more stringent than what is required by the FDA," Insco says. "What we also built into the system is the ability for the study team to develop its own AE reporting plan and to submit that to the IRB for approval."

The IRB might suggest a clinical trial team develop an AE reporting plan when IRB staff has noticed that the site has reported a lot of AEs that are unrelated to the research intervention. "We suggest they develop a plan that's appropriate to their study so they're not overburdened with reporting, and we're not overburdened with their reporting," Insco says. "And the IRB will determine if the AE reporting plan is adequate to protect subjects and then approve it if it is."

Before developing the ORIO reporting system, the IRB had asked investigators to report the additional incidents to the IRB on their progress reports. But investigators found it to be counterintuitive to report problems on a progress report, she notes.

"We tell investigators that the ORIO reporting doesn't represent a new regulatory burden, the reporting requirement was always there," Insco says. "What we did was systemize it, develop methodology and procedures to make it more self-evident." ■

COMING IN FUTURE MONTHS

- Improving the clinical trial agreement process
- Improve site workplace and create employee resilience
- Make the most of academic and industry partnerships
- Enhance education program for investigators, others

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CE/CME Objectives / Instructions

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.

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. ■

CE/CME *questions*

13. Which of the following is a new way to design protocols so that conclusions can be reached faster and participants are more likely to benefit?
A. frequentist approach
B. Bayesian statistical method
C. adaptive design
D. both B and C

14. One human subjects research definition states that a serious adverse drug event is any adverse drug experience occurring at any dose that results in which of the following outcomes?
A. death, life-threatening adverse drug experience
B. inpatient hospitalization or prolongation of existing hospitalization
C. a persistent or significant disability/incapacity, a congenital anomaly/birth defect
D. all of the above

15. What is the first step an institution takes once it decides to become accredited?
A. schedule a site visit
B. conduct a self-assessment
C. establish a corrective action committee
D. none of the above

16. For an adverse event submission to the Food and Drug Administration, which of the following is <u>not</u> one of the questions asked?
A. the date of the event and responsible site for the event.
B. the grade of event according to FDA's definition of serious
C. whether the event resulted from human error or a problem with the study device/drug
D. whether the event is related to the intervention and whether the event was expected

Answers: 13. D; 14. D; 15. B; 16. C