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Subjects' decision-making capacity must be part of the selection process

Don't confuse competency with capacity, experts warn

Clinical trial investigators and research staff have a responsibility that goes beyond obtaining IRB approval when working with vulnerable adult populations and making certain all research subjects are capable of making decisions related to their participation in a study, experts say.

"This really is a developing area," says **Virginia D. Buckles**, PhD, research associate professor of neurology and executive director of the Alzheimer's Disease Research Center at Washington University in St. Louis. **(For more information, see related article, p. 100.)**

"Capacity assessment is an extra protection," she adds. "Where people sometimes get into trouble is in when there is pressure to recruit subjects and they think they have to get people into the study, so they're not paying attention to this stuff."

While there have been more published data about decision-making capacity in recent years, the clinical trial industry still has a way to go in implementing the knowledge at the study level, says **James M. DuBois**, PhD, DSc, an associate professor and PhD program director at Saint Louis University.

To learn more about vulnerable study populations, he has conducted focus groups with people who have mental health disorders and who participated in research.

"One participant said he had attempted suicide while in a study," DuBois explains. "He was very calm about it, and he said, 'They did mention there was this risk that I could become suicidal.'"

Other participants said they were never told or else they had forgotten some information about the clinical trial, DuBois continues.

"One person talked about participating in a trial where they allowed them to smoke crack cocaine because they wanted to study the effects on the brain, and that raises ethical issues," he notes.

In designing studies for vulnerable populations — which DuBois defines as participants who have a compromised ability to grant voluntary informed consent because of cognitive or other difficulties — a variety of factors need to be considered, DuBois and Buckles say.

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Editorial Questions

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For one, investigators should avoid using the term mental competency because it has legal connotations, Buckles advises. Instead, researchers should assess decision-making capacity, which has four elements:

1. Expressing a choice

The research participant needs to be able to express a choice, saying, "Yes" or "No," or saying, "I want to" or "I don't want to." This can be difficult for aphasic patients, she explains.

2. Reasoning ability

"They have to have reasoning ability so they are able to talk about and think about benefits and risks and weigh them," Buckles adds.

3. Appreciation/interpretation

Research subjects also need to be able to demonstrate higher level reasoning, deciding what their participation in a study will do for them personally, she says.

This may be the toughest element of decision-making capacity to measure because it is so subjective, Buckles notes. "When someone is considering treatment for a life-threatening disease that will extend life only a little longer, that gets to their appreciation of whether living like that is worth it to them," she says.

4. Basic understanding

Do the subjects have a basic understanding of what they're being told by research staff? This includes an understanding of both written informed consent and a discussion with investigators about it.

While it's ideal for subjects to meet all of these elements of decision-making capacity, for vulnerable populations capacity is determined on a sliding scale, DuBois says.

"When a research project is considered likely to benefit an individual and is of low risk, then a lower threshold for capacity is used," he adds.

"For example, in minimal-risk research, it might be enough that the person understands the information and agrees to it," DuBois points out.

"In very high-risk research, you want to make sure the person really understands how the research relates to them and that they're capable of reasoning with the information, weighing risks and benefits," he says.

It's also important to not assume that someone with a severe mental disorder lacks decision-making capacity, DuBois says. "Someone with a mental disorder may retain these capacities."

While a court decides whether a person is mentally competent, decision-making capacity is not as rigid a determination. It can come and

go, DuBois continues. "In recent years, a fair amount of research has been conducted on ways to improve decision-making capacity.

"And I think the most promising approach is to quiz participants on the information that's communicated; and [for] any pieces of information that participants do not understand, you have to provide further education," he says.

Education could include several repetitions of the information, which has been found to improve participants' ability to understand and retain the information, DuBois notes.

Additionally, there are two types of tools available for assessing decision-making capacity, Buckles explains:

- the vignette method;
- a test tailored to an actual protocol.

The vignette method works this way — The patient is told a story about a person who has a brain tumor and who has two choices to make.

One choice is to try treatment with a drug or surgery, and the storyteller provides risks and benefits of each, leading the patient through the vignette, Buckles says. "Then they say, 'Pretend you're this person. What should this person do? And what does it mean when they talk about the risks of this drug or surgery?'" she adds.

However, the problem with the vignette method is that it's difficult to use in a population of people with dementia, Buckles notes.

"For one thing, you're telling people with cognitive impairment to suspend reality. A couple of the patients who were told the brain tumor vignette asked the interviewer: 'You're telling me I have a brain tumor problem?' They couldn't make this leap," she says.

"The vignette tool has good literature to support it, but there are downsides to it in terms of appreciation and telling some one who has cognitive impairment to assume or interpret relative to their own personal feelings," Buckles adds.

Another problem with this method is that decision-making capacity is a very specific concept. So someone might have the ability to manage his or her finances, but cannot make a health care decision, she explains.

The other method for assessing decision-making capacity is to tailor a test to an actual protocol, hitting on the four decision-making capacity elements discussed previously, Buckles suggests.

With this method, the person making the assessment would look for the following:

- Does the person comprehend what he/she was told?
- Does the person think about the risk and what it means to him/her personally?
- Does the person make a choice?

"The good thing about this method is it's valid and it has a specific application," Buckles says. "The downside is you have to tailor it to every person."

However, it may not have to be tailored a great deal. There is an available tool for determining capacity for clinical research, called the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR), developed by Paul S. Appelbaum, MD, and Thomas Grisso, PhD.

This tool contains a set of questions requiring some adaptation to ask potential subjects, adds Buckles.

"It's not a criterion-based tool; it's a norm-based tool," she notes. "You compare their scores to your control group, but a lot of times clinical trials don't have a normal control group."

Nonetheless, the MacCAT-CR is the most popular and most studied of the tools available for assessing decision-making capacity, DuBois says.

"You can use it with mental health and substance abuse populations, and its purpose is to determine whether or not they have the capacity to make decisions," he says. "Capacity is determined on a sliding scale with no fixed cut-off point."

Use of study partners

The Washington University Alzheimer's Disease Research Center provides an example of another safeguard for dealing with vulnerable populations in research: an informant, who can be a family member or close friend.

About 90% of the time, this close informant is a spouse or adult child and meets the state of Missouri's legal requirements of being a legally authorized representative, Buckles says.

"Usually when doing clinical trials in dementia, there is a study partner because participants forget things, and sponsors want someone there who can remind and help them," she explains.

"We try to educate our subjects and informants about research proxies, a concept that depends on state law to determine who can be a research proxy or designated surrogate," Buckles says.

"In Missouri, they have a clause for the medical research of determining who can give consent to participate." But this law only goes into affect if the person cannot consent for him- or herself, she adds. ■

No one-size-fits-all tool for assessing capacity

Expert makes these suggestions

When it comes to studying vulnerable populations, investigators and clinical trial staff may have to develop their own tools or adapt existing tools to assess a person's decision-making capacity to participate in clinical trial research.

The Alzheimer's Disease Research Center of Washington University in St. Louis has been working on an assessment method that provides an additional protection for human subjects, while also allowing enough flexibility to permit needed research.

"We have been experimenting with an open-ended assessment process where the social worker goes through the informed consent, spends a lot of time with the subject, and asks the subject open-ended questions," says **Virginia D. Buckles**, PhD, research associate professor, neurology and executive director of the Alzheimer's Disease Research Center.

The process addresses the main elements of informed consent, all federal guidelines, and touches on the elements of decision-making capacity, especially basic understanding, she says. "We concentrate on the understanding part. We don't measure all four elements, but we hit understanding and comprehension very hard."

Determining subject's alertness

For instance, the social worker conducting the assessment will ask nine questions that relate to the main elements of consent. They include these examples:

- Why are you here?
- What will you be doing when you participate in this research with us?

"Then when the person answers, the social worker writes it down verbatim," Buckles says. "Our social workers are highly trained and know when somebody does not understand what's going on."

Since the center's studies are longitudinal with some subjects continuing to make visits annually for 25 years, the center also has a short quiz that is used to confirm that a person's capacity for making decisions continues through follow-up visits, she adds.

"The quiz has true-or-false items and hits on the same information, although it's a lot easier to administer and score," Buckles explains. "Every year, we review elements of the informed consent, give them a quiz using a criteria requiring they score at least better than chance — 80%."

Each participant has an informant — a spouse, adult child, or a close friend — who is present during the informed consent process but who does not assist with answering the assessment questions, she says.

If the patient loses the capacity to consent, or if the social worker is uncertain about the person's capacity to consent, then the center may approach a legally authorized representative to make the decision, Buckles explains.

"If someone has a power of attorney in place and they are found to lack decisional capacity, then the power of attorney must make the decision," she says.

The center chiefly assesses potential subjects who may be asked to participate in research and clinical trials for Washington University and outside researchers, Buckles adds. "We recruit the subjects, giving them a diagnosis and assessment; and other investigators ask us for permission to use our pool of subjects, and then we ask the subjects if they want to participate," she explains.

"When we're running a clinical trial that involves greater than minimal risk, then that increases the importance of the capacity assessment," Buckles says.

Also, when the subjects have moderate or severe dementia, then the center will require a legally authorized representative to sign the consent as well, she notes.

While the center's process is thorough, some experts in human subjects protection say investigators should not do their own decision-making capacity assessments, and these should be conducted by outsiders, Buckles says.

"But that's really impractical," she says. "How independent? How do you pay for it? Do they have to be present for each session?"

Nothing about capacity assessment is a black-or-white answer, Buckles notes.

"If someone's involvement is minimal risk, then we use their individual consent and their study partner is just there as a witness," she says. "But if someone comes in and has suspicions about the study and doesn't pass the test, then we have to check to see if there's a power of attorney in place before we can let them participate in research." ■

Data review committees offer additional protection

DRC stays on top of adverse event issues

Data review committees (DRCs) could provide an additional layer of protection for human subjects at clinical trial sites where research often involves high-risk populations or high-risk studies.

The Texas Children's Cancer Center and the Center for Cell and Gene Therapy at Baylor College of Medicine in Houston have used DRCs to review protocols for adverse events for five years, and the system has worked very well, says **Bambi Jo Grilley**, RPh, CCRP, CCRC, CIP, director of the clinical protocol research and regulatory affairs for the two centers.

"I think the DRCs are really helpful," she says. "I don't think IRBs are capable of providing the proper oversight at the level that a data safety monitoring group does because the expertise in an IRB is quite diffuse."

The members of the centers' DRCs are oncology specialists, including oncologists, oncology nurses, and research staff, Grilley explains.

"They all have experience with oncology or oncology patients," she says. "How could a cardiologist or dermatologist assess whether we're seeing a high level of a subset of malignancies among patients."

Also, the DRCs, which meet twice a month, have a caseload of about 270 phase I and phase II studies, whereas the IRB will review more than 2,000 studies, Grilley adds.

The DRCs fit into the research institution as one part of a multifaceted process with the purpose of ensuring high-quality research and high-quality subject protection.

The Texas Children's Cancer Center and the Center for Cell and Gene Therapy also have protocol review boards that assess each study for scientific soundness before the protocols are approved and sent to the IRB.

The protocol review board also decides whether a study will require data safety monitoring and, if so, how frequently it will be reviewed by the DRC, Grilley explains.

"If there's an external review process, we don't require it to go through ours," she notes. "If the study involves treatment, it definitely goes to the DRC, and the third criteria is any study that has risk for patients."

For instance, a cancer/genetics study that does not involve treatment may have important implications for the patients whose tissue samples are used, so this kind of study also would be reviewed by the DRC, Grilley continues.

While the DRC serves the same purpose as a data safety monitoring board (DSMB), which mainly monitors phase III studies, the chief difference is that all 25 members of the DRC are affiliated with Baylor College of Medicine, she adds.

Federal guidance defines DSMBs as boards that have outside representation to ensure objectivity in the review of studies.

"There is only one study that requires a full DSMB, and this is where we'll have conference call meetings and include researchers from different time zones," Grilley explains.

Although the DRC members are not outsiders, they include members from all of Baylor's different branches, so physicians are not looking at their own data, and the membership includes a statistician, she says.

The centers also have quality assurance and quality control staff who monitor internally sponsored studies, performing the same type of checks and balances as does a sponsor's clinical trial monitor, Grilley says.

DRCs provide annual review

The DRC's role typically begins either at one year from when the protocol was approved by the IRB — or with studies involving higher risk, at an earlier date if a designated number of patients have been enrolled, she says.

Grilley and her staff spend a total of about 10 hours per week on DRC business, including the time spent mailing DRC meeting reminders to principal investigators whose studies are up for review and sending out review packets to DRC members.

The rest of their time is spent on quality assurance and quality control and protocol review, she says.

"For all of the DRC meetings, we have 21 binders at half-way through the year," Grilley explains. "It takes a lot of maintenance, and having a DSMB is an unfunded mandate."

Before each weekday meeting, which lasts about one hour, DRC members receive a packet of one to five studies they will need to review. Investigators may be called in to discuss the study and to answer questions.

The investigators then leave, and the DRC deliberates and discusses the study in private. There is no required quorum, although the DRC always must have at least one physician and statistician in the room, Grilley says.

"We do sometimes have members who send their comments when they can't attend, and we'll discuss those comments, as well," she says.

Finally, the board makes a decision about whether the study should continue and mails the principal investigator a letter that states that decision. The PI must send a copy of that letter to the IRB, which asks for proof that a study is safe to proceed, she explains.

"Ninety-nine percent of the studies are found safe to proceed," Grilley notes.

Here's one example of how the board works: "We had an emergent adverse event that was long term, so it was discovered when patients were off the therapy," she says. "The PI came to the DRC to describe what had happened and to have a discussion about whether we should tell all the patients, and if so, would it be by letter or by bringing them in for a visit. In this case, we decided to send letters to the patients' parents, because the patients were children; and we contacted local physicians because many patients go back home."

The advantage to having a DRC is that PIs sometimes overlook trends due to their professional bias of finding what they expect to find, Grilley notes.

In another case, there was a study that was designed with the objective of achieving a 70% success rate, she says. Investigators recruited many patients, and when the DRC reviewed the research, members found that the study treatment had not achieved anywhere near the 70% success rate, although the patient recruitment was 50% complete, she says.

"The PI said, 'If every patient I enroll now does well, I'll have my 70%,' so the DRC asked, 'What is the likelihood of that happening?'" Grilley recalls.

The result was the DRC decided to close the study since the treatment obviously was not working, she says.

"Prior to having the DRC, the study would have played out, whereas with the DRC we were able to stop it early," Grilley adds. "Ultimately, the PI was in agreement with us, but it helps to have people outside the immediate circle of the study say, 'Have you thought about this?' and 'Logically, does this make sense to you?'" ■

Overcoming barriers to Hispanic participation

It's more than language

In the past few years, Hispanics have become the largest minority group in the United States, numbering nearly 41.3 million in the most recent U.S. Census estimates.

But they still make up a relatively small portion of the participants in clinical research. That gap is important and troubling, since diseases such as diabetes, hypertension, and heart disease are more prevalent among Hispanics and minorities in general than in the population as a whole.

The barriers that stand between Hispanics and research are varied and require a multifaceted approach to overcome, say those who work to improve minority participation in human subjects research.

At the University of Michigan (UM) in Ann Arbor, an outreach program that seeks to involve minorities of varied ethnic backgrounds in research has begun to make progress in winning the trust of the Latino community and to overcome logistical barriers to Hispanic participation in clinical trials. But there are no quick fixes, warns **Louise Hahn**, BSN, MSA, research subject advocate for the university's General Clinical Research Center (GCRC).

She says institutions that want to beef up Hispanic participation need to be ready with the basics, particularly providing translators to decipher informed consent documents and to speak with potential participants.

Providing bilingual services — everything from the consent forms to the support staff — is essential for recruitment and retention of participants whose first language may not be English explains **Hector M. Gonzalez**, PhD, assistant research scientist in epidemiology at UM.

For example, the group he's following in a longitudinal cohort study in California all are older than 60, and more than 60% prefer speaking Spanish. Gonzalez currently is conducting research among elderly Latino residents of both California's Central Valley and Southwest Detroit.

"Many of them have lived in the country for 40-odd years, and they can communicate in English," he says. "But we want to ensure, starting with the informed consent, that they fully understand the relationship they're engaging in as a partner in research."

Researchers must educate themselves about the cultures in their community and how to ensure the views of different ethnic groups are represented.

While lack of proficiency in English comes to mind immediately as a barrier to participation in research, it's not the only problem encountered by researchers in recruiting the Hispanic population.

David Gordon, MD, associate dean for diversity and career development at UM Medical School, who heads up the school's Minority Health Research Program, says the undocumented Hispanics often harbor mistrust, so it can be difficult to get Hispanics to trust a government entity such as a university, particularly when they may be in the country without proper documentation. "When we say we're looking for Latino/Latina individuals to participate in research, there's the barrier of: "What is this institution? Is it part of the police? What are you really looking for?'"

"Particularly when you're doing something like signing people up for registries, where you're asking people to identify by name, you find more concern from Hispanic individuals," he adds.

Gonzalez notes that when he began his work in California, the state had just been through a series of propositions that were seen as anti-immigrant, and community leaders were concerned that people wouldn't be interested in volunteering for research through a state university. "There was concern that participants would be fearful that we were working for the government and turning in people with questionable immigration status."

Gonzalez says he dealt with the issue simply by not asking about a participant's immigration status. And while participation in the research did require people to give his staff a lot of personal identifiable information, staff always explained the purpose of the questions and tests.

Gordon and **Amelie G. Ramirez**, DrPH, a cancer researcher and deputy director of the Chronic Disease Prevention and Control Research Center at Baylor College of Medicine in San Antonio, both note that Hispanics also raise the same trust issues that many other research participants do: "Am I being used as a guinea pig? Why are you trying out this drug on me?"

Both researchers say participants need to get basic information about clinical trials, emphasizing the amount of research that's already been done on the treatment, and noting that patients will receive the best standard care in addition to experimental treatment.

Joel Escobedo, a third-year UM medical student, recently conducted interviews with elderly residents of a Hispanic community in Chicago to discern their attitudes about participating in research. Despite lower education levels (most only had completed elementary school), most of the elders he interviewed knew about clinical research and believed it to be valuable.

The barriers most identified to participating in studies were logistical rather than cultural or psychosocial, says **Cathy C. Lee**, MD, assistant professor of internal medicine, with a focus on geriatrics, at the UM Medical School.

The participants said they would be more willing to participate if clinical research studies were conducted on weekends. While it was important to most that the researchers spoke Spanish, their ethnicity was not as important to these seniors. And nearly all said they would be more willing to participate if there was personal benefit or benefit to the Hispanic community as a whole.

Community advisory boards

As part of its effort to increase diversity in clinical research, UM's Minority Health Research Program set up a small extension program at a health center in Ypsilanti, MI, which has a more diverse population, Hahn says. It also set up a community advisory board with representatives from various community, religious, and other groups in the Ypsilanti area.

Protocols accepted by the GCRC also are reviewed for suitability by the board; if the advisory board approves them, patients can be recruited at the Ypsilanti site.

Nancy Lowenbergh, BSN, RN, a community research nurse for the Ypsilanti Health Center, says she extends the university's reach into Ypsilanti's various minority communities. She speaks at churches and health fairs and passes out multilingual brochures at festivals and other community events.

"It's very hard to touch our Latino community," Lowenbergh says. "That's why I've been so active with [a local Latino festival], advising them on their health tent, so I can get to be known. Now, enough people have told other people, 'Yes, you can trust her,' and they'll talk to me now."

She says there's a grocery store in town where it has taken two years for her to be given permission to post notices on a community bulletin board.

Lowenbergh and Hahn are adamantly opposed to so-called "helicopter" studies — where a

researcher descends on a community, does a study, and disappears without ever coming back to let participants know the results of the work.

"These people are used to being used; therefore, they have no trust; and one of the things I'm doing is proving to them that I'm here to stay, and I'm not going anywhere," Lowenbergh adds. ■

Compliance Corner

University makes effort reporting more consistent

Faculty buy-in is ongoing process

Administrators at East Carolina University in Greenville, NC, decided three years ago to use a web-based, automated effort reporting system to replace the outdated paper-based system, and bids were requested. After sifting through six vendors' proposals, administrators finally decided on a system proposed by MAXIMUS of Chicago, but requested additional changes to what was available, says **Bonnie Kautsky**, central administrative manager for effort reporting.

"It was a five-month process from the day we signed the contract until we did the first training session with administrative staff," she says.

The new system has helped administrators and staff by simplifying the effort reporting process, says **Brian Farmer**, director of grants and contracts. "So there's less time spent in the process recording, reviewing, correcting, and certifying effort."

Also, the new system provides a consistent and accurate means of connecting reported effort to contracts and payroll, Kautsky notes.

The electronic effort reporting system takes the percentage of time employees confirm spending on a particular research project and use this figure to calculate payroll from each fund or grant account, she says.

"It works beautifully," Kautsky adds. "It converts the sum of the hours into a percentage and then ties it to a dollar amount."

Once information is uploaded into the system, the system generates an automatic e-mail to assigned effort reporting administrators of each department, and it creates a screen with the payroll and how the money is divided by grants and other accounts for the administrator to review and certify, she explains.

"The job of the administrator is to look at each of the forms generated by payroll to see if they have a correct representation of how that employee should be getting paid. If that employee is supposed to be paid 25% on a grant, it will show the administrator whether the 25% of the employee's salary is covered by grant funds," Kautsky says.

If the administrator sees there is a missing form that would assign the employee to a grant, then the administrator can make an adjustment at this time, she adds.

"They are able to see right away that an action needs to be taken," Kautsky says. "Once they get that form, they can look at the salary distribution to make sure it's correct, and 90% of the time it is as it should be."

Occasionally, there are paperwork delays, but the system catches these in time, she notes. From the investigators' perspective, most personally certify the hours or percentage of time they have spent on a grant after the electronic system sends them a monthly report, Kautsky says.

The time investigators spend on certifying their effort could be as little as one minute per month, she adds.

Another method for determining effort is for research staff to keep track of time spent on each project, using 15-minute increments, and this is the method used by research nurses and study coordinators in the clinical trials department, says **J.C. Cedars**, MD, director of the clinical trials office.

"That's how we chose to do it in our office," Cedars explains. "Staff fill in a code for what they're doing for each 15 minutes; and for each study, there is a code, and then for the month an Excel spreadsheet will say, 'Study A — 20 hours; Study B — 10 hours,' etc."

The university spent considerable time educating staff about the new effort reporting system, starting with two mandatory, six-hour sessions of training for department chairs, upper administration, and administrative or clerical staff who would have hands-on involvement with the system, Kautsky says.

"The first session was to let everyone know of the federal requirement of effort reporting and to explain the monthly reporting," she notes.

Staff had one month in which to take the two sessions, which were offered multiple times for their convenience. "After that, we had a second

training which was scheduled in our computer lab, and this was hands-on training for all administrative staff and clerical staff at the department level," Kautsky says.

This session included various effort reporting scenarios with dummy data installed, she adds. Department administrators were expected to train their faculty and research staff, Kautsky says.

The institution worked on obtaining faculty and staff buy-in even before signing a contract with MAXIMUS, she notes.

"We had department chairs from academics and the medical school and four of us on the working committee fly to Johns Hopkins University in Baltimore to see their MAXIMUS system in action," Kautsky recalls. "We spoke to department chairs there and got their opinions on it, and we did this primarily for faculty buy-in."

The two department chairs were satisfied with what they saw and expressed their opinions to their faculty when they returned, she adds.

Despite these educational and buy-in efforts, it has taken time to get the complete buy-in of all the faculty and staff, Kautsky says.

The real difficulty in obtaining buy-in and converting to this system was in creating an atmosphere of change at the university, Farmer and Kautsky say.

"People don't want to change, and they feel they don't have the manpower in their department to handle this," Kautsky points out.

Since the program has been up and running, administrators have found it to be easier and more efficient than the previous system, and so their support has been won over, she adds.

Some faculty members continue to dislike anything having to do with effort reporting, but the institution's revised policies and procedures leave no room for dissent.

There is a built-in e-mail notification process that lets people know if they're tardy in certifying their hours and salary, Kautsky says. If researchers neglect to complete the required certification of effort, there is a system of reminders, she adds.

If effort still is not certified following the reminders, policies make it clear that there's an option of freezing the research account, Farmer explains.

"Effort reporting is an issue that we all have to deal with, and we have found certain tools at our institution have improved the process greatly," he says.

"The bottom line is we feel we have a good comprehensive system in place, and we certainly are not perfect, but we're continually working to improve the system," Farmer adds. ■

FDA senior advisor discusses GCP goals

Look for new guidance on risk-based approaches

[Editor's note: ***David A. Lepay****, MD, PhD, senior advisor for clinical science and director of Good Clinical Practice (GCP) Programs for the Office of Science and Health Coordinator, Office of the Commissioner, U.S. Food and Drug Administration (FDA) in Rockville, MD, provides* Clinical Trials Administrator *readers with an update on federal regulations and guidance governing the clinical trial industry in this Q&A report.]*

CTA: What is the FDA's most important focus these days with regard to the clinical trial industry?

Lepay: The most important is research subject safety and communications on safety. That's been a big focus for our agency and office as a whole, and it will continue for some period of time. We held a hearing March 21 on IRBs, and this is a hearing we will follow up on several levels.

At the hearing, we heard a consensus opinion that there are problems in the system of reporting of adverse events, and that's a systemwide view. It's not a problem restricted to IRBs; it's an issue we have to deal with at the most fundamental level of how adverse event information is acquired, how it is synthesized, how it is interpreted, analyzed, and ultimately how it is communicated and reported among the parties.

We heard very much from IRBs that single serious adverse event reporting coming to an IRB are almost uninterpretable, and clearly we have to go back and look at what kind of information could be provided in this system. Right now, of course, the drug and biologic regulations don't provide for direct communication of information between the sponsor and IRB.

They all move through the investigator, which also creates a large amount of paper and office time for the investigator and puts them in the very difficult role of interpretation. So we are going to have to look at making some changes in that fundamental direction into which information flows. I expect we're going to do as much as

we can through guidance. This will be coordinated very closely, not only with the FDA, but also with other agencies that have a stake here, particularly the Office for Human Research Protection (OHRP). I think that would be, probably, one of the very large areas of focus for us.

CTA: So do you have any proposed changes or committees that are going to look at making any changes, such as allowing direct communication from the sponsor to the IRB?

Lepay: That would require a regulatory change. We'll see what we can do in terms of the way the regulations are currently written, what kind of guidance we can provide both to the IRBs under their regulations, as well as the sponsors under their regulations. We can see how far we can take that. Ultimately, regulation development and writing is a much slower process.

CTA: In the meantime, what is it you need? Do you need sponsors to start sending in the information in a more systematic way that IRBs can read? What needs to be done?

Lepay: We're starting to look at comments we received from that public hearing. I expect we will provide agency guidance in this area. But I'm not going to precede what we're going to do in the way of that guidance. Obviously, when we issue the guidance, it will go out for public comments; and we'll use those comments to further refine.

CTA: What's another area that is of top importance these days?

Lepay: We're looking very much at the issue of risk and risk-based approaches. We're trying to figure out how best to use resources in the clinical trials enterprise to achieve the greatest benefit from the standpoint of both subject protection and data quality. This is part of a broader initiative within the agency: the critical path initiative, which also is very much focused on trying to streamline processes in a risk management-based fashion. This is an area where we have solicited public comments and public information with the intention of providing a synthesized list of those comments and the opportunities or areas in which streamlining may be possible, based on those public comments. There should be a critical path opportunities list coming from the agencies sometime fairly soon.

But it extends as well to GCP and our oversight of clinical trials. We're trying to apply risk-based approaches internally, within the FDA, in the way we develop assignments and the way we choose sites for inspection, in the way we talk with industry about study monitoring and study oversight.

Fundamentally, when we're talking risk-based approach, the concept here is some sort of analysis of risk goes on prospectively during the developments of the study and development of a monitoring plan. By corollary, a risk-based approach would say, "You're going to put more of your resources into those areas that are of higher risk than you're going to put into those areas of lower risk."

So this is a very fundamental sort of initiative that is going on at multiple levels. It's going on internally in our agency and starting to develop communication between our reviewers — those who are involved in developing inspection assignments, the policy-makers in the GCP areas, as well as our inspection cadre.

CTA: What would you recommend clinical trial sites do to be proactive? Are there some models or tools they can find to do these risk assessments?

Lepay: There is some guidance available from the FDA. I don't know if it's directed to clinical trial sites at this point, because that is again part of a broader initiative than what we are in the process of undertaking. Our expectation is there will be more guidance developing out of the agency in specific areas.

CTA: When will there be more guidance available?

Lepay: I think about two years probably is the time frame over which we are looking at reviewing our GCP program, our bioresearch program of inspection, our processes by which our reviewers assess data quality and data oversight, and some of these risk-related issues to data management. I would expect it will be about a two-year time frame. That's not to say there will not be meetings or dialogues with our stakeholders — I'm certainly expecting that throughout the course of it — but we have to do some of our internal analysis first, think about the kind of guidance we want to provide, and then start communicating more directly with stakeholders.

CTA: Now with some of the unfortunate media attention that has been paid to pharmaceutical clinical trials in the past year, like with Vioxx and some other drugs, do you have any plans to change the way information is accumulated and reported publicly?

Lepay: Again, I think this is not so much a GCP arena. I think we're certainly working with groups on several levels. We're working with industry, as well as the National Library of Medicine, and in the area of clinical trials registries, as well as

making information available about clinical trials. This is something again that is being explored very much by industry. We are certainly part of that dialogue.

We have to work within our own authorities. Our authorities are largely in the area of clinical trial posting for serious and life-threatening diseases, but it's also a broader dialogue to try to get more information out there. Most if not all of the FDA believe it's important, in fact, for the public to know information that's part of a clinical trial, whether that information is positive or negative.

CTA: What are other big areas and hot points that you've been speaking about in FDA updates?

Lepay: There are a few other areas also in the forefront, and one is the international. At that level, we certainly recognize the positive contributions that GCP harmonization has made between ourselves, Japan, and the European Union since the advent of ICH.

The recapitulation of some of those successes now in the device arena, as harmonized standards also are being embraced, not only in drug and biologic studies, but also in devices studies through harmonization efforts there.

But a lot of our efforts are being directed, as well, to the extent that we have resources to do these sorts of things is working with international or foreign regulatory authorities to assist them in capacity building.

We try to assist them in putting into place internationally recognized standards, as well as mechanisms to be able to ensure those standards are implemented and enforced. So we're working with a large number of governments in the world that are interested in developing their own GCP review or GCP inspection unit.

We're also working quite closely with the World Health Organization (WHO), which in October should be coming out itself with some implementation guidance on GCP, which is fully harmonized with other venues, such as ICH, which we have worked with, but which WHO will provide more directed implementation information.

We worked with the Pan American Health Organization across the Americas to, again, work with those countries that have or are developing inspections, so there's unified guidance from the Pan American Health Organization on inspecting clinical trials.

So we certainly recognize that the pharmaceutical industry is ever globalizing and information that is coming to FDA as to other regulatory authorities is not coming from within a single country. And we have to find ways to be sure there are real-time systems to ensure the quality not only for us when it comes to FDA but also for subjects who are participating in those trials.

The other big issue we're trying to work through is to increase consistency across government and to work more closely with other government agencies, particularly those within our own department, be that the Office of Human Research Protection, the National Institutes of Health, the Centers of Disease Control and Prevention, or the Office of Research Integrity. As we are now working to develop guidance in these areas, we're also working to share our thinking as well as our contributions to these guidances from one agency to another. We have certainly heard over time how information coming to investigators, to sponsors from government may not all be as consistent as they would like it. So we want to be sure, at least to the extent that we can develop consistency ourselves in what we put out as government agencies, that that's not going to confound the system for those that we serve.

CTA: Will that make things more efficient and cut down on paperwork for sites?

Lepay: There's no question that our goal across HHS is to reduce paperwork where it's not adding value. Those individual safety reports, as we discussed earlier, getting into the system from investigators and ethics committees in ways that are uninterpretable — to us that just adds useless paperwork to the system.

I think we can expect to see some important developments in the area of streamlining, in the area of using resources more effectively, in the international arena within the next year or two years, and it will involve stakeholder participation and process. ■

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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.

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*

9. Which of the following are the four elements of assessing decision-making capacity among vulnerable research subjects?
   A. Basic understanding, knowing right from wrong, critical thinking, making a choice
   B. Basic understanding, reading ability, discerning benefits and risks, selecting the best option
   C. Expressing a choice, reasoning ability, appreciation/interpretation, basic understanding
   D. None of the above

10. Which of the following is not one of the responsibilities of a data safety monitoring board or data review committee?
   A. Evaluation of study progress including risk/benefit outcomes and consideration of new scientific or therapeutic developments that may affect the risk/benefits of the study
   B. Review of interim data analyses and summaries of cumulative toxicity data to determine if the study should continue as designed, be revised, or be terminated
   C. Review of any major proposed study modifications prior to implementation (for example, terminating one arm of a study based on toxicity results or increasing the sample size)
   D. All of the above

11. Which of the following is a best practice method for determining effort among research staff?
   A. Investigators personally certify hours or percentage of time they have spent on a grant after an electronic system sends them a monthly report.
   B. Research staff keep track of time spent on each project, using 15 minute increments.
   C. Investigators have an assistant keep track of their hourly work on various projects.
   D. Both A and B

12. According to David Lepay, MD, PhD, senior advisor for clinical science and director of Good Clinical Practice Programs for the Office of Science and Health Coordinator, Office of the Commissioner, FDA, the most important clinical trial focus for the FDA is which of the following?
   A. Accurate regulatory documentation
   B. Research subject safety and communications on safety
   C. Serious adverse event reporting
   D. None of the above

Answers: 9. C; 10. D; 11. D; 12. B