CLINICAL TRIALS ADMINISTRATOR

An essential resource for managers of clinical trials

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Don't be confused by the rules governing adverse event reporting

Rules confusing you? Here's some advice

Reporting rules for adverse events in clinical trials only seem straightforward in the case of death or injury requiring hospitalization. Otherwise, those involved in clinical trials have to figure out how soon they need to report, what information needs to be included in the report, and who should get it.

There is help available. Take the on-line tool developed by **Jeremy Wood**, PhD, a communications consultant based in Merion Station, PA. Using a series of yes and no questions, the tool — located at www.saetool.com — guides users to a determination of who needs to know about an event and how soon, based on the severity of the occurrence. For instance, a several-step inquiry about a trial involving an investigational new drug (IND) that results in a serious and unexpected adverse reaction results in the following final message:

"According to the SAEtool, the study sponsor should inform FDA [the Food and Drug Administration] and all participating investigators about this serious and unexpected adverse experience in a written IND safety report. The notification should be made as soon as possible and within 15 days of the sponsor's initial receipt of the information."

At every step, there is a link to any relevant federal regulations — in this case, the Code of Federal Regulations, Title 21, Volume 5, or the FDA's April 2002 regulations on investigational new drug safety reports.

Wood says he developed the tool after doing work for an institutional review board at the University of Pennsylvania. "I was asking people about what forms people involved in research might need, and the answers were always along the lines of, 'That's a complicated question.' I did a tool to help sort it all out," he says.

Some of the users of the tool have had Wood link it to the specific forms researchers would need to fill out given a specific set of events. It is one more step that larger institutions are taking to simplify the many steps researchers have to go through and do it in a paperless way.

Another area of trouble involves those adverse events that may not be unexpected and may not be serious, but are important for researchers to

note, particularly if they happen more frequently than those researchers expected. Oftentimes, such reports do not come to the attention of researchers for months.

A group of cancer researchers at the Mayo Clinic in Rochester, MN, developed a way for quick — indeed, nearly real-time — reporting of these events. Initially reported in the *Journal of the National Cancer Institute*, the tool was reprinted most recently in the *Journal of Clinical Oncology*.[1]

While there are some common-sense suggestions that could probably be extrapolated to any study, one of the creators of the tool, **Daniel Sargent**, PhD, director of cancer center statistics at Mayo, is quick to note that this was developed for cancer trials.

That said, Sargent notes that there are a wide number of reporting requirements for adverse events. With INDs in Phase I trials, every single event has to be reported, "even if it's just a sneezing fit by one person," he says. "But if you get to a Phase II trial of an existing drug, only life-threatening events resulting in hospitalization or death are required."

But research by Sargent and his colleagues turned up events that were expected, not individually isolated, but occurred at greater frequency than was expected. "If things are happening a lot more often than you thought it would, even if it's not fatal, we need to know about it and take action."

They developed a single-page form that could be faxed in — or filled out electronically — that includes the kinds of information the researchers need. "The existing expedited reports were cumbersome," says Sargent. "We didn't need that level of information."

Among the information included on the tool:

- the protocol number;
- the patient ID number and initials;
- the date the clinical research associate was made aware of the event;
- the dates of the event occurrence;
- the type of event;
- whether it was a grade four or grade five event;
- whether the event was, in the opinion of the reporting party, related to the study medication;
- whether hospitalization was required;
- if yes, the date of admission;
- the reason for admission — toxicity (of study medication), prophylactic, or other.

The information goes into a central database daily, and a program generates an automatic e-mail to the study chairperson, the data monitor, and the statistician about any new reports. "It's real-time toxicity monitoring for us," says Sargent. "Every day when I open my e-mail program, I get a report. If there are no events, I don't

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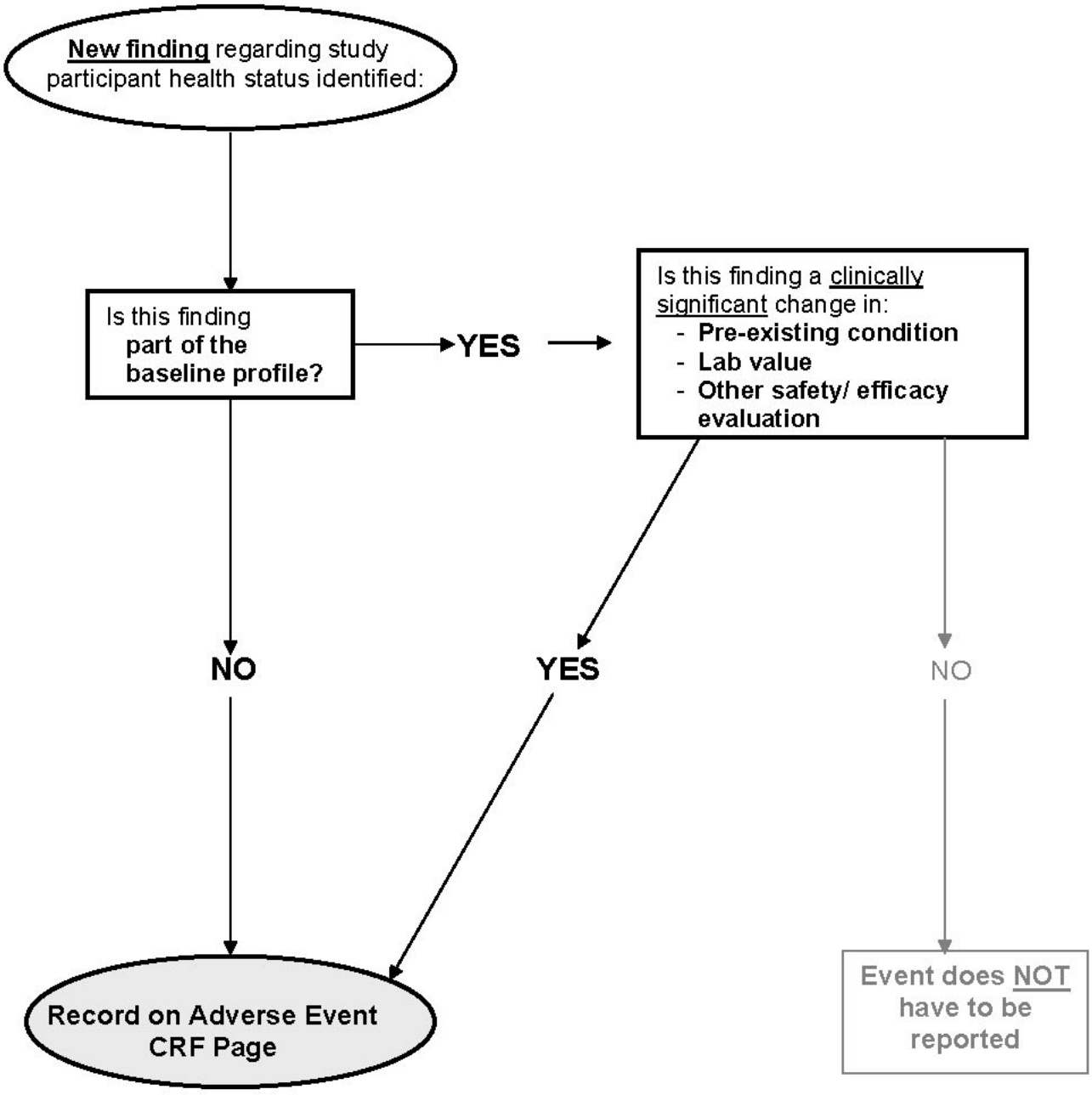
Adverse Event Reporting

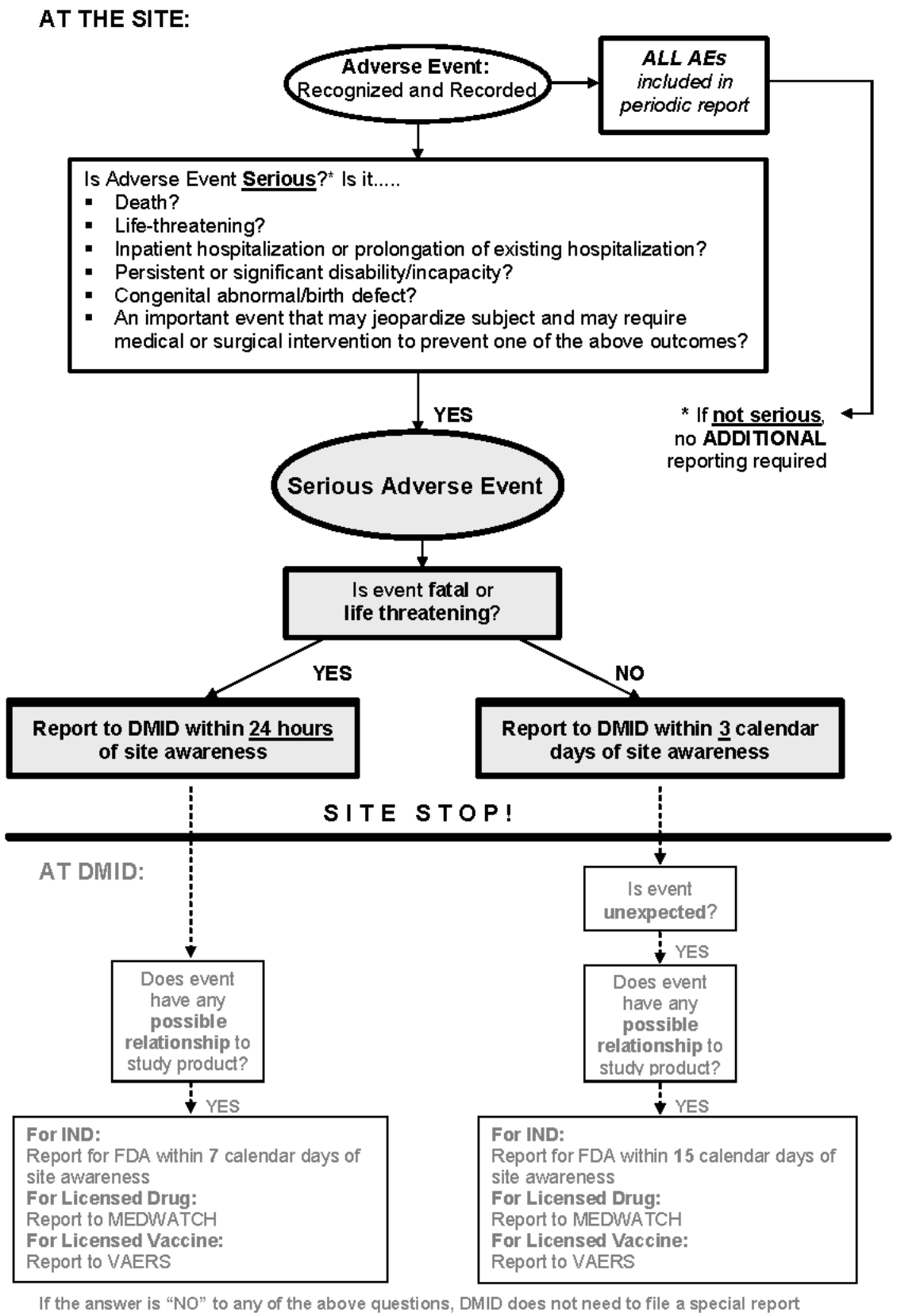
AE Decision Flow Chart

AT THE SITE:



Source: National Institute of Allergy and Infectious Diseases. *International Centers For Tropical Disease Research Network (ICTDR) Investigator Manual: Monitoring And Reporting Adverse Events*, Bethesda, MD; 2003.

SAE Reporting Flowchart



Source: National Institute of Allergy and Infectious Diseases. *International Centers For Tropical Disease Research Network (ICTDR) Investigator Manual: Monitoring And Reporting Adverse Events*, Bethesda, MD; 2003.

(Continued from page 14)

get any e-mail. If there are events, I can get the information and determine what, if anything, we can do. It takes days to react, not months."

As an example of the kind of event he is talking about, Sargent suggests a subject who gets diarrhea that wasn't bad enough to cause hospitalization, but because it was six or eight loose stools a day, it had the potential to be life-threatening. Or a patient who had a low blood count that wasn't accompanied by fever or chills. "If too many of our patients have low counts, then it's only a matter of time before one develops a fever and we are in real trouble. This helps us be aware in a much more timely manner."

The tool has certainly helped in the three years it has been in use. "We know that 75% of the relevant events are reported within three days of occurrence, and we know about them within five days," he says. "Compliance isn't perfect, but it is good and getting better as we continue to do training."

Investigators have been very positive about the tool, and the National Cancer Institute has commended Sargent and his peers on the tool several times, he says.

"It also has a real impact on the way we do

Grading the Severity of Adverse Events (AEs)

All AEs will be assessed by the investigator using the protocol-defined grading system. The use of a standard table for interpreting and grading abnormal signs, symptoms, and laboratory parameters is recommended. If the protocol has no defined grading system, or if the AE is not described in the existing grading system, the following guidelines should be used to qualify severity:

- **Grade 1:** Mild — transient or mild discomfort (< 48 hours); no medical intervention/ therapy required.
- **Grade 2:** Moderate — mild to moderate limitation in activity — some assistance may be needed; no or minimal medical intervention/ therapy required.
- **Grade 3:** Severe — marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.
- **Grade 4:** Life-Threatening — extreme limitation in activity; significant assistance required; significant medical intervention/therapy required, hospitalization, or hospice care probable.
- **Grade 5:** Death.

Source: National Institute of Allergy and Infectious Diseases. *International Centers For Tropical Disease Research Network (ICTDR) Investigator Manual: Monitoring And Reporting Adverse Events*, Bethesda, MD; 2003.

AE Relationship to Study Product

The possible relationship of an adverse event to use of study product is assessed by the investigator. The terminology for these assessments can vary from one reporting system to the next. The DMID (S)AE reporting system uses the following terms to describe the relationship of an AE to the study product:

- **Definitely:** Clear-cut temporal association and no other possible cause.
- **Probably:** Clear-cut temporal association, and a potential alternative etiology is not apparent.
- **Possibly:** Less clear temporal association; other etiologies also possible. Temporal association between the AE and the study product and the nature of the event is such that the study product is not likely to have had any reasonable association with the observed illness/event (cause-and-effect relationship improbable but not impossible).
- **None:** The AE is completely independent of study product administration; and/or evidence exists that the event is definitely related to another etiology.

Note: Not all study sponsors use the same SAE terminology when determining severity and relationship. In your studies, you MUST use the system provided by the respective sponsor.

Source: National Institute of Allergy and Infectious Diseases. *International Centers For Tropical Disease Research Network (ICTDR) Investigator Manual: Monitoring And Reporting Adverse Events*, Bethesda, MD; 2003.

things," Sargent concludes. "There have been six studies in the last three years where these reports have resulted in protocol changes. In five of the six cases, we were able to reduce the toxicity of the drug. In the sixth, we were not, so we shut that trial down."

Reference

1. Goldberg RM, Sargent DJ, Morton RF, et al. Early detection of toxicity and adjustment of ongoing clinical trials: The history and performance of the North Central Cancer Treatment Group's real-time toxicity monitoring program. *J Clin Oncol* 2002; 20(23):4,591-4,596. ■

Getting consent from non-English speakers

Don't avoid this population in your research

According to the U.S. Census Bureau, in 2000, just under 18% of the population — that's more than 46 million people — spoke a language other than English at home. For researchers doing work that can apply across populations, that has one big implication: Minority groups need to be actively recruited for clinical studies; and since many don't speak English, informed consent documents should be translated into a language they can read and understand.

Presenting the subject with a form written in his or her primary language is not just beneficence; it's the law. Federal regulations require that informed consent documents be in a language understandable to the subject and in the same language in which the consent interview is conducted. And before even recruiting patients, institutional review boards must ensure that the translation is accurate.

How to do that? "We ask for an English original, a translation into the language in question, and then a translation of that document back into English," says **Helen McGough**, MA, CIP, director of the human subjects division at the University of Washington in Seattle. "Then we ask the researcher to compare the two and make any changes necessary until the two English versions have the same meaning and intent. They don't have to be the same word for word, but the intent must be equivalent."

Even though providing for the needs of non-English-speaking subjects requires additional effort, that's not reason enough to exclude them, McGough says. "There is a long history here going back to the Belmont Report. Recruitment should be equitable. You have to enroll a representative sample of the people who will be affected by the outcome of a study. If a disease has an impact across various groups, you have to recruit from a wide range of those groups. That would be easy if everyone spoke English, and in many areas that really isn't an issue. But in many areas — and increasingly so in some — it is an issue."

In states such as Texas, where the number of Spanish speakers is large, there is no tendency to avoid non-English speakers, says **Diana L. Anderson**, PhD, CEO of D. Anderson & Co., a patient recruitment services firm based in Dallas. "But I could see people wondering in smaller sites and with some languages whether you can take on the responsibility involved in recruiting non-English speakers."

Still, the idea that whole communities of people would be left out of research because recruiting them is troublesome or adds additional costs is worrisome to McGough. "The only good enough response for not enrolling people from different groups is that there is no difference in outcomes. You have to understand the science and determine if it is relevant. If it is, then you have an obligation to recruit appropriately. Only if you have science that says race, ethnicity, age, or gender doesn't matter can you just recruit who it's easiest to recruit."

That said, McGough says there are some other reasonable arguments for not recruiting certain groups who don't speak the language. If a data collection instrument hasn't been validated in the language you need, then you can't do it. "For instance, if you are using the Beck Depression Index, it is done in English and scored on the assumption that it is done in English. If it hasn't been tested in another language, then you don't know if a given translation will give the same results. Many such tools and tests have been validated in other languages, but you have to know."

Ongoing communication

Translating consent documents only is the first step, says McGough. "What are you going to do for the rest of the study? If you are doing a study that includes Hmong people, do your nurses speak Hmong? If there is an adverse event, do you have someone available 24 hours a day who can speak the language?"

In high-risk studies that are in first or second phase, McGough says she would consider the need to keep participants to English speakers or those who speak languages where good translation services are immediately, readily, and constantly available.

Consider, too, a global perspective, McGough says. "If you are one of multiple sites in a study, and one site is heavily Asian, and another is heavily Hispanic, and another is heavily Caucasian, then no one site has to meet all the criteria. The study as a whole can meet the need for adequate representation."

Finding resources

The process for getting informed consent from patients who don't speak English is the same as for English speakers with one caveat: regulations allow for a short form in cases where a subject is recruited and no translated long form is available. The short form must be presented in conjunction with an oral presentation in the language that the participant understands. What was stated orally must be documented. While the FDA regulations seem to grudgingly accept the notion of short forms, the regulations clearly state that the "ramifications" and "ethics" of recruiting someone without complete informed consent should be considered. On the other hand, the OHRP seems much more willing to accept the notion of the short form. Full regulations for the FDA are available at www.fda.gov/oc/ohrt/irbs/informedconsent.html#non-English and for the OHRP at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ic-non-e.htm.

Don't rely on family

Finding good translators is pretty easy in big cities, places with diverse populations, and university towns. It is best to make use of outside translation services and not rely on relatives or caregivers. There isn't any federal rule stating you can't use them as translators, but McGough sees several problems.

First, it might not be appropriate for a bilingual child to act as translator to a parent involved in the study. Second, there are privacy issues that have to be dealt with. There also may be cultural issues that preclude using someone close to the subject as a translator. "In some places, older people, younger people, and women may be sheltered from bad news," McGough points out. You could conceivably run into a situation where the translator may not reveal all the important information to the subject, or where something could be revealed to the translator that might cause a problem within the family.

Anderson says another issue with caregivers doing the translating is that they may not be familiar with medical terminology. "It is best to have someone who is familiar with clinical trials doing the translating for you," she says.

If you find yourself stuck on a particular medical word, there is a web site with a medical terminology dictionary in several languages available at http://allserv.rug.ac.be/~rvdstich/eugloss/language.html.

In the end, the money spent on good translations is worth it, McGough explains. "Translation may be expensive, but it pays off. In a clinical research setting, the quality of the data must be better if you have good translation services."

Language Translation

- **All Language Alliance Inc.**, Highlands Ranch, CO. Phone: (303) 470-9555. Web site: http://Language Alliance.com. E-mail: translate@language alliance.com.
- **CREO International**, Minneapolis. Phone: (800) 632-1388. Web site: www.creointernational.com. E-mail: info@creointernational.com.
- **ForeignExchange Translations**, multiple locations, Boston: (617) 926-2791; Denver/Boulder: (303) 926-7177; Providence, RI: (401) 383-9046. Web site: www.fxtrans.com. E-mail: info@fxtrans.com.
- **International Translation**, San Diego. Phone: (888) 893-9391. Web site: www.international translation.org. E-mail: intertran@aol.com.
- **Mondial Translations & Interpreting Inc.,** Fort Lauderdale, FL. Phone: (954) 370-1223/1225. Web site: www.foreigntranslations.com. E-mail: Info@foreigntranslations.com. ■

Reference

1. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research.* DHEW Publication No. (OS) 780012; 1978. This can be seen in its entirety at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm. ■

Parents often don't understand research

Information overload is a problem

Imagine you had a very sick child and were approached about him or her being in a study. In your worry for your son or daughter, how much of the informed consent process would you understand? Would you be clear on what the study entailed? According to several studies published in the last year, maybe not.

The most recent study appeared in the *Journal of the American Medical Association* and related to parental understanding of randomization in childhood leukemia trials.[1] The study found that fully half of the parents didn't understand randomization despite oral and written explanation of the concept.

The findings of that study are hardly surprising to **Mary Jo Kupst**, PhD, a professor of pediatrics at the Medical College of Wisconsin in Milwaukee. She has also done studies on the informed consent process in pediatric studies. Her most recent study appeared last October in the *Journal of Pediatric Hemoatological Oncology* and looked at looked at how well parents involved in cancer studies understood what they had signed their children up for.[2] The study did interviews of 20 parents of newly diagnosed pediatric cancer patients. While they were able to recall the diagnosis, treatment plans, and statistic related to survival and cure, the research natures of clinical trials — and particularly of randomization — were not well understood.

Despite this lack of understanding, Kupst and her colleagues found parents generally happy with their informed consent discussions. But it begs the question: Regardless of their satisfaction with the process, if they don't really understand what is going on, are they truly giving informed consent?

"The pilot had 13 children on randomization protocols, but only five of the parents understood that," says Kupst. "And only half of them knew this was research."

Despite that, she thinks that the process is well explained. "I think there are a couple of issues at play here," says Kupst. "First, they are focusing on treatment and what is it is going to do for their child. Second, these are parents who are under a great deal of stress. There was an overload of information, so they had incomplete recall of what they were told. Their perception was that they got enough information and that they understood what they were told. But I think their emotional distress colors this."

Parents of children with cancer are not focusing on what is in a consent form or what the research is, she continues. "First and foremost, they want to know about the child's chances of cure and survival. Then they want to know the treatment plan. Then they want to know what the effects of the treatment will be, what side effects there might be, and about the quality of life their child will have under the treatment."

Parents do read the consent form and listen when they are told about it, "but that is not their concern. It is our concern. They are worried about their children's treatment. And even if they are happy with the process, we have to improve it."

Easy steps to take

There are some simple things that researchers can do to ensure that pediatric studies are done with truly informed consent. Kupst says repeating the consent discussion a couple of times is a good idea. Also, ask the parents outright what their understanding is of what was just said. "Ask them to paraphrase what you said. If they can tell you what it's all about, then they understand. Don't limit yourself to asking, 'Do you understand?' or 'Do you have any questions?'"

Parents involved in Kupst's study were asked what they thought would help them better understand the process. They suggested going slowly and breaking the process down into parts. Doing the entire process and asking about understanding or questions the parents may have requires them to take in too much information at once. Break the discussion down and ask about understanding after each section, she says.

Another suggestion – one that isn't always possible, particularly with sick children — is giving parents more time to digest the information.

That isn't possible in many of the anesthesiology and surgical studies that **Alan Tait**, PhD, an associate professor of anesthesiology at the University of Michigan in Ann Arbor, works on.

Tait and colleagues published a study in *Anesthesiology* a year ago on the topic of parental consent for children involved in anesthesia and surgery.[3] It looked at parental understanding of 11 elements of consent. The findings: Parents thought they understood, but largely overestimated their understanding of the research.

Because a lot of recruiting for surgery and anesthesiology studies occurs on the day of surgery, there is an added element of stress that might impair understanding, says Tait. "They just aren't assimilating all the information we give them," he says. "Our feeling is that it is not that the information is above their heads, but that there may be different learning styles and that different ways of presenting the information may help."

Tait has an upcoming study in *Pediatrics* this April that confirms what Kupst has found: Too much information also can have an impact on parental understanding. "Too much information may be as bad as too little," he says.

The work he has done has led Tait to think that presentation is the key to improving understanding. "This is really our problem. The regulations say informed consent documents should be written at the eighth-grade level. But if you actually look at the documents, they are probably at the 11th- or 12th-grade level. Institutional review boards don't check this."

Reducing the grade level, however, only will go so far. Tait's most recent work suggests that format of informed consent documents also makes a difference. Making use of bold, underlining, and bullets can help better crystallize the information in the parents' minds.

The problem is that most institutions have template forms for informed consent. "These are standard forms, and in large institutions, there is a reluctance to change. I think it will be a slow process."

Like Kupst, Tait favors going over the information multiple times and asking parents to repeat it back. "If you do this and they can't, then you cannot enroll them," he says.

Generally, Tait says, the informed consent process is well done. Certainly most parents think so. "But I think we can do better. We have to look not just at where they are given the information, but whether they truly understand it."

References

1. Kodish E, Eder M, Noll RB, et al. Communication of randomization in childhood leukemia trials. *JAMA* 2004; 291:470-475.

2. Kupst MJ, Patenaude AF, Walco GA, Sterling C. Clinical trials in pediatric cancer: Parental perspectives on informed consent. *J Pediatr Hematol Oncol* 2003; 25(10):787-90.

3. Tait AR, Voepel-Lewis T, Malviya S. Do they understand? (Part I): Parental consent for children participating in clinical anesthesia and surgery research. *Anesthesiology* 2003; 98(3):603-8. ■

Education vital in litigious clinical trial arena

Ongoing training keeps you up to date

Right now in Seattle, a lawsuit is pitting families of five research patients against the Fred Hutchinson Cancer Research Center. At issue is whether leukemia patients participating in a study on T-cell depletion fully understood the risks of the proposed treatment and gave informed consent. The study took place in the 1980s, and defense lawyers say that there are plenty pieces of paper with the patients' signatures on them indicating they knew what they were getting into. The families counter that the informed consent documents were terribly confusing.

This highlights how much things can change over time. Informed consent isn't a document, but a process. It's something that those involved with clinical studies are taught as a matter of course now.

Keeping up with changes — not just in law or regulation, but also in ethics — is vital for clinical trial administrators and those they work with, and there are plenty of opportunities and options for how to make sure you are up to date.

Organizations wanting to take advantage of the knowledge gained by the National Institutes of Health (NIH) in Bethesda, MD, can take courses for free at the NIH Clinical Center, or arrange to take the courses off-site through teleconferencing hookups. More than 1,000 health professionals from as far away as Peru and Puerto Rico took part in the classes last year. There are three core courses:

- **Introduction to the Principles and Practice of Clinical Research** — A curriculum on how to effectively conduct clinical research and design a successful clinical trial. Since it was established in 1995, this course has trained more than 3,000 people, a third of them off-site.
- **Principles of Clinical Pharmacology** — Training in the scientific basis of clinical pharmacology. The course is designed to meet the needs of researchers who have an interest in the clinical pharmacologic aspects of contemporary drug development and use. Nearly 1,600 people have taken this course in the five years it has been offered.
- **Ethical and Regulatory Aspects of Clinical Research** — A seven-week course in its sixth year, this is led by two doctors from the Clinical

Center Department of Bioethics.

"This is your tax dollars at work," says **Frederick P. Ognibene**, MD, FCCM, FACP, director of the office of clinical research training and medical education at the NIH Clinical Center. He adds that in the future, there probably will be additional course offerings, including one on how to do informed consent.

Anyone can sign up to take the courses at the center, he says, but if you want to take it off-site, your organization has to foot the bill and provide the infrastructure to do a live video feed of the lectures. Those who have registered for the courses also can access the lectures they may miss on-line.

"Eventually, we may get to the point where individuals can do this, but right now, we do this only institution to institution," says Ognibene.

As the pre-eminent clinical research organization in the country, Ognibene says that what the NIH offers is of the highest standards, even if some of the material is dry. "It's hard to make statistics and epidemiology interesting," he admits. "But there are more exciting parts of the courses, too, like the parts dealing with interacting with the media and learning about technology transfer."

Nongovernmental options

Another place to go for a wide range of courses is the Association of Clinical Research Professionals (ACRP). One course scheduled for this year involves the ins and outs of pediatric research and costs $600 for members and $695 for nonmembers. Another course, which is repeated throughout the year in several sites around the country, is a two-day seminar called *Fundamentals/1st Steps of Clinical Research*. It is designed for clinical research professionals who manage studies at clinical research sites or monitoring studies, as well as product managers, clinical investigators, institutional review board members, clinical pharmacologists, research pharmacists, and others with less than one year's experience conducting clinical trials.

Course content includes a historical perspective on regulation of clinical research, the principles of good clinical practice, the drug development process, the differences between drug and device research, current regulatory and ethical issues, a description of the informed consent process, and the regulatory requirements for reporting adverse events.

There are similar seminars of one- or two-day's length on topics as varied as project management and budgeting for clinical trials to successful strategies for medical device trials. Seminars cost between $360 and $845 depending on the length of the seminar and membership status in the ACRP.

There also are audio conferences available for $250 including adjunct materials, and tapes and CDs of previous audio conferences available for $100 to $175, depending on whether users order the accompanying materials. Topics for those audio conferences include: patient recruitment under the Health Insurance Portability and Accountability Act (HIPAA); managing research subjects, FDA inspection process; and patient retention.

Contact hours credit, as well as continuing education credit (CE)for nurses, physicians, and pharmacists, often is available through the courses.

There are several options for self-study. Thomson's Center for Clinical Research Practice has two books appropriate for administrators and others involved in clinical research. First is the *Foundations of Human Subject Protection*. An independent study course written specifically for IRB members, staff, clinical researchers, and health care professionals involved in the conduct and management of clinical research, the course covers federal regulations and guidance, informed consent process, the makeup and function of IRBs, and how IRBs carry our their mandate. It offers 15 CME or CE credits and costs between $125 and $225, depending on whether and which kind of continuing education credits are desired.

A second course is the *Foundations of Clinical Research.* Recently updated to include information on HIPAA, this book covers the basic principles and practices of clinical trials. It comes with an accompanying CD-ROM on regulatory references, course questions, and an answer key and costs between $180 and $295, depending on whether and which type of the 16 available CE credits is desired.

Another option is to do an on-line course. One engaging course is IRBEducator.com. While it is available free to any user, institutions can license the program for $800 per year. Licensees can then receive weekly reports on researchers' use of the training, or modify the program and install it on their own servers.

Course creator **Jeremy Wood**, PhD, says he developed the program to be entertaining yet taken seriously. "They can't cheat their way through this," he says. Indeed, there are gentle nudges if users do try to cheat — like screens that say, "That you tried to lie your way through an ethics curriculum is worrisome. That you abandoned the lie pretty readily suggests that there may be some hope for you."

The course, says Wood, includes the kinds of

issues that those involved in research may face, the kind of trouble they can get into, and what has happened in the past. "Take Tuskegee," he notes. "I show people how what led to the abuses is understandable — akin to what researchers do every single day. But education has to be about more than saying something is bad. It has to be about changing people's behavior." ■

Better outcome not guaranteed for cancer research volunteers

Does taking part in a controlled clinical trial of cancer therapy improve one's chances of surviving that disease?

The U.S. authors of a report in the Jan. 24 issue of *The Lancet* dispute the widely held belief that people with cancer who take part in clinical trials have better treatment outcomes. Its title: "Comparison of outcomes in cancer patients treated within and outside clinical trials: Conceptual framework and structured review." The medical oncologists who tested the supposition are at the Dana-Farber Cancer Institute in Boston.

The group surveyed 26 previously published studies that compared the health outcomes of cancer patients enrolled in clinical trials vs. those not enrolled. Although 14 of their studies suggested a beneficial health outcome for trial participants, most studies did not effectively control for bias. For example, only nine studies required the same entry criteria for participating and nonparticipating patients. Only three of those found that trial participants had better outcomes than nonparticipants.

After developing a conceptual framework for comparison of trial and nontrial patients, they did a comprehensive literature search to identify studies comparing outcomes between those groups. They identified 26 comparisons from 24 published articles of outcomes among cancer patients enrolled and not enrolled in clinical trials.

Of those, 21 comparisons used retrospective cohort designs; 14 comparisons provided some evidence that patients enrolled in trials have improved outcomes. Only eight comparisons restricted nontrial patients to those meeting trial eligibility criteria. Of those, three reported better outcomes in trial patients than in nontrial patients.

The American Federation of Clinical Oncology Societies maintains that treatment in a clinical trial often is a cancer patient's best chance of survival, and that trial access is one of the "basic requirements of quality cancer care." Such claims suggest that trials are viewed not only as a way to improve future treatment, but also as the best therapy for current patients. ▼

FDA wants clinical trial database improvements

The Food and Drug Administration (FDA) wants to better assist patients who have serious or life-threatening diseases access investigational treatments by improving its database of clinical trials.

Patients who cannot be treated with existing therapies or who do not meet eligibility requirements for certain drugs can gain information about ongoing clinical trials via the FDA's Clinical Trials Data Bank. The agency is looking for ways to increase and improve the information available and is asking interested parties to comment on proposals related to providing the information in a more straightforward and efficient way.

For example, the agency has established a web-based system in which firms can submit clinical trial information electronically. Companies are asked to submit a description of the location of the trial sites and a point of contact.

Once the information is entered, studies will be available to the public on ClinicalTrials.gov within two to five days. Information contained in the Data Bank is considered part of a long-term registry, which will remain available through accrual, analysis and even after the product is approved.

Beyond basic information about a trial, the agency encourages firms to submit more detailed notes including projected enrollment as well as information about other trials under the IND, such as trials for a disease or condition that is not serious or not designed to test effectiveness.

The entire proposal is available on the *Federal Register's* web site (www.gpoaccess.gov/fr/index.html; Jan. 27, 2004; 69(17): 3,923-3,925.). Comments and suggestions will be accepted through March 27 via U.S. mail at the Division of Dockets Management, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. ■

BRAAN gets smarter

In the December 2003 issue of *Clinical Trial Administrator*, we ran a profile on Baylor College of Medicine's integrated system for institutional review boards — BRAAN. API, the company that markets BRAAN to the public, now offers BRAAN 2. According to API, the new product features expanded flexibility, which clients were asking for. Staff now can add, delete, or modify questions, sections, or entire forms. BRAAN 2 also can be used beyond the compliance office, offering study data management for both animal and human protocols. For information, visit: www.apibraan.com. ■

CE/CME objectives

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

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

CE/CME questions

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. ■

5. Adverse event reporting requirements are dependent on:
A. The severity of the event and the phase of the trial.
B. How many people experience the event.
C. What kind of drug is being under investigation.
D. None of the above

6. If you don't have time to get a translation of the complete informed consent document, you should:
A. Find a translator to do an oral translation.
B. Use a friend or relative of the subject to translate.
C. Use an approved short-form translation.
D. Contact the OHRP for advice.

7. When doing pediatric studies, remember that parents:
A. Don't understand the concept of randomization.
B. Are usually under significant stress and may not recall all you tell them.
C. Don't understand informed consent.
D. Are reluctant to have their children participate in research.

8. Among the places to look for information on good educational courses is:
A. The ACRP
B. The NIH
C. The Center for Clinical Research Practice
D. All of the above

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