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IN THIS ISSUE

■ Those who have been through the accreditation process say it yields a clear picture of strengths and weaknesses 52

■ New HHS committee looks at research protections practices, with a special eye on vulnerable populations such as children 54

■ Pediatric trials of psychotropic drugs present ethical challenges for investigators, draw fire from critics 56

■ **News Brief**
— Electronic labeling of drug info new must. 59

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Compensation for subjects is fine as long as it doesn't cross the line

When does inducement become coercion?

In November, national news outlets reported on Steve Rucker, a nurse at the National Institutes of Health and one of two people to receive an experimental vaccine for Ebola. He did it, he told reporters, because he knew how important vaccines were to areas of the world where medicines and expertise for treating diseases are hard to come by.

Unfortunately, sometimes clinical trials aren't peopled with test subjects who volunteer out of the goodness of their hearts. Usually, there is some compensation involved. The problem is making sure the compensation isn't so great that you coerce people into being part of a clinical trial.

At Duke University in Durham, NC, **Debbie Brandon**, RN, PhD, CCNS, director of the neonatal program and an assistant professor, says for some of the families who participate in her research, even offering a toy for a child on each visit could be considered coercive. "They may not have any toys for their child at all at home," she says. For some families, offering $35 — the amount Brandon's most current study pays to cover parking, travel expenses, and lunch — seems like a lot.

"The compensation we give is minimal, and our IRB is very specific with us in limiting compensation to cover out-of-pocket expenses," says Brandon. She said she doesn't know of any studies in the neonatal program that cover more than out-of-pocket expenses, and the total amount offered rarely reaches the $50 level.

That notion of limiting the amount of money given to study participants isn't unique to Duke. A quick search of policies published on the Internet reveals similar concerns at organizations from the academic — the University of California for instance — to for-profit companies such as Pfizer **(see box on p. 51 for a look at its compensation policy)**.

When determining compensation amounts, there are two things to consider, says **Wajeeh Bajwa**, PhD, research subject advocate/regulatory consultant at Duke's General Clinical Research Center. "First, look

at the difficulty of the study and how much time is involved," he says. "If it takes eight hours or overnight, that's much more of a hardship than something that takes an hour. Similarly, if a test involves one blood draw, that's not as bad as one that requires a dozen of them. Compensation should reflect the level of difficulty of participation.

Bajwa adds that you shouldn't just look at the impact of the particular day of the study on the participant, but on whether there are lasting effects. For instance, a sleep deprivation study may only take one day. But the next day is a total loss too, for the participant.

Second, you have to consider what costs the participant will incur, says Bajwa. "Will they have to pay for their own meals or will you provide them? Do they have to pay for parking? How much travel will they have to do to participate?"

What you shouldn't consider are facts such as the going wage rate in your area, he warns. If you are keeping someone from work, you can't try to compensate for that lost time because one participant might make $20,000 and another $100,000. How would you determine what to pay?

Sometimes, compensation is directly related to the budget of a protocol, Bajwa says. "If you have a budget of $2,000, and you want 200 patients, you have a problem if you want to offer them more than $10."

At Duke's School of Nursing, **Elizabeth E. Hill**, RN, DNSc — an assistant professor, and director of the Clinical Research Management Program — is studying women who are or have been in abusive situations. "I always try to think about paying for child care, parking, and/or bus fare, and a small lunch," she says. Subjects can't concentrate on what they are doing if they are hungry, and that's often the case in the populations she works with, she says.

Usually, Hill pays an additional $50 for each assessment the participant attends, and says she would be uncomfortable paying up to $75 for each assessment. But that is dependent on whether she can build that amount into the grant. "I would be comfortable going up to $400 or $500 per subject on the research I do, depending on how much time they have to commit to the study, but I probably wouldn't go much above that."

Participants in Hill's studies are not told they won't get paid until they complete the entire study. "I think that's coercive and not really ethical, as they have given us their time whether they complete the study or not." In addition, if women complete an initial assessment, and Hill and her colleagues find they aren't eligible for the study after all, they are still paid for the time they have committed, to include the child care, parking, and meal reimbursement.

She usually keeps some cash on hand to cover

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Pfizer's Study Participant Compensation Policy

Compensation to Subjects:

- Shall be reviewed and approved by an Institutional Review Board (IRB) or and Independent Ethics Committee (IEC).
- Shall be based on subjects' time, nature of the procedures, and/or anticipated (or actual) expenses incurred during participation in a clinical trial (e.g., parking, travel, lodging expenses, baby-sitting costs).
- Shall be prorated (e.g., per visit) and not wholly contingent on completion of the trial by the subject.
- May include incentives of minimal value (e.g., phone cards with a monetary value of $10).
- The nature and amount of compensation or any other benefit should be consistent with the principle of voluntary informed consent.
- Subjects are free to withdraw from a trial at any time without penalty or loss of benefits to which they are otherwise entitled.
- The nature and amount of compensation to research subjects shall be disclosed in the informed consent form.
- For each individual clinical trial, the clinical team is responsible for developing a compensation structure for subjects that is tied to expenses relevant to the trial (e.g., time, travel costs, nature of procedures) and is not at a level that would be considered coercive. In that regard, given that the appropriateness of compensation depends on the patient population for a given clinical trial, the compensation structure for subjects for each clinical trial will be reviewed by an IRB or IEC, as it is best qualified to assess the appropriateness of a given compensation scheme to a particular pool of research participants.
- Pfizer generally assumes the cost of all investigational products supplied during clinical trials it sponsors. In addition, Pfizer will arrange for medical care for any physical injury or illness that occurs as a direct result of taking part in a company-sponsored clinical trial. This medical care is provided at no expense to the research subject.

Source: www.Pfizer.com.

the reimbursement portions of the compensation as many of the participants can't wait for a check to be cut and mailed to them.

Hill says she's careful to make sure the dollar amounts are not so high that people would participate just for the money. Sometimes she offers products rather than money — gift certificates to local department or grocery stores or phone cards.

When she's working with focus groups for studies, Hill tends to use door prizes and a meal. "That's especially important if you pull people away from their dinner or lunch," she says. "It also helps them understand you are concerned about their comfort, and helps you to develop an interactive, social environment, which is important for focus groups."

Different for children?

Working with adults is one thing — money is probably the best compensation you can offer. But what about studies involving younger participants? Brandon says what to offer in protocols with children depends on the age of the children involved. For the pre-term infants with whom she works, money to cover costs the parents incur is appropriate. She also may offer a stuffed toy at the end of the study. Even for a child as old as 12 months, though, cooperation won't likely improve with the promise of a toy. But for a 5-year-old, offering a toy at the end of participation can be an appropriate reward. Most of the studies in which older children participate involve developmental issues. In those cases, the toy provided usually is oriented to provide some developmental stimulation or intervention.

"The fact that our participants are little and very sick means that the families are often in a state of crisis," says Brandon. "That means we have to be especially careful that what we offer isn't coercive in any way.

"You don't want the amount to be coercive, but it has to be meaningful," Bajwa concludes. "There will always be arguments that we shouldn't compensate people, that you should find people who are willing to do this for purely medical reasons."

The problem, he says, is that there are far too few people like Steve Rucker in the world who will roll up their sleeves to further medical knowledge. "If someone has a disease, they may be happy to participate in research on that illness," he notes. "But there probably not enough healthy participants who would do research without compensation." ■

Is accreditation the next big thing?

Self-evaluation is selling point

If you look on the web site of the Association for the Accreditation of Human Research Protection Programs (AAHRPP), you'll find a half-dozen reasons for why organizations that are involved in human research should consider going through the lengthy accreditation process. They range from the obvious "Builds Public Trust" to some reasons that are perhaps not as easy to understand, like "Improves Research Quality."

Ask **David L. Wynes**, PhD, associate vice president of research at the University of Iowa in Iowa City, why he put his organization through the half-year long effort, and he quickly notes the value — whether you win accreditation or not — of going through an extremely comprehensive self evaluation of the program. "There is no better way to know your strengths and weaknesses than to go through this process," says Wynes.

In a time of budgetary constraints, this kind of navel gazing has a concrete financial result, too, he adds. "Going through this tells me areas where I need to spend my limited resources and areas I don't. I know I don't have to throw money at some policy once outside experts have reviewed and reached the conclusion that it's OK."

Wynes was keen on the idea of accreditation when the AAHRPP was formed in 2001. He commented on the proposed standards and when they were released in 2002, wanted to make sure the University of Iowa was among the first to get a completed application in. "I was a little upset that we didn't get it in on the first day they accepted them," he says. "But we got it in the first month."

From the start, Wynes says he was convinced of the value the process could bring his organization and the necessity to get on the bandwagon early. He cites the example of the Association for Assessment and Accreditation of Laboratory Animal Care, the accreditation organization for animal research. "They are about 40 years old now; and if you are a major research institution and you aren't accredited by them, it's a red flag. Money won't flow to your research programs."

This is a way, Wynes adds, to show the federal government that additional oversight isn't needed and that those who conduct research on human subjects can regulate themselves.

So far, just five organizations have achieved accreditation. Four have full accreditation: Hunter Holmes McGuire Veterans Affairs Medical Center in Richmond, VA; New England Institutional Review Board in Wellesley, MA; the University of Iowa; and the Western Institutional Review Board in Olympia, WA. Baylor Research Institute in Dallas has qualified accreditation.

A number of labs from the federal Department of Energy are the latest to seek accreditation in 2004. According to AAHRPP executive director **Marjorie Speers**, PhD, hundreds of organizations have sought information and applications for accreditation. Many of those still are undergoing assessment; others haven't completed the application forms yet, she says.

The entire process takes from six to nine months from start to finish. First, the organization fills out an application and conducts a self-assessment **(for an outline of the application requirements, see p. 53)**. When completed, the organization sends it in with a fee ranging from $7,000-$23,000, depending on the number of IRBs involved and the number of open protocols an organization has. If the AAHRPP awards the three-year accreditation, there is an annual fee to pay; but as long as the organization remains continuously accredited, there is no additional application fee assessed for re-accreditation.

Once the application and self-assessment are completed, AAHRPP spends about a month reviewing the materials and schedules a site visit. Most visits average about three days. The inspectors spend time interviewing investigators, administrators, and study participants. While there is some file audit work done, most of the visit is dedicated to talking to people.

After the visit, the inspectors write a report and send it to the applicant, who then has 30 days to either correct errors of fact, make any necessary changes in policies and procedures, and document those changes. The ultimate decision about accreditation is made by the Council on Accreditation, who award one of four outcomes: full accreditation (the organization meets all standards); qualified accreditation (the organization meets almost all standards and any issues that need addressing are minor and administrative); accreditation pending (there are substantial problems, but the council believes the organization is willing to make necessary changes); or accreditation withheld (there are many problems and the council doesn't believe the organization will

What's in an Application?

- **Overview and Purpose** — a brief overview of the organization, its purpose, and how the human research protection program relates to the organization's mission.
- **Description of the Organization** — including organizational charts, names and titles of staff from supervisor on up, and the number of personnel under each supervisor.
- **Key Organizational Representatives** — including the organization's contact person, IRB chairperson(s), organizational officials, and individuals likely to participate in the site visit.
- **Accreditation History** — whether the organization has been accredited before by AAHRPP or another body.
- **Types of Research Conducted** — brief description of the major types of research involving human participants (e.g., clinical research, social science research, etc.); the approximate number of investigators and protocols involving the use of humans; the percentages of protocols reviewed by the full IRB, reviewed using the expedited process, or that are exempt; the proportions of human research sponsored by private or public sources; descriptions of research facilities, such as a clinical research center or a survey research center; and information on all current research studies.

Summary of Other Organizations that are part of the Human Research Protection Program — brief descriptions of other organizations that are part of your human research protection program.
Other Relevant Background — anything else that might help the AAHRPP in its review of the program.

Note: The above is an abbreviated list of elements appearing in the application.

Source: Association for the Accreditation of Human Research Protection Programs, Washington, DC.

make the necessary changes). No actual numerical scores are given, but rather a narrative report. Organizations that don't meet the standards are told in the report where they have to improve to achieve one of the two accreditation statuses.

Wynes says once the University of Iowa decided to go for accreditation, one staff member spent about half of her time for four months going through the application and the self-evaluation. "There is a lot of time and effort involved in this," he says.

Luckily, the evaluation pointed out minimal need for change. Wynes says that most of what they found was a lack of documentation — or clear documentation — of processes, policies, and procedures. "Most of what we did involved clarifying or adding to our written materials to make sure it was all crystal clear."

Worth the effort

Despite the rigors of the process, Wynes is quick to tout the value of the experience. "This is the most concrete way I know of to get validation of what you do," he says. "Whether we recognize it or not, we all spend a lot of time and effort evaluating what we are doing, trying to implement change, do the right thing, and accommodate new interpretations of existing issues and new issues as they arise. In the end, it can save you time, energy, and money because you have that external expertise telling you what you are doing is right and appropriate."

That Wynes found the process both rigorous and valuable doesn't surprise Speers. "What we have heard from those who have gone through or are going through is that it adds value to their organizations," she says. "Every institution has said to us, 'Our program is better having done the self-assessment and having gone through the site visit.'"

Since the standards are almost all based on Department of Health and Human Services or Food and Drug Administration rules, going through the process can also help organizations comply with federal regulations. "If they meet our standards, then they are meeting regulatory requirements," she says, adding that this compliance comes without a government audit or inspection.

This amounts to an expert review of the human protections program at any organization seeking accreditation, Speers notes. At the very least, it can help ensure public trust in research. It also may speak to sponsors of research, be they public or private.

"Most importantly, the oversight system for protection is based on the good will of those who are involved in it doing what they have to do —

IRBs and staff reviewing appropriately, investigators conducting research appropriately," says Speers. "If what we as a society want to achieve is deeper penetration of regulatory compliance, the only way I think that will occur is if institutions embrace it themselves and regulate themselves."

Another way to go

There is another accreditation option for organizations, too. The Partnership for Human Research Protection was formed about a year ago by the Joint Commission on Accreditation of Healthcare Organizations and the National Committee for Quality Assurance.

Ten organizations signed up for accreditation in March. Among them are Aurora Health Care, Milwaukee; Baylor Research Institute, Dallas; Chesapeake Research Review, Columbia, MD; Essex Institutional Review Board, Lebanon, NJ; Hartford (CT) Hospital; National Jewish Medical and Research Center, Denver; and Patient Advocacy Council, Mobile, AL.

Final standards for the PHRP accreditation process were announced at the end of May, and the 10 initial organizations were expected to undergo surveys late in 2003. To date, no organizations have completed the accreditation process with the PHRP.

You may get additional information on PHRP accreditation by going to www.phrp.org. More information on AAHRPP accreditation is available at www.ahhrpp.org. ■

Special committee looks at subject protections

Research with children a focus

The newly formed Secretary's Advisory Committee on Human Research Protection has its work cut out — committee members already have three subcommittees establishing work plans, and there many more top priorities to be chosen from the federal regulations.

The committee, established by the Department of Health and Human Services (HHS), has been charged by HHS Secretary Tommy Thompson to advise him on human subjects, placing particular emphasis on special populations, including children. **(See "Research with children raises ethical questions," p. 56.)**

Committee members also will identify research issues involving the use of tissue samples, investigate conflicts of interest, and monitor activities by the Office of Human Research Protections, says **Ernest Prentice**, PhD, chair of the Secretary's Advisory Committee and an associate vice chancellor for academic affairs at the University of Nebraska Medical Center in Omaha.

Here are some of the issues that the committee will address:

• **Adverse event reports:** "Although it's not specifically included in our charter, we're looking at adverse event reviews by IRBs," Prentice says. "IRBs are being inundated with IND [investigational new drug] safety reports from all over the world in multicenter clinical trials, and they often do not have sufficient data to allow anybody to make an assessment of an adverse event."

Some institutions receive more than 11,000 adverse event reports a year, Prentice says. "Even smaller institutions feel this is a significant problem," Prentice adds. "So our committee is going to be looking at the adverse event problem and at ways to help IRBs resolve this tremendous workload."

One issue the committee will address is whether and how IRBs should review external adverse events, since the regulations don't require such reviews, he says.

"IRBs are not prepared to review adverse events that occur thousands of miles away and that involve patients about whom they know nothing," Prentice says. "This has been a phenomenon that has developed over the last 20 years, and we see every year more and more of these IND reports come across our desks."

One solution might be having a data safety monitoring board serve as a gatekeeper to the reports, deciding which need to be sent to IRBs, he suggests.

• **HHS regulations, subpart D:** A subcommittee is looking at the subpart D regulation that provides additional protection for children. The HHS regulation is 20 years old, and the Food and Drug Administration (FDA) issued an equivalent regulation in 2001, Prentice says.

"It's been my experience over the last 20 years that many IRBs do not understand subpart D," he says. "We want to examine subpart D in detail and advise the secretary on appropriate interpretation of subpart D, so that we neither underprotect children or overprotect children."

Pediatric research serves the greater public

good, benefiting children everywhere; however, sometimes trials are not conducted because IRBs do not approve or understand the regulations," Prentice says. "And there are other trials that shouldn't be approved but are."

Another aspect of subpart D that the subcommittee will address involves the 407 panel review process in which a pediatric research project is reviewed by a HHS expert panel if the research doesn't fit into one of four categories of research, he says.

"These categories are based upon the level of risk associated with the research and whether or not there are any direct subject benefits," Prentice says. "As the risk increases in the absence of direct benefit to the child participating in the research, the requirements are more stringent."

When an IRB sends a protocol to HHS for a 407 review, the expert panel must review the entire protocol and make a recommendation to the secretary of whether the protocol should be funded by the federal government, he explains.

"Now it's interesting to note that between 1983 when the regulations first came out and somewhere around the latter part of 2000, there might have been no more than seven expert panel reviews," Prentice says. "Then since 2000, we've maybe a half-dozen of 407 reviews."

407 case study

• **HHS and FDA reviews:** One proposed pediatric clinical trial recently became the first proposal to be subject to both a HHS 407 review and an FDA review, and the controversy that surrounded this trial is another reason why the 407 review requirements need to be addressed by the secretary's committee, he says.

The study proposed to evaluate the potency, dose, and safety of vaccinia virus vaccine (Dryvax) when administered to 40 children, ages 2 to 5 years, at two sites, including the University of California — Los Angeles (UCLA) Center for Vaccine Research and the Cincinnati Children's Hospital Medical Center.

At the time the trials were being considered, the country was preparing to go to war with Iraq following the Sept. 11, 2001, terrorist attacks in New York City, and the public mood could be described as fearful, Prentice notes.

There were fears at the top levels of government that terrorists could obtain the few remaining samples of smallpox and create a virus that quickly would decimate populations.

Alternatively, the Dryvax vaccine, which routinely had been given to children and adults decades earlier, is considered by 21st century standards to be high risk because it may produce dangerous side effects among individuals with autoimmune diseases, emphysema, and other conditions, and it may pose serious health problems for pregnant women and infants.

"It's hard to identify exactly what is the bioterrorist threat associated with utilizing smallpox as a bioweapon," Prentice says.

The public's fear of Iraq and terrorism during the pre-war period may have created a mindset that thought of smallpox as a greater risk than it was, he suggests.

But there were no hard data showing that smallpox had ever been used as a bioterrorist weapon or that it was indeed a part of Iraq's biological weapons arsenal, as was suggested by some bioterrorism experts, or that Iraq or anyone else would use it on an unvaccinated nation.

Both the public and individual subject interests were being considered by the IRBs that reviewed the pediatric Dryvax protocols, and the IRBs came to different conclusions. The Kaiser Permanente Southern California IRB decided in favor of the protocol, while the Harbor-UCLA Medical Center IRB voted 6-to-5 against it.

Also, the Cincinnati Children's Hospital Medical Center IRB voted to approve the protocol after deciding that it would fall under subpart D, 405, meaning that there was indeed a prospect of direct subject benefit, Prentice says.

"Whereas the UCLA IRB didn't find the protocol approvable and referred it to a 407 review," he explains, "two institutions utilizing the same set of regulations came to different conclusions because they interpreted it differently."

Had both IRBs approved the protocol, then the trial would have been conducted, but because one of them referred it for a 407 review, the trials were never begun. In fact, the trials also were called for an FDA equivalent review, and eventually after some public scrutiny, the pediatric Dryvax trials were canceled, Prentice says.

The HHS expert review itself was controversial because it lacked public transparency, he notes.

"It was not conducted in an open forum, although the materials were posted on web sites," Prentice says. "Many of us would contend that [the review] was an inappropriate mechanism for performing a review of pediatric research."

The panel had asked a group of experts, including Prentice, who declined to participate, to write

a review with their conclusion of whether the pediatric Dryvax trials should be conducted. Then the reports were posted on the Internet, but they were never discussed between the participants at a meeting where a consensus might be reached, he says.

"It was like having an IRB review meeting and having people send in reviews that are never discussed," Prentice says.

So the secretary's committee is going to look at how the 407 review system could be changed and improved, he reports.

"We're looking at whether or not it might be appropriate for the 407 review to take place under the auspices of a subcommittee," Prentice says. "The subcommittee would meet three times a year and make recommendations to the Secretary's Advisory Committee on Human Research Protection."

What the committee agrees upon is that it's not appropriate for the 407 panel reviews to be held behind closed doors, he adds.

"One of the benefits to having a face-to-face meeting is so you can listen to the opinions of others, which might serve to modify what you think," Prentice says. "But there was no opportunity for dialogue in how the smallpox vaccine protocol was reviewed." ■

Research with children raises ethical questions

Risk, informed consent top list

In recent years, changes in federal law and guidelines on federally funded research have encouraged the inclusion of children as research subjects in clinical drug trials.

Passage of the 1997 Food and Drug Administration Modernization Act (FDAMA) granted pharmaceutical companies a six-month extension of patent exclusivity for drugs tested in children. And in 1998, the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) changed their policy guidelines for research grant applications to state that children "must be included in all human subjects research conducted or supported by the NIH unless there are scientific and ethical reasons not to include them."

Both measures were designed to ensure that children with life-threatening medical conditions had access to experimental drugs that might help them — and that children would not be prescribed drugs that had not been specifically tested and deemed safe for pediatric populations.

The result of the changes, however, has been a dramatic increase in the number of clinical trials in children. But, some critics say, there still are many unanswered ethical questions about the appropriate way to include children as research subjects and whether the inherent risks outweigh the potential benefits.

"Determining the ethics of a child research protocol requires attention to specific elements, in addition to the general rules for human research," wrote **Benedetto Vitiello**, MD, chief of the Child and Adolescent Treatment and Preventive Intervention Branch of the NIH, in a recent issue of the journal *Psychopharmacology*.[1] "Currently, few empirical data are available to guide investigators, families, and ethics committees in the interpretation and application of the ethical principles to the reality of specific research protocols."

The challenges are particularly acute for researchers undertaking trials of psychotropic medications in children, Vitiello tells *Clinical Trials Administrator*.

Diagnostic criteria for many behavioral disorders are not clearly defined for pediatric patients, making it very difficult to determine which children have a true potential for benefit from trial participation. And many of the drugs to be tested present significant risks of toxicity, side effects, and possibly permanent alterations in brain chemistry.

Investigators and coordinators conducting psychopharmacological research in children must proceed cautiously, he warns.

Federal regulations concerning children

In addition to satisfying all of the ethical requirements for human research in general, research in children must also fall into one of the approvable categories outlined in subpart D (Additional Department of Health and Human Services Protections for Children Involved as Subjects in Research) of part 46 (Protection of Human Subjects) of the Title 45 Code of Federal Regulations.

The categories are as follows:

• **Research with prospect of direct benefit —** The study presents the probability of direct benefit to the child participant. For example, a child suffering from a condition for which the study drug offers potential for treatment. Note: The risk-benefit ratio

must be favorable to the child subject in order to be approvable under this category of research. The risks posed by participation in the trial cannot outweigh other risks the child might ordinarily face either in daily life or in other, accepted, treatment protocols for his or her condition.

• **Research without potential for direct benefit, but which presents only a "minor risk" to the participant —** Studies aimed at studying mechanisms of action of drugs, pharmacokinetics, or metabolism do not typically offer a direct benefit to research participants. But these studies can be approvable in children as long as their participation does not expose them to "risk of harm not greater than ordinarily encountered in daily life, or during routine physical or psychological examinations or tests."

• **Research without potential for direct benefit, but which presents only a "minor increase over minimal risk" —** This category of research is only approvable if it: a) presents "experiences to the subjects that are commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; or b) the study has the "potential to generate new knowledge" considered of "vital importance" for understanding or treating the subject's disorder or condition.

The inherent problem with these categories is that there are no concrete definitions available for the terms "direct benefit," "minor risk," and "minimal increase over minor risk," says Vitiello.

That determination has been left up to institutional review boards, which have frequently come up with vastly different interpretations of the regulations.

"The regulations contain very good general statements, but they are just general statements," Vitiello says. "One needs to apply them to a particular project that is being reviewed by an IRB. But the IRBs sometimes disagree and have different interpretations."

For example, some IRBs would not approve a placebo-controlled clinical drug trial in children because of the potential for an individual child subject to be randomized to the placebo group and thus not end up having a potential for direct benefit, he notes.

However, many IRBs would consider the overall potential for direct benefit to some subjects, even though a portion would be given only placebos.

"Most IRBs would interpret it as there is potential for direct benefit because some children are being randomized to active treatment," Vitiello says. "It is not that there must be a certainty of benefit, but there must be a prospect of benefit. That is what the regulation requires."

It is appropriate to allow individual IRBs leeway in determining concepts such as "potential benefit" and "minor risk" on a study-by-study basis, he notes.

"The risk may change from setting to setting. For instance, in a very specialized hospital, a procedure might be considered routine and that IRB would deem it minimal risk, but at a hospital where they don't do that procedure in high volume and they don't have a lot of skill in doing it, it would become a greater risk," Vitiello explains. "So it is very difficult to have general guidelines that can apply to all settings throughout all the possible scenarios. It requires a lot of interpretation; that is why IRBs have a very important task in trying to make sense using these general principles."

Questionable studies

Some consumer advocates argue, however, that IRBs are inherently biased in favor of allowing research at their institutions — too willing to minimize or rationalize the potential for harm that some protocols pose to child subjects.

In the current research climate, IRBs across the country have approved "high-risk, high-impact" experiments even when those protocols lacked ethical or scientific justification, says **Vera Sharav**, president of the watchdog group Alliance for Human Research Protection.

Sharav published an article in a recent issue of the *American Journal of Bioethics* criticizing the recent trends in pediatric research.[2]

"As currently constituted, IRBs cannot claim to be independent," Sharav says. "IRBs are compromised by an inherent conflict of interest and their decisions bear this out. IRBs are not protecting human subjects who have no voice in the research approval process; they are protecting their institution."

As an example, Sharav cites a study by Pine and colleagues, published in 1997 in the *Archives of General Psychiatry*,[3] that detailed a fenfluramine challenge experiment performed on 34 African-American and Hispanic boys, ages 6 to 11. The child subjects were drawn from a larger study involving 126 brothers who were deemed at risk of following in the footsteps of older brothers who were incarcerated juvenile delinquents.

The investigators stated that there was evidence of a correlation between reduced serotonin activity

and aggressive behavior, and hypothesized that by measuring the boys biochemical responses to fenfluramine, a drug thought to be effective in treating some behavioral and personality disorders, they would be able to replicate earlier findings and find a predictive biological marker predisposing the children to violence.

The children were required to follow a special diet for four days, fast for 18 hours prior to the administration of the drug, and then had an IV catheter inserted in their arm, which remained in place for more than five hours, during which time blood was drawn.

The researchers were able to justify the risks and discomfort the children would bear by stating: "Research on the relationship between adverse rearing and serotonin may enhance understandings of the association between serotonin and aggression across development."

The parents of the subjects also were paid $125, and the children received $25 gift certificates to a toy store, Sharav notes.

The drug fenfluramine, she notes, carries the risk of neurotoxicity and heart valve damage.

Although federal regulations prohibit the use of children in research involving "greater than minimal risk" if there is no potential direct benefit to them, four prominent institutional review boards approved this experiment — though there was no potential for direct benefit — the subjects were exposed to a drug known to cause heart-valve damage, and the results of the study were not thought to yield information of great importance to treat a condition the subjects had, Sharav emphasizes.

Researchers argued that the boys were appropriate subjects for participation in a risk-bearing research protocol because they were considered by some to be at risk for exhibiting antisocial behavior in the future.

Even when pediatric drug trials of psychotropic medications are targeted at children with a diagnosed medical condition, the mechanisms to protect the rights of children seem hard to discern, Sharav says.

In November 2000, the National Institutes of Mental Health sponsored the multisite Preschool ADHD Treatment Study (PATS), to test the safety and short-term effects of the drug Ritalin in children ages 3 to 5 years.[2]

Though the study's lead investigator admitted that ADHD is not a "well-defined" disorder in such a young age group, the government-sponsored study will recruit 312 3-year-old children into a study in which they will be given increasingly larger doses of Ritalin in order to test their tolerance of the drug.

The investigators cannot possibly provide any scientific evidence to validate an abnormal medical condition in the children being recruited, Sharav says. Yet, they will be given a drug that has the potential to permanently alter the functioning of their brain and central nervous system.

Children are not capable of understanding the risks and benefits of the projects they are asked to participate in, and, at any rate, cannot legally consent to participate. Parents, who can give consent for their children are often not privy to all of the scientific data available — and not available — to support a thoughtful decision on the part of their child.

An independent body dedicated to overseeing all research involving children, and whose makeup includes community representatives, is the only way to ensure that the rights of children are protected, Sharav argues.

What can be done

Without question, more efforts need to be made to improve protections for children involved in research. And some research protocols do expose children to dangers that cannot be completely known or guessed at, currently, says Vitiello.

But, he argues, halting controlled trials of psychotropic medications will mean that these drugs will continue to be prescribed for young children without any available data on the drugs' safety or efficacy in those populations, he says.

"If research conducted in adults could adequately inform the pediatric use of psychotropics, there would be no need for direct experimentation in children," he says. "Unfortunately, experience has painfully taught us that this is not the case. Developmental differences between children and adults have important implications for pharmacological effects. Even though adult data are relevant to pediatric psychopharmacology, research directly in children is necessary for safe and effective use."

To better protect children, Vitiello says that more research needs to be done on how to improve informed consent procedures in pediatric trials.

"I think it is quite important because in the last few years there has been a lot of attention to providing medical information to the family, and to the child, but also to the family particularly because they make the decision ultimately," he says. "But we don't have enough information to know whether this effort is really successful or

not. Consent forms are becoming really thick and detailed, with many pages and they provide a lot of details. The question is, do people actually understand, and read, and appreciate that information. We are trying to follow up with families who have gone through that process to find out how much they understood."

More information is needed about how IRBs consider and evaluate pediatric research protocols and how they determine their definitions of "minimal risk" and "minor increase over minimal," he adds.

It's important also for IRBs and data safety monitoring boards to take a full role in monitoring trials, Vitiello says.

Careful monitoring procedures for research subjects, with prompt rescue procedures (identification and treatment of children who deteriorate during the study) can substantially decrease the risk of participation and improve risk-benefit ratios, he states.

Clinical trial investigators and coordinators should also take the added step of developing good assent protocols to ensure that children are willing to participate. Though they cannot legally consent to participate — their parents or guardians must make that decision — children can and should give their assent, an explicit agreement to participate.

Written assent forms, with language appropriate to the child's developmental stage are used in parallel to parental consent forms, Vitiello says. Assent should be an explicit, affirmative agreement to participate and not just the absence of an objection.

Conversely, if, during the course of a study, a child expresses a desire to stop participating, that decision should be respected.

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3. Pine DS, Coplan JD, Wasserman GA, et al. Neuroendocrine response to fenfluramine challenge in boys. *Arch Gen Psychiatr* 1997; 54:839-846. ■

Electronic labeling of drug info new must

Under a new rule, the Food and Drug Administration (FDA) will begin requiring electronic submission of labeling information for most drug applications.

The agency believes electronic labeling will improve the review process and speed the approval and public dissemination of labeling changes, enabling it to get up-to-date information on medications to doctors and patients quicker. The rule will take effect in June.

It applies to new drug applications, certain biological license applications, abbreviated new drug applications, supplements, and annual reports. The rule does not require full applications to be submitted electronically.

FDA commissioner Mark McClellan issued a prepared statement saying the use of modern information technology to improve public health is no longer optional at the agency.

Electronic submissions will cover the content of the package insert or professional labeling, including all text, tables and figures. The new labeling system is part of the FDA's larger initiatives involving electronic medical records and electronic health information systems.

FDA says the final rule is intended to supplement existing requirements, which stipulate that copies of the label and labeling and specimens of enclosures be submitted. Indeed, copies of the package insert still must be submitted in an NDA, and they must be identical to the label and labeling and specimens of enclosures that appear in the package insert, on the immediate container, or in any other form distributed.

The complete rule can be viewed on-line at www.fda.gov. ■

COMING IN FUTURE MONTHS

- Ethics of phase one oncology trials
- Involving students in research
- Reports on misconduct on the rise
- Advertising do's and don'ts

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.

17. When considering how to compensate human research subjects, always consider:
A. How much money they earn.
B. How much their day care costs.
C. The difficulty of the test requirements.
D. The average pay rates of your region.

18. AAHRPP accreditation lasts:
A. one year.
B. three years.
C. five years.
D. 10 years.

19. The newly formed Secretary's Advisory Committee on Human Research Protection will review and make recommendations on:
A. adverse events.
B. HHS regulations, subpart D.
C. HHS and FDA reviews.
D. all of the above

20. Regarding inclusion of children in federally funded research protocols, which of the following is true?
A. The research must not present more than minor risk.
B. The research must present at least the potential for direct benefit to the subject.
C. For research involving more that minimal risk, the study must either present the probability of a direct benefit to the subject, or offer researchers information of vital importance to the disease or condition the child has.
D. None of the above

Answers: 17. C; 18. B; 19. D; 20. C.