IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Antidepressants and children debate yields lessons for IRBs

IRBs seen as checking point in clinical trials registry

The recent warnings that children using certain antidepressants may be at increased risk to become suicidal — and charges that previous studies pointing out the problem were kept from public view — have reverberated throughout the research community.

The controversy could have a long-term impact on the work of IRBs — from their participation in a new recommended clinical trials registry to causing boards to review such issues as placebo controls, say those who have studied the issue.

The antidepressant debate also reinforced the need for careful study of drugs first being used with children, says **Richard Gorman**, MD, FAAP, chair of the American Academy of Pediatrics' Committee on Drugs, and a member of an FDA advisory panel that recommended a so-called black box warning on antidepressant drug labels.

"[Antidepressant use] was something that we had a real sense of comfort with, from the fact that it had such a long, widely used and minimally reported side-effect profile in the adult population," he says. "IRBs, as they move forward in their reviewing and questioning and examining protocol design and safety monitoring, have to remember that these drugs have not been studied in this population before.

"Pediatricians say over and over again, 'Kids are not little adults.' This was a case where children turned out not to be little adults," Gorman says. "I think that's a message to take home as a cautionary tale — to remember that drugs, widely used, perceived as safe in the adult population, when they're studied in children may have different benefit profiles and different risk profiles."

Currently, Prozac (fluoxetine) is the only drug that is FDA-approved for use in children and adolescents for the treatment of major depressive disorders. However, a number of other antidepressants have been prescribed for children off-label.

In October, the FDA issued a public health advisory, warning that children and adolescents being treated with antidepressants are at

increased risk for suicidal thoughts and behavior. The agency directed drug manufacturers to add a black box warning to the labeling.

The labels would warn health professionals of the risk and advise them to closely monitor young patients taking the drugs.

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Editorial Questions

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The FDA's Psychopharmacologic Drugs Advisory Committee and Pediatric Drugs Advisory Committee jointly recommended the new warnings after reviewing evidence from two dozen clinical trials and listening to testimony from physicians and from parents whose children committed suicide after being treated with antidepressants.

There were no suicides among the children in the clinical trials that the panel reviewed — an important point, reports **Robert M. Nelson**, MD, PhD, associate professor of anesthesia and pediatrics at The Children's Hospital of Philadelphia, also a member of the FDA panel.

He says because the children in the trials were being closely monitored, he would conclude that getting the drugs within the research setting was much safer than getting them as an off-label use.

"I think both the public and the IRBs need to be cognizant of the fact that the choices here are not between research and don't use the drug at all. They're between research and off-label use," Nelson says.

He says just because an IRB disapproves a carefully controlled pediatric study of an antidepressant drug doesn't mean the drug won't be dispensed off-label to children — even at its own institution.

"I realize that IRBs don't think they're supposed to evaluate the sort of policy implications of what they're doing," Nelson says. "But on the other hand, I don't think we can put blinders on and ignore the fact that that's the choice."

New registries could involve IRBs

Earlier this year, New York Attorney General (AG) Eliot Spitzer sued GlaxoSmithKline, manufacturer of Paxil (paroxetine), one of the drugs involved in the review. He alleged that the drug company withheld studies that had suggested a possible increased risk of suicidality.

In August, GlaxoSmithKline signed a consent order with Spitzer's office. While the company called the AG's charges "unfounded," the company agreed to continue posting on-line all company-sponsored clinical studies of Paxil in children and to create a clinical trials registry to provide Internet access to clinical trial data on its marketed medicines.

The drive for a publicly accessible clinical trials registry for all pharmaceutical research is proceeding on various fronts:

- The trade group Pharmaceutical Research

and Manufacturers of America (PhRMA) announced the creation an on-line database, www.clinicalstudyresults.org, containing information about the clinical trial results of studies sponsored by its members.

• The International Committee of Medical Journal Editors announced in September that researchers will have to register their clinical trials with a publicly accessible database to have their reports considered for publication in any of the top-tier medical journals. That requirement would affect research that begins enrollment after July 1, 2005; studies already under way would have to register by Sept. 13, 2005.

• The Fair Access to Clinical Trials Act was introduced in both houses of Congress in October. The bill would require researchers to report all results from clinical trials for drugs and medical devices, using the existing www.Clinicaltrials.gov database. Most importantly for IRBs, the act would mandate participation in the registry as a prerequisite for IRB approval.

If a federally mandated registry ever becomes law, then IRBs are the logical checking point, says **David Korn**, MD, senior vice president for biomedical and health sciences at the Association of American Medical Colleges. But he says the plan needs to be crafted carefully, both to minimize the burden on already overburdened IRB staffers, and to avoid needless registration of trials.

Korn says requiring a researcher to register his or her clinical trial proposal before submitting it to the IRB for review could result in studies being registered that are never approved.

"There's no point putting stuff in a registry that's never going to happen at all," he says. "It would be better to have IRB approval conditioned on registration of that particular trial," a process Korn says could be made relatively painless by technology.

The IRB tentatively could approve the trial, but withhold formal notification for a few weeks, requiring the investigator to register the trial in whatever national registry becomes the standard, he says. The registry could have a function that automatically notifies the IRB once a trial has been registered: "Sort of like when you order something on the web, on Amazon or wherever, and you get an e-mail back."

The job of the IRB would be simply to ensure that notification from the registry gets filed with the proper trial. That could then trigger a formal notification of IRB approval to the investigators, Korn says.

"I think the IRB's the right place to do this," he says. "And we are in an age of advanced technologies, where things that used to be very burdensome can now be done with a double-click or the press of a key. However this is set up, it should be set up to be minimally burdensome."

Gorman, a researcher who served on an IRB for 14 years, agrees that IRBs are up to the task of monitoring such a system.

"IRBs live by regulations," he says. "We are sensitive to regulations and therefore we'll find ways to implement them without much disruption to our operations.

"This, compared to HIPAA, is nothing. HIPAA was a major nightmare; this is a little speed bump."

But what if the proposal never becomes law? Could IRBs decide on their own to refuse to approve studies that aren't registered with a public database, or to require that results from the studies be made available to the public?

Gorman says that's unlikely. "We have no control or power or ability to cajole, force or mandate that negative trials reach public light," he says.

Nelson notes that an IRB that requires registration could find itself at a disadvantage if the sponsor could go to another institution that doesn't require it.

"If everybody does it, there's not going to be a problem," he says. "But if there are holes, then individual IRBs could be put in a bind as to whether they should hold the company to this standard, knowing they might then just withdraw the protocol and go elsewhere."

But Nelson says he's hopeful that the litigation risk introduced by Spitzer's lawsuit against GlaxoSmithKline will lead to a standard for registration of trials and publication of all results, even if that's not federally mandated.

"I would say that if someone doesn't do it, there would be a way that if that drug is sold in New York, that Eliot Spitzer would go after them," Nelson says. "And I would say that's a good thing."

Korn says it's unclear at this point what form

Clarification: A November 2004 article referencing the Public Responsibility in Medicine and Research conference confused some readers. We should have explicitly stated that speakers were interviewed before the conference began. We apologize for the oversight.

the publication of results might take — whether it would include a notation in the registry and, if so, what amount of detail would be required.

"Even a brief entry would at least give people a piece of information — maybe the trial failed to demonstrate what [the sponsor was] looking for, or it was costing too much money and the company lost interest," he says. "That's a way of publishing it, putting it in a publicly accessible database that can be accessed by those who have interest in knowing about it."

Nelson says keeping track of such follow-up information could easily fit within an IRB's existing continuing review process.

Placebo controls — important for safety

Beyond the logistics of registries and publication of results, the debate over antidepressants also points to a number of lessons for IRBs, say Nelson and Gorman.

Both say the issue underlines the importance of placebo-controlled trials when a drug is introduced to a new clinical population.

"There was a time when people would have argued, 'Oh, it's unethical to give placebos when you've got proven effective treatment for depression,'" Nelson says. "Well, the only way these data came forward is with placebo-controlled trials. People often think of placebos purely in terms of efficacy. But placebos are part of safety evaluation, too.

"I think IRBs are going to have to think through carefully issues of research design in a much more sophisticated way and recognize that in fact, there may be important questions that need to be answered that can only be answered with the conduct of appropriately controlled trials."

Gorman says it's also important to have studies that use real-world populations, not just narrowly controlled groups.

"On some of our IRBs, we get used to the Phase 3 pharmaceutical controlled clinical trial, which tends to be a very select, narrow population, looking for a fairly select and narrow indication," he says. "And that's not how drugs get used when they go out into the real world. They get used in complicated people on other medicines.

"I think we need to start thinking about including those people. Excluding them is safer for the clinical trial, it's true, but it then becomes more risky for the population when it gets generalized," Gorman adds. ■

Use visual aids, testing to improve informed consent

Indian study looks at comprehension

Using visual aids in the informed consent process can significantly improve comprehension of issues such as risks and confidentiality, according to a study of pregnant women in Pune, India.

The study looked at an informed consent process the women underwent before receiving HIV testing, but has great relevance to the use of informed consent in clinical trials, says **Anita V. Shankar**, PhD, assistant scientist in the department of international health at the Bloomburg School of Public Health, Johns Hopkins University in Baltimore.

"We feel very strongly that in most settings, women don't understand as much as they need to when participating in clinical trials," she says.

Shankar says that time constraints and long and complicated consent forms can be major obstacles to comprehension, particularly when dealing with populations where literacy or awareness of legal and medical rights is low.

"Simplifying this process and emphasizing the main points with the use of visuals is an important way to enhance understanding by individuals participating in any clinical trial," she says.

Shankar's group, which included researchers from Johns Hopkins and from BJ Medical College in Pune, interviewed the women at a prenatal clinic at a hospital in Pune, which is located near the west coast of India in the state of Maharashtra.

The team tested the women's knowledge of information they had received during the informed consent process for an HIV testing program. During that process, the women participated in a group session of eight to 10 people, and then received individual counseling. Observers also watched the sessions to see how well the necessary topics were covered.

The women were retested after the group made enhancements to the informed consent sessions — most significantly, introducing posters and flip charts with photo illustrations that depicted key concepts for both the group and individual sessions.

The women's comprehension of the information jumped from 38% to 72% with the addition of posters in the group sessions. After similar visual aids on flip charts were used in one-on-one

counseling, the women's level of understanding rose to 96%.

Shankar notes that previous studies at this clinic had shown that about a third of the women were illiterate or had only a primary education. However, she says it's still possible to convey the necessary information with some effort.

"This study demonstrates that complex constructs such as informed consent can be conveyed in populations with little education and within busy government hospital settings," she says.

Another enhancement to the sessions was to provide areas with greater privacy for both the group counseling and the one-on-one sessions. Giving the women a chance to talk privately with a counselor allowed them to ask questions that they may have been unwilling to discuss with the group, Shankar notes.

She says a small team of behavioral scientists developed the visual materials, using digital cameras and computer software.

"We tried to keep the visuals simple and covering only one main issue," she says. "The amount of text was limited and did not cause any problem in comprehension among the patients."

The visual aids, which can be reviewed at the group's web site, www.bjjhumit.org, use photographs to convey different messages, including modes of HIV transmission and statistics about infection.

One page shows two photographs, one of a finger stick and another of blood being drawn from an arm, to illustrate the testing process. Another shows a woman in a screened area, with text describing confidentiality concerns. Yet another shows a person signing a consent form in one photo, and using a thumbprint to sign the form in a second photo.

Shankar says the group originally planned to use cartoons to illustrate the key concepts, but discussions with the women at the clinic showed they preferred to see photographs.

"We tested and retested various versions of the visuals on a representative sample of women to see what they understood from the pictures, and if anything, from the text," she says. After making several changes and reviewing the materials again with counselors, doctors and nurses on the team, the visuals were approved.

Shankar says it's important to take local cultural concerns into consideration when preparing materials. In this case, for example, the study noted that many women in the population have relatively little sense of autonomy — decisions often are made by a woman's father or husband. So the visual aids and counseling sessions reinforced concepts of a woman's right to refuse to participate, and the meaning of her signature on a consent form.

"The type of cultural issues that might arise will, of course, vary by location," Shankar says. "The main difficulty is to convey the complex constructs embedded in most informed consent forms, which are often devised in a country different from where the research is taking place.

"Issues such as confidentiality, autonomy, individual responsibility, individual rights, may or may not be understood by the local population," she says. "Also, the sheer length of many informed consent forms is often a barrier to comprehension."

Shankar says that in an effort to include all the necessary technical and legal information required, the form itself can be so cumbersome that it distracts from true informed consent, rather than enhancing it.

In some studies, the original consent document is composed in English and then translated almost word for word into the local language, which further complicates understanding.

"The informed consent process is exactly that, a process," Shankar says. "The signing of an informed consent paper does not ensure that an individual has truly understood the material discussed."

When setting out to create a more understandable consent process, Shankar recommends that at least a sample of participants be tested on their understanding of informed consent concepts.

"Once the level of understanding has been assessed, the informed consent process should be modified to enhance this understanding," she says. "If visuals or other aids are required, they should be developed and included."

"We need to make the informed consent process effective in communicating the key information to the participant, and properly designed visual aids are one simple way enhance this," she says.

(Editor's note: A complete electronic version of the article can be found on-line at www.biomedcentral.com/1741-7015/2/28. The visuals used in the study are available to be viewed in both English and the local language at www.bjjhumit.org.)

Reference

1. Sastry J, Pisal H, Sutar S, et al. Optimizing the HIV/AIDS informed consent process with visuals in India. *BMC Med* 2004; 2(1)8. ■

Willingness to participate in trials varies by race

Non-Caucasians more suspicious of true intent

Non-Caucasian cancer patients, while just as interested as Caucasian patients in learning about clinical trials, approach their decision to enroll in one differently, according to new study.

They tend to talk to family, friends, and other patients while considering enrollment rather than looking to sources such as the Internet. They are less likely to sign up for a trial unless the chances are high that they'll benefit from it.

And non-Caucasian patients are more than twice as likely as whites to believe that they have been treated as part of a clinical trial without their knowledge — likely a legacy of the infamous Tuskegee study that ended in the 1970s, says the study's lead author, **Charles Wood**, MD, a radiation oncologist at the Hospital of the University of Pennsylvania in Philadelphia.

Wood presented the study in October at the annual meeting of the American Society for Therapeutic Radiology and Oncology.

He says the challenge for investigators and IRBs is to recognize the differing attitudes of white and nonwhite patients and to address them, particularly during the informed consent process.

"I think it's our responsibility to get better," Wood says. "We think we communicate much better with patients than we actually do. If this is going to improve, it's not going to be making the non-Caucasian patients change their attitudes. It's going to come from us."

He also noted that patient-to-patient networks that allow prospective participants to talk to patients who already are part of a clinical trial could be helpful in recruiting minorities.

Study didn't focus on race

Wood's group surveyed 166 cancer patients over eight months in 2003 at two radiation oncology clinics regarding their attitudes toward clinical trials. Patients ranged in age from 15 to 84. The most common cancer diagnoses were breast, prostate, and head and neck cancers.

Wood says that his study didn't initially focus on race, but looked at a variety of factors, including gender, age, and the differences between patients at the two clinics — one a Veterans Affairs hospital and one at the University of Pennsylvania.

But it was the attitudes expressed by patients of different races that became clear in analyzing the data, he says:

— While both groups showed about the same interest in learning about clinical trials, Caucasians were more likely to seek out more information from the Internet (31% vs. 11% for non-Caucasians) or from their doctors (50% vs. 34%).

— Non-Caucasians were more likely to talk to other patients about enrolling in a clinical trial (25% vs. 12% for Caucasians).

— Minority patients were more likely to feel that they would need a better than 50% chance of benefiting from a clinical trial to agree to it (64% vs. 45% for Caucasians). Both groups, however, had similar expectations regarding potential side effects from the treatment.

— Non-Caucasian patients were more than twice as likely as whites to believe they had been treated in the past in a clinical trial without their knowledge (22% vs. 9%).

That last statistic leapt out at the researchers, Wood says.

"We put the question there almost as an afterthought because we didn't think we'd get much of a response," he says. "And that was when our jaw dropped."

Infamous study blamed

Wood, who is Caucasian, says he believes the attitude expressed in the question relates directly back to the U.S. Public Health Service's Tuskegee syphilis study, in which black male patients in Alabama were enrolled in a 40-year study to examine the effects of syphilis.

The men enrolled in those studies weren't told they had the disease or given effective treatments for it. The study ended in 1972, after word of it was leaked. Patients' families sued, and won a $9 million settlement. In 1997, President Clinton formally apologized to the victims.

Wood says the effects of the notorious study still resonate in the minority community decades after it ended. Knowledge of the Tuskegee study combine with conspiracy theories about other public health threats — AIDS, drug addiction, Agent Orange — to create a deep well of distrust that doctors may not be aware of, he says.

"We have the expectation that trust for us on the part of the patient is inherent — that they're automatically going to trust us because we are

their doctor," Wood says. "We need to understand that we are not automatically trusted and at least according to this question, [some of the time], we are not trusted at all."

He says that if researchers know that mistrust exists, they can work to overcome it, and that an understandable, unpressured informed consent process can be a key tool in doing that.

"The non-Caucasian patient sees [informed consent] as a legal loophole for the physician to be protected, regardless of how he acts," Wood says. "I think when you go before the IRB board, they should put a lot of emphasis on the consent form being educational to the patient — explaining in very basic language why they're doing the trial, what you could get out of the trial, and how the trial might hurt you. I think the IRB is a crucial step."

Wood says patients shouldn't be pressured to sign the form immediately, but encouraged to take it home and discuss the clinical trial with friends, family, and community members.

He's unsure how to address the finding that non-Caucasian patients want a higher chance of benefit from a study.

"It's not like you can make any guarantees in the trial," he says. "You shouldn't put any more emphasis on the positive vs. the negative. Just have the knowledge that non-Caucasian patients expect more from the trial."

Wood advocates for an organized patient-to-patient contact that would allow people considering a clinical trial to talk to those already in it. Patients interested in being contacted could give consent to have their names released.

"Patients trust other patients, perhaps more than they trust physicians, because the patient's interest is in getting well," Wood says. "A patient might think the physician's interest is financial, or fame, or any number of other things. I think a patient-to-patient network would just be a huge help."

Most importantly, Wood says, researchers and IRBs need to place the burden of overcoming attitudes such as those identified in this study squarely on themselves.

"We're targeting ourselves because we're just not getting the job done," he says. ■

Do PIs really understand the submission process?

Education specialist offers tips you can pass along

You're all on the same team — right? At times it doesn't seem so. "Sometimes, the way people look at the IRB process and its documentation is that it's just one more hurdle they have to jump through in order to conduct their research," says **Sarah Frankel**, PhD, education specialist at the Human Studies Committee of Washington University School of Medicine in St. Louis. "And, yes, it's part of a process, but the real goal of the IRB is to protect the participants in the study, so it's not being done to prevent research."

It's always a good idea to build rapport with the IRB office and to think of the IRB as a service provider that can assist clinical trials staff and investigators in conducting good research and keeping subjects safe. Keeping this in mind, there are a number of ways the clinical trials office can improve the IRB submission process, including the following:

1. Be proactive.

"Call the IRB and ask questions," Frankel says. "Don't wait until you get a letter from the committee."

Clinical trials staff also should familiarize themselves with the entire IRB review process and learn what the board is looking for in a protocol, she notes.

"Here, we're happy to help people understand the process and why there are different processes in place," Frankel says.

"If you have any questions about a trial that may be submitted, the IRB staff are available and willing to talk to you about how to submit through their system," she says. "At Washington University, we spent a lot of time developing forms to guide the submitter through the process."

It's preferable to give IRB staff a quick call with a question than to submit a proposal that may be incomplete or inaccurate, Frankel adds.

It's also a good idea to observe an IRB meeting, which will help clinical trials staff and investigators gain insight into why certain questions arise and who the IRB members are, she adds.

2. Develop a good foundation in research ethics.

Clinical trials staff who have a good foundation in research ethics and clinical practice will understand better why things are done the way they are during the IRB review process, Frankel notes.

"Having that foundation helps you to know what to expect," she says. "We're fortunate at

Washington University because we have workshops and course offerings by the IRB."

And human subjects protection and ethics courses need to be taken by study coordinators, as well as researchers, Frankel says.

"This is so they will understand their role and what's happening and help the investigator that much more," she says.

3. Build bridges between IRB and study coordinators.

The IRB should have a lot of contact with study coordinators since this is part of building rapport between the research team and IRB, Frankel says.

This bridge includes an open door policy in which study coordinators can call the IRB whenever there's a question or concern.

"Principal investigators [PIs] are not always available and many have other duties besides research, so that's why it's important that the study coordinator is well trained," Frankel says.

Also, it helps if a protocol is written with a lay audience in mind, since some IRB members are not scientists and may end up asking more questions if the technical writing of a protocol is too complex, she says.

4. Make certain study coordinators do not serve as PI substitutes.

One common mistake is that busy PIs will send a study coordinator to the IRB meeting, and this could lead to inadequately answered questions and a delay in approval, Frankel says.

"When the committee invites the investigator to speak, they really want to see the investigator," she says. "It's all right to invite a study coordinator to come along with the investigator, but occasionally an investigator will send a study coordinator instead."

When the IRB begins to ask questions about the fundamentals of the study, including design and methodology, the investigator is the person who will need to answer these items, Frankel says.

"The study coordinator may give an answer, but maybe not give as in depth an answer as the committee is looking for," she says. "Usually, if the investigator is asked there's a point of contingency that needs to be qualified, and they may need background to clarify a contingency point so they can move forward."

5. Check IRB application to make certain everything is included.

Another common mistake is that PIs sometimes forget to include a minor point in their description of a study, and this could lead to more paperwork down the road.

For example, a study designed as a retrospective chart review for the years 1999 and 2000 should include both years in the proposal, but perhaps also include 2001 if there's a possibility researchers will want to analyze those data as well, Frankel says.

"That's something minor, but any change to your protocol you will want to get IRB approval first," she says.

6. Be very familiar with regulations regarding expedited review and exempt research.

"It helps if research staff understand the types of studies deemed minimal risk," Frankel says.

It also helps if research staff understand the policies the IRB has for using the categories of expedited review and exempt research, Frankel notes.

"At some institutions, everything goes to the full board, and other institutions like ours have an expedited review mechanism," she says. "We have individuals who sit on the full board and are designated to do the review."

Another benefit to learning the regulations is that when research staff begin to look at the types of studies that fit expedited and exempt, they have a better understanding of the study's level of risk, Frankel adds.

"Maybe someone expects a study to be a minimal risk study, but the protocol is much more complex than the other ones in that category," she says. ■

Public education program successful with PAD trial

Research coordinator explains process

The Public Access Defibrillation (PAD) trial experience offers clinical trial administrators a firsthand look at how to conduct extensive public education in the absence of individual informed consent.

The trial, funded by the National Heart, Lung and Blood Institute, was designed to evaluate how well nonhealth care providers, when equipped with training in CPR and automated external defibrillators, could improve the survival rate of sudden cardiac deaths in the United States, says **Shannon Stephens**, a research coordinator at the University of Alabama at Birmingham (UAB) in Birmingham.

PADs were installed in hundreds of public areas, including shopping malls and recreational facilities in 24 communities across the United States, and personnel at the PAD sites and control sites were trained in CPR, Stephens says.

"They were taught how to respond if someone has a cardiac arrest while on the property," says Stephens. "We trained volunteers and tried to identify staff who would be on site anytime the building is operational."

The 2½-year study showed that survival rates from heart attacks were double in the sites that had PADs, he says.

Part of the IRB process included a waiver of informed consent because cardiac patients, obviously, are unable to consent to enrollment at the time they could become a subject, he says.

"It was the goal of the IRBs to approve the process that's outlined under the waiver of informed consent," Stephens says.

There were 101 IRBs that approved the study, and the median time it took to achieve approval was 108 days.

The IRBs required study sites to conduct community consultation and public disclosure, as part of the regulations under 21 CFR 50.24, and investigators conducted nearly 12,000 activities to satisfy these requirements.

"Each IRB was responsible for their localized community," Stephens says. "Most IRBs requested about two revisions."

Full-scale campaign

The IRB handling the UAB study site required clinical trials staff and investigators to hold a public forum to discuss the trial, several press releases, the distribution of letters and brochures, and media coverage in radio, print, and television, he reports.

"Our public forum was held at a centralized community meeting facility on the UAB campus," Stephens says.

The principal investigator spoke about the clinical trial and why scientists felt it important to research the topic, he recalls.

"We gave a brief presentation of the project and opened the floor to questions," Stephens says. "We addressed a few concerns, and the community was very supportive of our research endeavors."

The forum was advertised in radio, print, and television, and a few dozen people attended it. Also, it was covered by print and television reporters, who conducted follow-up interviews, Stephens recalls.

"At our site, we had a localized steering committee representative of the general public," he says.

Committee members included local physicians, community leaders, politicians, local clergy, IRB representatives, and local emergency services and fire agency responders, Stephens notes.

Since PAD has been on the market for decades, investigators easily could answer public questions about its safety.

"Anyone in a pulseless rhythm can have the device placed, even if they have a pacemaker," Stephens says.

Also, investigators and clinical trials staff addressed religious objections by training sites to not use the device on people who wear a wristband that identifies them as having signed a do-not-resuscitate (DNR) document, he says.

Of course, each state has different DNR requirements and so this method of identifying people who would want to opt out of the study would be handled differently elsewhere, Stephens adds.

The UAB media office assisted with writing and distributing press releases about the trial, and the UAB clinical trial office ran advertisements in a variety of newspapers, and other media, Stephens says.

"We had a great deal of coverage when the trial began," he says.

A flyer was developed that informed the community of what the trial was, and it was distributed at all of the clinical trial sites, including the control sites, Stephens says.

The flyers contained basic information about the trial, including how long it would take place, who supported it, and contact information for the IRB director, principal investigator, Stephens, and the research team.

"We had another flyer that was circulated through the media relations office to local media outlets about the training for the trial," he says. "And we had media coverage when the devices were placed on sites."

Since the trial was blinded, the clinical trials office could not advertise the lives that were saved by PAD, so all trial updates simply reinformed the public that the trial was ongoing, Stephens says.

"We did have one incident where a local high school that was unaffiliated with UAB and the study had a PAD save," he says. "During that

media coverage, we notified the community that there was a nationwide clinical trial currently underway that as looking at automated external defibrillator placement in public."

The UAB clinical trials staff worked closely with the IRB and its director and chair to monitor this process and the study, Stephens says.

"For the first two years, our IRB required quarterly reviews; and after two years, they moved it back to biannual reviews," he says.

"The big thing is to have a close working relationship with the IRB office," Stephens says. "The earlier you can begin those discussions and help to identify the objectives and what the federal government requires and then collectively work toward meeting those requirements, the more efficient and effective the process will be." ■

Hopkins studies effect of violence on children

Particular attention paid to assent, consent

In a popular music video, the star is shot in one scene, then in the next, a small plastic bandage covers the purported wound as he continues singing with an arrogant swagger into the next verse. Guns and images of violence are popular entertainment in this country — featured in the plot lines of popular movies, music videos, TV shows, and video games.

A recent study by researchers at Johns Hopkins Medicine's Hopkins Injury Prevention and Outreach Collaborative (HIPCOC) shows that countering these popular images with realistic images of the consequences of violence can significantly alter the attitudes young people have about aggression and violence.

The study subjects, participants in a Baltimore-area Police Athletic League after-school program, were given a specially designed pre-test to evaluate their existing attitudes about guns and violence. Following that test and then a special presentation by members of the research team, the subjects were taken to visit the emergency department at Johns Hopkins Hospital.

"Our study suggests that the kind of romanticized version of violence shown on television can be countered by more frank and open discussions and displays of what violence really does to the body," says **David C. Chang**, PhD, MPH, MBA, a coauthor of the study and a graduate fellow in the Department of Health Policy and Management in the Johns Hopkins Bloomberg School of Public Health, and in the Division of Adult Trauma at The Johns Hopkins Hospital.

Researchers at Hopkins, led by trauma surgeon Edward Cornwell, MD, conducted a controlled experimental study exposing a select group of young people, ages 7-17, to Hopkins patients injured as a result of gun violence, then assessed the impact on their attitudes about violence and aggression.

Getting consent

As expected, getting informed consent from a minor population proved challenging.

The IRB required researchers to get at least assent from all subjects. The parents of all of the children were required to give their consent in order for the children to participate in the project.

"We talked to the kids directly and told them what it was about," Chang explains. "In really simple language, we said, 'We are going to take you to the hospital, see these patients, talk about violence, we are going to ask you some questions about your attitudes before and after.' So, that is the assent process and asking them to sign the assent form. We also sent home a more detailed consent form for parents to sign."

None of the parents objected to the children being taken to the hospital to visit victims of gun violence, he reports.

The biggest problem was getting the consent forms home with the potential subjects.

"The loss to follow-up was pretty high. We had about 97 kids initially, but only about 40 went through the post-test. There were only about 50% who were organized enough to remember to bring their consent slip. So, we had about a 50% completion rate," he notes. "That is actually where the missing link was, a lot of kids just lost the form on the way home. We had some parents come to pick up kids at the center and we asked them about the study at the center and consented them there — that is where we got a lot of the consent."

The study also was hampered somewhat by the loss of a planned control group for comparison. Originally, researchers planned to administer the pre-test and post-test questionnaires to a group of students of similar age and demographic distribution at a local alternative learning center, which at the beginning of the study had not yet opened

and would not have had access to the research intervention — the visit to the hospital and specific exposure to images of the real-life consequences of violence.

However, the administrators of the center withdrew their consent for the research after the initial questionnaire and meeting, so researchers were unable to include those subjects in the study results.

Protecting privacy

At the beginning of the study, researchers gave the participants the pre-test questionnaires assessing the youths' attitudes regarding interpersonal conflict, including their likelihood to act violently.

Only information about the participant's age and gender were collected by the surveys. All pre-test surveys were assigned a number, with the researchers asking subjects to remember their number and use only the number on the post-intervention questionnaire.

In this way, the survey results were anonymous.

As the intervention researchers conducted educational sessions with the children, in addition to the ED visits, showing explicit photos of actual trauma patients treated for gunshot wounds.

The HIPCOC team compared the photos to rap videos that glamorize violence. For example, one music video shown portrayed a singer getting shot, and in the next scene he continued life as usual, wearing a small Band-Aid on his face. By contrast, the images Cornwell and colleagues offered to the participants included those of a man whose abdomen was torn open by a bullet wound, and a pregnant woman who was shot in the abdomen, killing her 8-month-old fetus.

A follow-up survey completed by 48 youths showed a significant reduction in quantified beliefs supporting aggression.

Beyond the study

Going forward, the research team is putting together a video, using footage from music videos and footage from the *Hopkins 24/7* series, to be used by different groups as a violence prevention tool.

Once the video is finished, the researchers want to do another evaluation, similar to the original study using only the video as an intervention.

Portions of the youths' visits there were captured on the ABC television miniseries *Hopkins 24/7*.

"On MTV, you see people get shot and get up with a bandage on their head. On *Hopkins 24/7,* you see a patient who was shot talking about his life and how it has permanently changed," Chang says. "The show did a good job of capturing the kids' reaction. When they went into the room to see the patient, the wound was very clean, it was almost healing, it looked good for a clinical perspective, but many of the kids looked away and that was captured on camera. So, we actually contrast that to the cleaned-up image that MTV showed." ■

OHRP decision charts updated

The Office for Human Research Protections (OHRP) has released an updated set of Human Subject Regulations Decision Charts, which can help IRBs determine whether an activity amounts to human subjects research that falls within the realm of the IRB's review process.

The charts look at decisions concerning whether the activity is actual research, whether an IRB review can be conducted by expedited procedures and whether informed consent can be waived.

The charts are available at www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm. ■

COMING IN FUTURE MONTHS

- Charging sponsors for storage to defray IRB costs
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CE/CME objectives

For more information on this program, contact customer service at (800) 688-2421; e-mail: customerservice@ahcpub.com.

The CE/CME objectives for *IRB Advisor* are to help physicians, nurses, and other participants be able to:

- **establish** clinical trial programs using accepted ethical principles for human subject protection;
- **describe** the regulatory qualifications regarding human subject research;
- **comply** with the necessary educational requirements regarding informed consent and human subject research;
- **apply** the necessary safeguards for patient recruitment, follow-up, and reporting of findings for human subject research;
- **explain** the potential for conflict of financial interests involving human subject research;
- **discuss** reporting adverse events during research. ■

CE/CME *questions*

Physicians, nurses, and others participate in this continuing education program by reading the article, 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. **The semester ends with this issue.** 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.

21. The use of placebo controls in a clinical trial is useful only to determine the efficacy of the drug being studied.
A. True
B. False

22. A study of pregnant women in Pune, India, showed that comprehension of informed consent was improved by:
A. The use of flip charts and posters in educational sessions.
B. The use of question-and-answer forums in large groups.
C. Encouraging family members to attend informational sessions with the women.
D. None of the above

23. In a study of attitudes regarding clinical trials, what percentage of non-Caucasian cancer patients believed they previously had been treated in a clinical trial without their knowledge?
A. Fewer than 5%
B. More than 20%
C. Nearly 50%
D. More than 75%

24. Regulations of 21 CFR 50.24 permit studies to obtain a waiver of consent if they meet which of the following stipulations?
A. Surrogate consent
B. Community consultation and public disclosure
C. Distributing opt-out wrist bands
D. All of the above

Answers: 21-B; 22-A; 23-B; 24-B.

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