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## Creative suggestions for getting consent from decisionally impaired

*Study with schizophrenia patients yields best practices*

**A** trial studying antipsychotic drugs provides best practices for handling ethical issues involving decisionally impaired persons. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study was an 18-month study in which it was anticipated that some participants would lose decision-making capacity during the course of the study.

Decisional impairment concerns a person's potential inability to protect his or her own interests, and it encompasses both the capacity to provide consent and how voluntary the consent is, says **Susan J. Delano**, CIP, deputy managing director of the Research Foundation for Mental Hygiene Inc. of Menands, NY. The Research Foundation is a nonprofit corporation that administers grants and contracts for research conducted in facilities operated by the New York State Department of Mental Hygiene.

"This was a study where they thought carefully about building in additional protection for subjects and created a subject advocate mechanism," Delano says. Delano has an oversight role relative to IRBs that function in all of the department's facilities.

"The CATIE study brought in this subject advocate who participated in the consent process and had the authority to withdraw subjects from the study under certain circumstances," Delano says.

For example, if the original risk-benefit ratio changed substantially, the subject advocate could withdraw the subject from the study, she says. "They were careful about assessments of capacity up front and processes to make sure the consent process was informative for subjects," she says. "This was quite a step forward in terms of providing a protective mechanism for subjects."

Even with the added protection of a subject advocate, there needed to be an analysis to see whether the subject advocate mechanism was sufficiently protective, Delano notes. "Decisional impairment creates vulnerability, and there's a potential inability for a person to adequately protect his or her own interest," Delano explains. "They might be

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unable to evaluate how their own participation is affecting them or to look at any changes in their own situation.”

IRB considerations might include the following, Delano says:

- capacity assessment;
- decisional impairment versus diagnosis;

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#### Editorial Questions

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- decisional impairment that is not related to mental illness, and this could include substance abuse, stress, and medical conditions;
- other factors creating vulnerability, including incarceration, stigma, lack of health insurance, and educational level.

A further step ethically would be to allow capable participants to appoint someone who can act as a surrogate decision maker should the participant lose decision-making capacity, Delano suggests.

“Within our system we do allow this,” she adds. “The surrogates have a broad range of authority to withdraw subjects from research, and they have the ability to make amendments in the study.”

For example, if new information becomes available about side effects, and these need to be communicated back to participants, who will then need to provide consent, the surrogate decision maker could say that the participant could continue in the study, Delano says.

Surrogates are used sparingly. “They are usually a family member,” Delano says. Typically the surrogate is selected by a participant who has full decision-making capacity at the beginning of a study. If the participant loses decision-making capacity, the surrogate would provide consent within the limitations determined by the participant when the surrogate was chosen, she explains.

“The subject would say, ‘This person has authority to act as my surrogate, but if the risk level increases significantly, then I must withdraw from the study,’” Delano says.

There are other protections that could be used, including:

- Using different methods, timing, locations in the consent process;
- involving family members or friends of participants;
- educating the surrogate;
- making consent an ongoing process;
- limiting or excluding participation of vulnerable populations;
- providing a consent auditor who assesses the quality of the consent process and procedures;
- providing a medical monitor who has the authority to withdraw the subject;
- using a data safety monitoring board.

It's important to note the decisional impairment can occur in situations other than mental health research, she adds.

“People need to understand that just because they aren't reviewing psychiatric research doesn't

mean these issues aren't relevant to them," Delano says. "There are other situations in which lack of capacity is clearly an issue."

Another issue to consider is that states have different laws regarding decision-making capacity, and these must be a part of any policy regarding providing greater ethical safeguards for subjects with limited decision making capacity, Delano says.

The CATIE study's use of participant advocates is a good model for IRBs and institutions that desire to improve their ethical oversight for vulnerable populations, she notes.

"The CATIE study was a very thoughtful and well-planned protective mechanism, and it's one that, while we could tweak, it really went a great distance toward providing additional protections," Delano says. ■

## IRB puts its imprint on recruitment registry

*Confidentiality of collected information is key*

Thanks to a volunteer recruitment registry at Vanderbilt University, potential research subjects — even those not currently being treated at the university's medical center or by affiliated doctors — can make their names and health information available for future use.

Though the project doesn't sign potential subjects up for a particular protocol, the IRB had a strong hand in ensuring that the registry advertised itself appropriately and kept registrants' personal medical information confidential, says **Denise Roe**, LPN, CCRP, CIP, director of the IRB at the Nashville-based institution.

"It's sort of that first step of recruitment," Roe says. And that's why they decided to run it through the IRB. "The real issue for us was separating it out — to actually make it a true recruitment protocol, so it's not tied to any specific treatment protocol."

The project was begun in an effort to create a simple tool that could direct potential research volunteers to the researchers who might want to enlist them in their studies. Often, unsolicited volunteers would call Vanderbilt telephone operators, who would have a hard time deciding where to route calls.

Developers from the biomedical informatics department created web-based software that

allows volunteers to submit their own health information. A volunteer filling out the web questionnaire is asked about demographic information, tobacco use, and to list any diseases or conditions he or she has.

The information is stored in a secured database available only to researchers with IRB approval for studies. Researchers can use the software to pull out potential volunteers with health histories that meet their needs, and then solicit them directly for a study.

It's different from Vanderbilt's clinical trials center web site, which lists available active studies at the university.

Roe says the volunteer registry has been successful in drawing people from both inside and outside the university community. (To access Vanderbilt University's Clinical Research Volunteer Registry, visit the web site at <https://www.volunteer.mc.vanderbilt.edu/>.)

### **Confidentiality concerns**

The project first went before the IRB in 2002 in a fairly simple form, which prompted volunteers for less health information than the current version does. At that time, the board's chief concern was the security of the information, says **Dena Johnson**, CCRP, CIP, a protocol analyst at Vanderbilt.

"[IRB members] have always wanted to make sure that participants who volunteered for this would not be at risk for any of this information being disclosed," Johnson says. "That was a lot of the reason they kept it at a full committee review for several years. They wanted to see what types of things might need to be reported at the time of continuing review."

Roe says that at the time, the IRB had several tech-savvy members who questioned the developers closely about how the software would work. Some members even went to the trouble of registering, so they could test the process themselves.

Over time, Johnson says, no one came forward with concerns related to security breaches.

In 2004, the IRB, satisfied that the security of the system was working, decided to allow continuing review to be expedited, Johnson says. The IRB reviewed the project in full again last year, when more direct questions about volunteers' health were added to the online form.

Johnson says the developers had wanted to ask volunteers to allow researchers to access their

medical records prior to a formal consent process, but the IRB had reservations about the idea, and the developers withdrew it.

Roe and Johnson say there are other issues the IRB looked at in reviewing the volunteer registry proposal:

- **Advertising.** Ads promoting the registry in the local newspaper and elsewhere had to adhere to the same strict standards Vanderbilt requires of all study advertising, even though the registry doesn't solicit for a particular study. The advertising includes a toll-free telephone number people can call if they don't have Internet access and want to submit information to the registry.

- **Explaining privacy protections.** Johnson says a statement in the online form explains exactly who may access the volunteer's information and for what reason. Some of the language in that section was taken directly from the university's HIPAA template language.

The notice explains that the information will be kept indefinitely unless the volunteer requests deletions or wishes to withdraw his or her name entirely. Roe says a volunteer can unsubscribe online, in the same way that he or she registered, or by phone or mail.

- **Excluded groups.** Roe says certain groups are not included in the registry, including vulnerable groups such as pediatric patients and dementia patients who are unable to fill out the form themselves.

Oncology patients use a registry system through Vanderbilt's cancer center, a distinction Roe says is deliberate. The cancer center has its own toll-free number for research volunteers, answered by the center's staff.

"I think they very much wanted to have that human contact, she says. "Because they don't do just research, they arrange for treatment — doing intake forms and facilitating appointments."

### **Working with IT**

Roe says that for a project like this to be successful, there needs to be a partnership between those on the information technology side and human subjects protection experts who can ensure volunteers are being protected.

"Oftentimes, what you see happening is really great developers going off and developing something and they've never once taken the time to get the input from the content experts," she says.

She credits Paul Harris, PhD, a research associate professor of biomedical informatics who

spearheaded the project, with working closely with the IRB members and staff throughout the development of the registry.

"Dr. Harris was very open in the beginning to hearing the committee's concerns," says Roe. "That's why they collected so little information, until they felt certain that they had enough checks and balances in place to really provide the confidentiality and privacy they felt was necessary. I think that's the way to make it successful."

She says IRBs will increasingly be asked to review more of these non-traditional types of projects.

"I think we're going to receive more proposals that require us to think outside the box," Roe says. "But if you do due diligence, it can work. You follow the regulations, you ask good questions and you make sure that investigators doing this type of research understand what the committee's concerns are. "I think that was just instrumental in this proposal." ■

## **QI program identifies deficiencies, educates**

*Program smoothes process with investigators*

A well-run human research quality improvement (QI) program can be an IRB's best friend, working with investigators to help them prevent common mistakes and to communicate better with the IRB, while avoiding the back-and-forth questioning that can drag out the review process.

At Partners HealthCare System in Boston, the Human Research Quality Improvement Program utilizes a combination of investigator-friendly onsite review and targeted educational sessions to bring investigators up to speed regarding regulatory and institutional requirements, clarifying what is needed and how to provide it, says **Delia Y. Wolf**, MD, JD, director of the Partners QI program and assistant professor of radiology at Harvard Medical School.

In fact, the IRB often refers investigators to the QI program when study submissions, particularly continuing review applications, need clarification, she says.

"The IRB is appreciative of our existence and our expertise," says Wolf, who for six years was one of the chairs of various Partners IRBs. "They advocate our program [to investigators] because

they know we can help both parties by expediting the review and approval process. Once the investigator gets the green light from the IRB to begin his/her research, we provide a valuable resource throughout the life of the study.”

Partners’ Human Research QI program recently received an Award for Excellence in Human Research Protection — Best Practice from the Health Improvement Institute.

### **Program starts small**

According to Wolf, the program was established in 1999 as a part of an overhaul of the Partners human research protection system in the wake of highly publicized problems with human subjects protection at other institutions.

Wolf says Partners chose to be proactive to ensure compliance with federal and state regulations governing human research, and to promote an environment in which research would meet the highest human protections standards.

“We realized no matter how hard we worked at the IRB end, if the investigators are not following what the IRB required them to do, it was still a wasted effort,” Wolf says. “For example, you can revise the consent form with multiple back-and-forth correspondences, and investigators could still later use the wrong version.

“Situations like these prompted us to establish a program that would work with investigators and help them, making sure they were doing what the IRB required and expected them to do.”

Although she was QI program’s only member at first, Wolf gradually built the program, adding staff as its size and scope increased.

The program initially was focused on conducting onsite reviews to determine what investigators were doing and to identify common deficiencies. Those onsite reviews still are an important part of the QI program; staff conduct up to two to three such reviews a week.

“We review study records and we interview study staff and investigators,” Wolf says. “We also review the IRB file before we go on site, so we know what the study is about and what documents should be on file.”

Wolf says the goal of the onsite review is to offer assistance to the investigators in a friendly manner, rather than functioning as auditors who may be viewed with resentment.

“People have a conventional concept that ‘quality assurance,’ means ‘audit,’” she says. “Right away they’re on the defensive, making it

hard to do our job. The improvement approach is a better one because it gives the message to investigators that ‘We’re not here to audit you — we want to provide more resources to you, to offer services.’”

In fact, Wolf’s staff do not report back to the IRB with their findings, unless the IRB had specifically requested the review.

“We are independent from the IRB, and that is a very attractive feature for the investigator,” she says. “If we conduct our routine onsite review and identify deficiencies, we follow up with investigators, explaining how to correct and avoid deficiencies and how to report violations to the IRB, if necessary.”

Wolf says one of the important accomplishments of the QI program is that it teaches investigators how to properly correct errors in documentation when they discover them in the future.

“There are so many mistakes that can be made,” she says. “Everybody tries their best to avoid them, but you still make mistakes. It’s part of being human.

“The good news here is that we’ve taught people how to correct mistakes they’ve already made — for example, writing a note to file, instead of back-dating and trying to ‘fix’ the mistake,” Wolf says. “We tell people, ‘Don’t be afraid to report your violations. It’s not the end of the world if you have to document a mistake, but it may get you into trouble if you try to hide them or correct them in your own, inappropriate way.’”

Wolf says the number of deficiencies identified in onsite reviews has substantially decreased over the life of the QI program. She says that while it’s impossible to review every study conducted at the institution, she’s made an effort to work with as many investigators as possible, so that they can learn from the process and make improvements with future studies.

### **Adding education to the mix**

The second prong of the QI program, its educational component, was developed in recent years, after Wolf’s staff had a chance to work with more than 500 investigators and had learned what the most common problems were with meeting regulatory requirements.

They began a series of education sessions, but kept them small and specifically targeted to particular study groups. “For example, when we realized there’s a lot of investigator-initiated IND

studies, we had a session addressing sponsor-investigator responsibilities," Wolf says. "In the smaller setting, people start to talk more freely and share their experience."

Wolf says that larger, more generalized educational sessions often don't provide as much substantive information to participants.

"With small, group-focused education, we provide more intensive information to the people who really need it and want it," she says.

The QI staff conduct about two to four such sessions monthly, on topics such as good clinical practice guidelines, data and safety monitoring plans, writing standard operating procedures for a study site, and continuing review submissions to the IRB.

Wolf works with the staff to develop the sessions, analyzing the findings from recent onsite reviews and utilizing case studies and hypothetical situations to illustrate the points.

While Wolf currently has six QI program staff members, she says smaller institutions with fewer resources shouldn't be scared away from attempting similar programs themselves. "When I talk with people from other organizations, they say, 'Oh, you have a huge organization,'" she notes. "Yes, right now I have six people, but I started with one. The majority of onsite reviews in the first three years were conducted by three people."

What's important, Wolf says, is that the staff be well qualified. She says most of her staff have graduate degrees — masters and PhDs — and direct experience in the field of clinical research.

"Some institutions tend to think this is an administrative role — they're auditors, looking at paper, so they don't need specialized background and training," she says. "I wouldn't agree. If you have very knowledgeable, qualified people, with terrific interpersonal skills, you really don't need to hire a lot of them. It is quality, not quantity."

Wolf also suggests using templates and checklists to help facilitate consistency and more efficient reviews.

While she currently doesn't see the QI program branching out into new activities, she does have a goal of working with all the institution's investigators, including those who may have been reluctant to participate in earlier years when the program was newly developed and working toward establishing a reputation.

"There's always a group of people who are very diligent, they have good records and they usually are the first ones to sign up for QI serv-

es," Wolf says. "There are others who say they're doing fine, but actually, they could use some help from us. These are the investigators we would like to find and work with."

"All of our education and services are offered on a voluntary basis. Our program's challenge is to attract those investigators who haven't volunteered to get help from us. Because based on our experience, after investigators have worked with us, they like us, and want us to be their regular resource." ■

## Electronic system improves IRB record management

*System reduces human error*

A well-organized record keeping system is essential to IRB functions. IRB and research offices might improve their office documentation and efficiency by following a best practice model established by a large research institution.

The Pennsylvania State University, located at University Park, has a research program that handles about 2,500 active study protocols per year, involving human participants research, and there are nearly 1,500 new protocols submitted each year, says **Mary Becker**, RN, CIP, associate director of the Office for Research Protections at The Pennsylvania State University. The research program's records include research protocols, committee functions, noncompliance reports, adverse events, training, conflicts of interest documents, and research misconduct reports, Becker notes.

"What we have is a wonderful system called the PRAMS system, for protocol review and management system, that is actually an electronic database," Becker says. "It allows us a checks-and-balance system because it shows us the associations between different protocols."

PRAMS, which stands for Protocol Review and Approval Management system, was created with an NIH enhancement grant, Becker says. Having the database reduces human errors and makes it easy for research staff and others to keep up with what's happening in various committees, she says. Also, PRAMS automatically generates a one-year expiration date based on the date of the protocol's last review, Becker adds.

"Reminders are sent out automatically to investigators 75 days prior to expiration and again 45 days prior to expiration, so our staff

does not have to generate reminders," she adds. "And if no continuing review application has been received, then it sends out an expiration notice the day it's due to expire."

The system also assists with training records. "We have an on-line IRB training course, and when people come in and take the training and complete a quiz, a record of it comes up on our system and it's entered into the automated PRAM system," Becker says.

When protocols are submitted, if the personnel involved have not completed training, then the system will notify the IRB office, she says.

"The system will not allow us to give a final approval in the electronic system if there's a missing training record for someone involved in the study," Becker explains.

There also is an automated flag for Health Insurance Portability and Accountability Act (HIPAA) training, she adds.

Likewise, if there's biosafety training or some other training that's required for a particular study, then the system notifies the research office about who has completed the required training and who has not, Becker says.

The system will not permit a user to skip through processes, and so it eliminates human error, she notes.

"It also gives us a profile of the reviewers, so the IRB office can go in and look at the IRB [workload] and office members and see how many protocols each person currently is reviewing, and it notes the training and expertise of each reviewer," Becker says.

The next step for PRAM will be online submission of protocols, Becker says. "We're half-way between electronic and paper submissions at this point," she says. "Once we have an online submission for applications, our reviewers will be able to access protocols online and review them through their own system, and the principal investigator could check the status of the review and application online."

The biggest challenge in switching from a paper to electronic system has been trying to customize the application, Becker says. "We call it our wizard because as you are coming to a question, if you answer it one way it will trigger another set of questions, and if you answer another way it will skip those questions and trigger a different set," she explains. "It has been challenging to try to capture everything in this on-line application and make it work so that investigators don't take hours completing it."

The goal is for investigators to spend 30 to 40 minutes on the electronic application, Becker says.

"The best part of the electronic management system is its accuracy," Becker says. "It puts a check and balance system in place, and I think that's a really positive thing." ■

## IRB can now move huge data files with technology

*Send large files without bogging down network*

A new technology solution can help research institutions with a nagging logistical problem — ever-larger files that must be routed within an institution or to external partners.

Accellion Courier, a product of Accellion Inc., in Palo Alto, CA, allows a user to attach huge, secured data files to e-mails without overwhelming an institution's computer system or those to whom the e-mails are sent.

**Y.F. Juan**, director of product marketing for Accellion, says the product has been particularly popular with researchers who must exchange data files with their colleagues.

But its features also have implications for IRBs, who can use Courier to ensure that privacy-protected information is being shared securely, or even to distribute IRB information to members.

Courier is not a software product, but a file transfer appliance that can move even multi-gigabyte files within and outside an organization, without the hassle of using a file transfer protocol (FTP). Used in conjunction with another Accellion product, Accellion Attachments, a file can be attached to an e-mail and sent to another user without causing system performance problems — slowdowns or crashes — on either end, Juan says.

"Typically, a user sends a file as an e-mail attachment. The problem is that when you attach a very large file, it has a severe performance impact," Juan says.

"There are a number of highly technical solutions you can use, but the average users are researchers and faculty and they just don't need this kind of headache," he says. "With an appliance configuration, it makes it much easier to manage. Essentially, you get a box, you plug it in, and you don't have to worry about it."

Instead of working through the institution's own e-mail system, the Accellion Courier sets up a separate, parallel channel, one that can hold

very large files and allow designated recipients to tap into it and download the files.

A user creates an e-mail in the normal way, but instead of using a standard attachment — for example, the “paper clip” icon in Microsoft Outlook or Lotus Notes — he or she instead clicks on an Accellion icon, linking the e-mail to the uploaded data file.

The recipient clicks on the link and is routed to a completely separate, secure file transfer channel, which doesn’t impact the recipient’s existing e-mail system.

“It creates a sort of tunnel that goes into the appliance, requests a file, and downloads the file,” Juan says.

### **Two way file transfers**

One of the unique advantages of this system is that the recipient can also send information back through that tunnel, regardless of his or her computer system limitations.

“There are a number of solutions out there that are designed to handle large files and it usually goes in just one direction,” Juan says. “When the external party working on a project may need to send a large data file back, it can’t. It’s a huge problem. What this does very well is that it allows external people to send (large) files to you.”

That ability to allow large files to be sent from external users was one of the factors that prompted Cornell University to begin using Accellion’s products, says **Steven M. Erde**, PhD, MD, Senior Director of the Office of Academic Computing at Weill Medical College, Cornell University, Ithaca, NY.

“We’re probably not that unusual an organization,” Erde says. “We had a lot of people who were increasingly frustrated with the ability to attach multi-megabyte e-mail attachments to other institutions and colleagues.”

He says Cornell developed its own FTP system to allow faculty to send out large attachments, but it became increasingly difficult to maintain. Accellion’s products solved a number of the institution’s problems. “It was really easy to use,” he says. “And it allowed outsiders to create accounts to send stuff in, because previously, we could only have people send stuff out.”

He says Accellion was able to configure the appliance so that external users connecting to it would see a screen that resembled Cornell’s existing web site.

In all, he says, adding on Accellion “has been a

pretty painless step. Zero complaints, zero down time. Just the kind of thing you like.”

Juan says there are a number of security features included in the Accellion products. The file transfer connections themselves are set up as https Web connections, ensuring the security of the file transfer. Files themselves can be encrypted.

There are three levels of authentication that a user can set to ensure that only the proper recipients see the file.

At one level, anyone receiving the e-mail link could download a file without authenticating themselves. The second level would require authentication, but allow a person to forward a link to anyone within his or her organization. The highest level would prevent usable links from being forwarded.

Organizations can configure the level of security they desire, Juan says. It can be integrated into the institution’s existing login and password protections.

Juan says health care research organizations are increasingly looking to these type of protections to ensure that privacy requirements of HIPAA are being met, as well as to protect proprietary information.

### **Potential IRB uses**

Other Accellion functions that IRBs could find useful include:

- **‘Sunsetting’ a file.** The user “sunset” a file, making it available on the appliance for a set length of time. This frees up space for other files, but Juan says users are increasingly telling him that they use this feature to ensure that they’re working with the most recent updated version of a file.

“Especially in research, where people exchange files very frequently, sometimes people get confused,” he says. “If you sunset a file, even if someone goes back to the old e-mail and clicks on it for whatever reason, it will not be there.”

An IRB, for example, could use the sunset function to be sure that as protocols are revised, only the most recent version is available.

- **Return receipts.** When the recipient of an e-mail clicks on the Accellion link to access a file, the sender is notified via e-mail. Juan says some commercial software vendors use this function as official notification that they can bill a client. IRB staff could use the function to ensure that members have received needed information for an upcoming meeting, for example.

At Cornell, Erde says the IRB is not an official user of the Accellion product, because the institution hasn't gone to a completely electronic system. But he believes it's probably being used informally for some file transfers.

He says it would be a simple way for an IRB to distribute packets to its members, particularly if there was printed material that needed to be scanned.

"If you have scanned [documents], you're going to start seeing massive files," he says. "You can have a distribution list set up and you can just plop it in and say 'Here are all your cases to look at,' he says. "Our IRB is not using it for that function, but it would work fine."

The cost of the Accellion appliance varies based the number of users and the configuration required for an institution. Juan says the cost ranges from about \$3,500 for the smallest available box to about \$40,000 for an appliance that supports 5,000 users.

In addition to that one-time cost, a client pays a yearly licensing fee of 20% of the price.

*For more information about Accellion file transfer products, call (650) 739-0095 or visit the company's web site at [www.accellion.com](http://www.accellion.com). ■*

## New journal focuses on research ethics

*June issue covers ethnography*

A new journal about research ethics includes articles in June 2006, that discuss how the ethics review process has gone wrong for qualitative research, including ethnography.

"The basic problem is that participant observation and ethnography, in which one becomes a part of the group and interacts in a natural way, does not fit the medical model that ethics protocols are designed for," says **Joan Sieber**, PhD, editor of the *Journal of Empirical Research on Human Research Ethics* (JERHRE, pronounced "Jerry"). Sieber also is a professor in the department of psychology at California State University, East Bay in Hayward.

JERHRE is a nonprofit journal published in print and online by the University of California Press. Its first quarterly issue was published in March 2006.

The journal's chief goal is to improve ethical problem solving in human research. Without evidence-based problem solving, many questions

about the ethics of human research are unsatisfactorily settled by applying a one-size-fits-all interpretation of principles or regulations, Sieber says.

"Most people agree on the basic ethical principles, but the intelligent application of those principles depends on understanding the context and culture in which they are applied, and that is an empirical matter," Sieber explains.

"Take, for example, the principles of respect for persons and beneficence," she says. "Suppose that a researcher wishes to interview poor victims of Hurricane Katrina — people who have been displaced to other states, lost family members, and do not speak standard English. The IRB will or should have some tough questions." The IRB's questions might be as follows:

- "How will you communicate so that you are understood in the recruitment, the informed consent, and the interview?"

The March 2006 issue of JERHRE included an article on cognitive interviewing which described how to communicate respectfully and effectively with research participants, using terms and concepts that are familiar to them, Sieber says.

- "How do you know you won't simply add to their trauma by re-opening wounds?"

A researcher might be experienced at interviewing trauma victims and knows how to turn a potential risk into a major, therapeutic benefit, but how could the researcher convince an IRB that this is possible? Sieber questions.

Again, the answer is to have more empirical research that examines these issues, she suggests. For instance, an article scheduled for publication in JERHRE in the December, 2006, issue will review the literature on trauma research to show under what conditions interviews of trauma victims constitute a therapeutic experience for them, and when it may do harm, Sieber says.

Suppose the IRB then answers, "But you are going to go in there and can't possibly know what kinds of ethical dilemmas you will find yourself in. How do we know you will do the right thing?" Sieber asks. This is where articles on ethnography and qualitative research become very relevant, she says.

JERHRE's aim is identify and promote meritorious research that will foster best research practices, as well as to educate investigators and IRBs in a variety of new ways, she says.

For example, JERHRE is sponsoring its first conference on July 28, 2006, at the California State University East Bay Conference Center in Oakland, with some funding from the National Institutes of

Health (NIH). For more information on the conference, titled "Creative Ethical Problem Solving in Human Research," visit the web site [www.csueastbay.edu/JERHRE/conference/index.html](http://www.csueastbay.edu/JERHRE/conference/index.html).

[Editor's note: The March 2006 issue of the Journal of Empirical Research on Human Research Ethics is being made available to subscribers of IRB Advisor as a free sample on-line, at <http://caliber.ucpress.net/loi/jer>.] ■



## UK clinical trial disaster: Five subjects sent home

A British investigation into a recent clinical trial disaster finds no apparent errors or cause for the adverse events that landed six men into critical care.

Within several weeks of falling ill during the clinical trial, five of the six patients who had participated in a London, England, clinical trial were discharged from the hospital, while the remaining patient was moved out of critical care.

TeGenero AG of Wurzburg, Germany, had been studying a humanized agonistic anti-CD28 monoclonal antibody, called TGN1412, to treat cancer and autoimmune diseases. TeGenero contracted with Parexel International of Boston, MA, to conduct a phase I clinical trial, which was conducted at the Parexel unit of Northwick Park Hospital in London.

Six young and healthy volunteers were injected with TGN1412, and two received a placebo. All six men who received the study drug became seriously ill, with inflammation, vomiting, severe pain, swollen heads, and unconsciousness. The two men who received the placebo were fine.

The sick men were transferred to critical care at Northwick Park Hospital, where they received organ support. By April 5, 2006, five of the men had been discharged from the hospital, but one remained.

Meantime, the Medicines and Healthcare products Regulatory Agency (MHRA) of Great Britain, which investigated the adverse events, issued an interim report that found no evidence of problems in the manufacturing of the product that was given to trial participants.

The MHRA report concludes, "Subject to the completion of the outstanding tests, MHRA takes the view that the adverse incidents did not involve errors in the manufacturer of TGN1412 or in its formulation, dilution or administration to trial participants."

The report further states, "The MHRA therefore concludes that an unpredicted biological action of the drug in humans is the most likely cause of the adverse reactions in the trial participants."

The MHRA also notes that the Secretary of State for Health has agreed to establish a group of leading international experts in the field to consider what changes to clinical trials may be required. ▼

## NIH launches *MedlinePlus Magazine* for public

Paul Rogers, former member of Congress and Chairman of The Friends of the National Library of Medicine, announced in May the launch of *NIH MedlinePlus Magazine*.

"The magazine sorts through the clutter of competing health claims that are out there to provide reliable information that can be used by the public," commented **Donald A.B. Lindberg, MD**, Director of the National Library of Medicine.

The quarterly publication will be distributed free of charge to patients and their families in the waiting rooms of selected practicing physicians across the nation. The magazine has no advertising.

Each issue of NIH MedlinePlus Magazine will link readers with celebrities and other individuals who share their own health-related experiences and discuss how these issues may affect others. The premiere issue features an in-depth MedlinePlus interview with athlete/Tour de France bicycle race winner Lance Armstrong, who talks about his own experience with life-threatening cancer.

NIH MedlinePlus Magazine is organized to help readers learn more about specific health conditions and offer the latest advice on prevention, diagnosis, treatment and research findings.

Regular features will include the latest information on how to stay healthy for a lifetime and will also profile some of the most fascinating people – from laboratory scientists and public figures to patients who are making a difference in the search for medical advances.

Those interested in subscribing should write Friends of the National Library of Medicine, P.O. Box 31130, Bethesda, MD 20814. The magazine will also be available online at <http://medline-plus.gov>. ▼

## GAO: Improve post-approval drug oversight

A Government Accountability Office (GAO) report on drug safety released in May came as no surprise to many FDA critics who have charged that the agency lacks teeth when it comes to enforcement on pharmaceutical products after they're on the market. Others said the findings shed light on issues that the FDA already is working to improve.

The GAO concluded that the FDA "lacks clear and effective processes" on post-approval safety issues, but the government's investigational division also commended the regulatory agency for some recent organizational and policy changes, such as its new Drug Safety Oversight Board. However, the report added that "more could be done" in its oversight of post-approval safety issues to improve the dispute resolution process and to strengthen collaboration between the FDA's Office of New Drugs and its Office of Drug Safety. Both are housed within the agency's Center for Drug Evaluation and Research.

In an interview with *BioWorld Today*, Michael Werner, president of the Werner Group, a Washington-based life sciences consulting firm, noted that the findings could be interpreted two ways, favoring reformers who have called for drastic changes but also supporting others who believe a bit of tweaking could go a long way. He expects that the GAO report will not have a

major impact on Capitol Hill. "The system is not broken," he told *BioWorld Today*. "But to be certain, safety issues have returned front and center in recent days, and expect more this summer when the Institute of Medicine issues another analysis on the FDA."

FDA critics warmed to the GAO's recommendation that Congress should consider giving the agency the authority to require post-approval drug safety studies, which also are referred to as Phase IV commitments or post-marketing studies. But that would require legislative change, because under current law, only accelerated approvals come with mandated Phase IV requirements.

Some regard the GAO's suggestion to better empower the agency when it comes to Phase IV requirements as a boost to those in Congress who have been pushing safety-related legislation.

Leading the charge is Sen. Charles Grassley (R-Iowa), who a year ago introduced a bill that would give the FDA's safety office independence from CDER. His measure would establish the Center for Postmarket Drug Evaluation and Research. Grassley's proposed bill is labeled S. 930, and its companion House bill is H.R. 4429.

Not everyone favors new laws, and there are many opponents of an independent safety division within the FDA. Notably, the GAO made no such recommendation. As the appropriations process moves forward, speculation continues that money could be directed toward improving the agency's existing infrastructure for pharmaco-vigilance, better funding for health care information technology that would prove useful in developing adverse event databases and matters related to the Critical Path Initiative.

In a response to the GAO report, the FDA called the findings "reasonable and consistent with" actions already under way or planned – namely additional efforts examining internal post-approval procedures.

The FDA took issue with the GAO's characterization that the safety office takes a backseat to the new drugs office. Instead, the FDA called both groups "co-equal partners" in identifying and resolving safety issues. ■

### COMING IN FUTURE MONTHS

■ Study sheds light on research violations

■ Privacy rule best practices are revealed

■ CIP designation becoming industry standard?

■ Reviewing research in a flu season

■ Are you on top of state human research requirements?

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## CE/CME Objectives

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

- **establish** clinical trial programs using accepted ethical principles for human subject protection;
- **apply** the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- **comply** with the necessary educational requirements regarding informed consent and human subject research.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

## CE/CME questions

21. What are some IRB considerations with regard to a study involving people with questionable decision-making capacity?
  - A. Capacity assessment
  - B. Decisional impairment versus diagnosis
  - C. Other factors creating vulnerability, including lack of health insurance, educational level, incarceration, and stigma
  - D. All of the above
22. As Vanderbilt University's Clinical Research Volunteer Registry has evolved, potential research volunteers have been asked to provide:
  - A. More personal health information
  - B. Less personal health information
  - C. Advance consent to have their medical records reviewed
  - D. The names of other potential volunteers
23. Some other issues the IRB looked at when reviewing Vanderbilt's proposed volunteer registry include which of the following:
  - A. Advertising
  - B. Excluded groups
  - C. HIPAA language
  - D. All of the above
24. Partners HealthCare System's Human Research Quality Improvement Program reports findings to the IRB only when the IRB has specifically requested the review.
  - A. True
  - B. False

Answers: 21. D; 22. A; 23. D; 24. A