IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Committee review, public review part of gene therapy oversight process

Federal panel examines safety of gene therapy research

Genetic therapies are rapidly moving from the laboratory into the clinical setting, with more investigators testing experimental gene delivery systems and therapies designed to fundamentally alter our bodies to prevent or treat disease.

But gene therapy trials involve a complex review process that includes a federal panel examination of the study protocol and technologies involved and — possibly — submission of the proposed treatment or therapeutic process for review and comment by the public.

"There are many, many trials going on all over the country, and there are lots of layers of rules and regulations — so much so that it takes a very long time to get anything done," says **Darwin J. Prockop**, MD, PhD, director of the Center for Gene Therapy at Tulane University in New Orleans. The center focuses on research involving adult stem cell therapies, providing standardized adult stem cells to laboratory researchers across the country, and advising a current clinical trial involving an experimental stem cell treatment for osteogenesis imperfecta that currently is under way at St. Jude's Children's Research Hospital in Memphis, TN.

The state of the science — and regulation — has come a long way since the controversy surrounding the 1999 death of research participant Jesse Gelsinger during a gene therapy trial at the University of Pennsylvania.

Now, Prockop contends, gene therapy experiments are much more closely regulated, and the oversight process is very stringent.

"Ten or 15 years ago, things might have been much looser, but that is not the case now," he states. "Even in privately funded research, no investigator really wants to contemplate a shortcut or bypass of the protections required."

All gene therapy research in any way sponsored by the NIH must be reviewed by the institutes' Recombinant DNA Advisory Committee (RAC), a panel of up to 21 national experts in various fields of science, medicine, genetics, ethics, and patient perspectives.

"If the sponsor of the research, the institution where the trial is to be

conducted, or the testing materials containing the recombinant DNA have received any NIH funding, then the human gene therapy trial must be reviewed by RAC," says **Terence R. Flotte**, MD, professor of molecular genetics and microbiology at the University of Florida in Gainesville, director of the university's Genetics Institute and Gene Therapy Center, and a member of the clinical and regulatory affairs committee of the American Society of Gene Therapy. "And privately funded gene therapy research may also be submitted for review."

RAC's purpose is to advise the NIH director and the NIH's Office of Biotechnology Activities (OBA) on appropriate policies to ensure safe and ethical research using recombinant DNA molecules, he explains. RAC recommends changes to the current NIH Guidelines for Research Involving rDNA Molecules, which outlines responsible research practices in both basic and clinical rDNA research.

"The process of public RAC review and discussion is intended to foster the safe and ethical conduct of human gene transfer experiments," Flotte says. "Public review and discussion of a human gene transfer experiment [and access to relevant information] also serves to inform the public about the technical aspects of the proposal, the meaning and significance of the research, and any significant safety, social, and ethical implications the research might have."

Appendix M of the NIH guidelines outlines the requirements for the design and conduct of gene therapy trials and the requirements for submitting a protocol for RAC review.

Submissions are made to the OBA and must include:

- A cover letter on institutional letterhead that acknowledges that the documentation complies with the requirements set forth in Appendix M, section I, subsection A (M-I-A) "Requirements for Protocol Submission" and identifies the institutional biosafety committee (IBC) and IRB responsible for local review and approval of the protocol.
- A scientific abstract.
- A nontechnical abstract.
- The proposed clinical protocol with relevant manuscripts.
- The proposed informed consent document.
- The curriculum vitae of the principal investigators (PIs).

The initial review is made by the RAC membership, which may request additional information or clarifications. RAC also may make specific comments or suggestions. All of this information is then forwarded to the PI or investigators, Flotte says.

The investigators also may be required to submit their protocol for public review at the RAC's quarterly public meetings if the OBA director initiates a public review following the recommendations by

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at least three RAC members or another federal agency or the NIH director initiates a public review. Factors warranting public review include:

- unique applications of gene transfer research;
- use of new vectors or delivery systems;
- unique clinical, social, or ethical concerns.

"If public review is requested, the principal investigator will be invited to make a 15-minute presentation of the submission at the meeting," Flotte says. "Several RAC members assigned to conduct an in-depth review will comment and ask questions. Questions may also be sent to the PI and responses received prior to the meeting. Other experts and ad hoc reviewers may be consulted and the public is also invited to comment and ask questions at the meeting."

The outcome of the RAC review is recommendations for the safe and ethical conduct of the trial. A letter summarizing the recommendations is sent to the principal investigator, the local IRB and IBC reviewing the protocol, and the FDA, which must issue the required IND approval before the trial begins.

IBC examines local safety issues

Once the RAC review is complete, investigators can seek local review by the IBC. The specific responsibilities of the IBC, with respect to gene therapy research include:

- Review of all proposals regarding recombinant DNA research conducted or sponsored by the institution to ensure compliance with the appropriate regulations and guidelines.
- Establishing and implementing university policies that ensure the safe conduct of rDNA research.
- Certification of research support agencies that personnel, facilities, procedures, and practices have been reviewed and are in compliance with the appropriate regulations.
- Creation and maintenance of a central reference file and library of communications related to all aspects of rDNA research at their institution.

The difference between IRB review and IBC review is that the IRB is primarily concerned with the safety of individuals involved as subjects in the proposed trial, and the IBC is charged with ensuring that procedures to protect the public, the researchers themselves, and others are put in place and adhered to, Flotte says. **(See related story, p. 100.)**

IRBs are concerned with the protocol's informed consent process, risk-benefit ratio for subjects, recruitment of study subjects, confidentiality and privacy issues, and adherence to good clinical practice.

The IBC will examine procedures related to the safety of the subjects, as well as clinical personnel and the surrounding community. The IBC also will want to see evidence of the training of research personnel in the procedures and practices of rDNA research, he says.

Coordination within the facility

Prior to the initiation of the protocol, investigators also must work collaboratively with other groups at the hospital or center where the clinical trial visits will take place.

Gene therapy often involves the use of an altered virus as a vector for delivering the gene therapy inside the tissues of the subjects. These virus vectors can pose a hazard to researchers and other health care workers or patients if the vector is mishandled. In some instances, the potential may exist for the vector to be transmitted to close contacts of the person undergoing therapy.

Investigators must develop a plan in conjunction with facility infection control professionals, waste management, and engineering to ensure that procedures are in place to keep the vector secure and that the trial is safely conducted.

Plans must be in place regarding the handling, preparation, and administration of the vector, protection of sexual partners of trial participants, protection of close contacts and offspring, and the protection of health care workers and the work environment, Flotte says.

Once the protocol has been reviewed by the RAC and IBC, it can be submitted for review by the IRB and submitted to the FDA as an IND application, he says. "The IRB is responsible for the protection of the rights and welfare of human subjects in all human subject research. They are regulated by the CFR to oversee all human research in their designated area."

Although the IRB and IBC monitor the conduct of the trial locally, investigators must also file annual reports and safety reports with the RAC. In particular, any serious adverse events that are unexpected and associated with the use of the gene transfer product must be reported to the OBA. Relevant findings from tests in laboratory animals that suggest a significant risk for a human research participant also must be reported to OBA. Assessments of the trial's safety are performed by

a working group of the RAC known as the NIH Gene Transfer Assessment Board.

"The IRB and FDA may review the protocol before or after the RAC review, but both the IRB and FDA will be informed of the RAC recommendations, Flotte says. "The RAC review occurs before the final IBC approval to ensure that committee is informed of the RAC's recommendations." ■

The unknowns of gene therapy pose challenge

Close monitoring can reduce worries

Gene transfer research offers new hope for people suffering from some rare or deadly diseases, but the research also has suffered major setbacks due to serious adverse events, including subjects' illnesses and deaths, and this creates a greater burden for IRBs reviewing such protocols, experts say.

"Gene therapy is an evolving area of therapeutics that has been unfortunately associated with adverse events due to studies in Europe involving immunodeficiency," says **Bruce Gaynes**, OD, PharmD, assistant professor of ophthalmology and pharmacology and IRB committee member at Rush University Medical Center in Chicago.

Although the research also has had some promising outcomes, a chief dilemma for IRBs is that subjects often have unrealistic expectations.

"You can imagine that with gene therapy, because it sounds promising and high tech, that subjects would think they are going to obtain benefit from the study," says **Alan Korenblit**, MD, CIP, senior attending at Rush University Medical Center and chair of the Rush IRB.

"We've been talking about gene therapy for decades, and so there are expectations by the medical community and patient population that deal with these diseases, which in some cases have very little treatment options," he says. "Gene therapy sounds as though it should result in improved quality of life and survival and eventual elimination of their underlying disease."

However, recent examples show that gene therapy sometimes can harm subjects. For instance, gene therapy studies in France involving the congenital disorder of Severe Combined Immunodeficiency Syndrome (SCIDS) patients resulted in some patients developing leukemia that was found to be directly related to their gene therapy treatment, Gaynes notes.

"One of the most important jobs of an IRB is to protect subjects from excessive risk," he says. "An IRB has to look at the risks and benefits of each therapy in patient-specific circumstances and trial-specific circumstances."

The challenge to doing so with gene transfer research is that such studies are few and infrequent, Korenblit says.

Many risks are unknown, and there haven't been enough studies to provide much data on benefits.

"There were quite a few subjects who did improve with gene therapy, and that was very promising," Gaynes says. "And it's now being used in a lot of disorders, including cardiac disease — trying to stimulate growth with new blood vessels."

So the fact that gene transfer research has also led to the deaths of subjects should not mean this area of research should be discontinued or considered to be too risky by IRBs, he notes.

"There have been instances where there have been adverse events occurring with other therapeutic agents that were definitely linked to the agent, which in the long term has shown significant promise in treating certain types of cancers," Gaynes says.

Gaynes, Korenblit, and other experts offer these suggestions for IRBs dealing with gene transfer research or with similarly higher-risk protocols:

• **Ask the researcher to provide data safety monitoring board (DSMB) information to the IRB.** For gene transfer research protocols, some institutions require oversight by a DSMB or data safety monitoring committee (DSMC), says **Deborah Barnard**, MS, CIP, director of the Office for the Protection of Research Subjects at Dana Farber Cancer Institute in Boston.

"For studies where we're concerned about safety issues, we'd refer the study to the DSMC," Barnard says. "And by default, some go to it anyway, including gene transfer studies."

The IRB reviews all of the DSMC's safety management information regarding protocols, Barnard says.

"We had a study where the DSMC noticed something in all of the adverse event reports that hadn't been picked up by the IRB," Barnard notes. "The DSMC recommended the IRB obtain more information from the investigator and then make recommendations to modify the study for safety concerns."

• **Use a serious adverse event committee to screen study adverse events (AEs).** At Rush University Medical Center, there's a separate serious adverse event committee that screens all adverse events and then determines which should be seen by the IRB, says **Howard Kravitz**, DO, MPH, associate professor of psychiatry and preventive medicine and associate attending in psychiatry. He also is the chair of the IRB 2.

"The IRB still sees its fair burden of adverse events, and we've had meetings where half of our work is reviewing adverse events," Kravitz says. "A lot of these are with oncology studies and deaths and determining whether this is the progression of disease or whether the drug has anything to do with the subject's death."

The serious adverse events committee enters AE information on a database and when studies come up for continuing review, the IRB receives a printout of the AE database for any particular study, he says.

"Then the IRB looks at this in the context of how ill this population is; this includes HIV studies and cancer studies," Kravitz adds. "Subsequently, the real goal is to reduce the potential risks to subjects."

If the IRB, when reviewing the committee's data, decides the study is posing significant risk, the IRB can close the study or suspend it until further information becomes available, he says.

• **Limit gene transfer research and IRB review to institutions that have the necessary expertise.** "The difficulty with gene transfer research is there is not much precedence in this type of research, so we don't have the luxury of large studies with large numbers of subjects," Korenblit says. "It's a relatively select population with unusual disorders and various medical issues that are not common, and therefore it become difficult to predict what complications, if any, will occur with any of these innovative treatments."

So it's challenging for IRBs to obtain expertise in this area when they are considering gene transfer protocols, he adds.

"Because of its rarity, you'd potentially want this limited to certain institutions that either have knowledge or expertise in this area," Korenblit says. "The question for an IRB is, 'How many subjects have undergone a procedure and who is administering the treatment and monitoring the patients?'"

When the answers show that the studies are very small with potentially high risk, then it may be best to limit the research to certain geographic areas where there's necessary expertise and knowledge, he says. "It allows the IRB in that locale to become more educated regarding that particular topic and to, hopefully, make the best decisions for the protection of subjects."

• **Ask for expert consultations when in doubt.** IRBs will have to make a reasonable estimate of risks vs. benefits on a case-by-case basis in gene transfer research, and doing so may require consultation with experts in this new area of research, Gaynes says. "If IRB members feel they have questions that need to be resolved, then the IRB is expected to bring in outside sources to act as consultants to inform them."

"As more novel treatments are studied, there is going to be a greater need for expertise and consultations with experts," Kravitz says. "It's an evolving process, and one way to stay on top of what's going on in the field is to get help when you need it."

Likewise, a centralized review of gene transfer research protocols would be a way to ensure expertise on the IRBs handling these cases, Korenblit says.

"I would like to see a centralized review of any of these potential studies prior to their being disseminated to the various centers," he says. "However, no group is infallible in its evaluation of the research project, and it's the responsibility of the local IRB to determine if it's an acceptable intervention and whether subjects are adequately informed."

• **Ask federal officials for guidance in reviewing research involving new treatments and research with large numbers of adverse events.** IRBs need to know how gene therapy research reviews are handled at other locations and there's a need for consistency in dealing with this type of research, Kravitz says. "We'd like to see more guidance on a broader scale.

"What happens is it is handled on an institutional level," Kravitz says. "There are 60 sites involved in a study, and you don't get deliberation from other sites on how they're handling it."

So one site may think a particular protocol has potential problems, and another one does not, he says.

"There's no clear guidance on handling these, so we do the best we can," Kravitz adds.

• **Address risks adequately on consent form.** With gene therapy research the risks are largely unknown, but they still must be adequately addressed on the consent form, Gaynes notes.

For example, even though a gene transfer research study at one institution may involve an entirely different disease and population than the

SCIDS studies conducted overseas, it's still a good idea to make a mention of those problems during the consent process, Gaynes advises.

"People have to know there have been failures in gene therapy that have led to death and that there are unknowns which must be mentioned in the consent form," he says.

The key is to make certain subjects know that serious problems occurred in another type of gene transfer study, but not in the study for which they are enrolling, Gaynes adds.

• **Use IRB auditors to keep fully up to date on higher risk research.** Some IRBs are beginning a system of using auditors to check studies where the risks are unknown or considered high, Barnard says.

The auditor will report back to the IRB, which then can make a determination of whether IRB members are comfortable with the study continuing as it has, Barnard says.

The auditor typically is someone in the IRB office who has the skills and ability to check the protocols on a regular basis, Barnard says.

"We have onsite auditors we send out for both random audits and to ensure protocol adherence," Barnard says. "We do for-cause audits, and the IRB can refer a study they have concerns about to the auditing team." ■

Students learn to work with deaf subjects

Hearing impaired often unintentionally excluded

Efforts to improve clinical trial participation among medically underserved populations often overlook one group in particular, say some cancer researchers in California.

Deaf and hearing-impaired persons face significant barriers to obtaining quality health care and are often afraid to participate as subjects in trials of cutting edge therapies because of an overall distrust of the health system, says **Georgia Robins Sadler**, BSN, MBA, PhD, clinical professor of surgery at the University of California-San Diego (UCSD) and associate director of UCSD Cancer Center's Community Outreach Program.

"One of the reasons we spend so much time educating health professionals and the public is to try to help [historically disadvantaged] communities to understand that no participation is really no voice, and no say in how treatments are developed and how people access them," Sadler says. "So, someone has to step up to the plate. Obviously, we are not saying everyone should do every study, but keep your eyes and ears open and don't have a knee-jerk rejection response. Don't let the consent document frighten you."

Most health care professionals believe that hearing-impaired patients are just like their hearing counterparts. But they face many obstacles to participating in health decisions and in participating in research.

For example, English is essentially a second language for many deaf people, Sadler says. They may learn American Sign Language (ASL), the dominant sign language in this country, to communicate with other people, but that language has no written counterpart. Most deaf people learn standard English as a second language with no auditory reinforcement, she adds. As a result, many hearing-impaired patients read English at only about a fourth-grade level.

Informed consent documents, typically written at a sixth-grade level or above, will discourage participation by many in that population, she says.

And many members of the deaf and hearing-impaired communities already have a tenuous relationship with the health care system.

Surveys of the deaf and hard of hearing community (DHHC) indicate many have a distrust of physicians. Medical students do not typically learn cultural sensitivity for the DHHC the way that they do for other populations, nor do they learn how to communicate effectively with and without the use of interpreters or even when to use interpreters.

With cancer a leading cause of death in America, the 20 million members of the DHHC thus experience more limited access to basic care, cancer information and, in the case of clinical trials, cutting-edge treatments.

To help improve health care for the DHHC and to reduce the disparities in access to new treatments, the National Cancer Institute (NCI) has funded the ASL, Deaf Culture, and Cancer Program at the UCSD School of Medicine.

The program's goal is to prepare medical students to become clinical leaders dedicated to improving the community's access to health care, cancer prevention, and cancer control information.

Students attend six quarters of classes, participate in deaf socials, and offer a yearlong health promotion seminar series in ASL for the deaf and hard of hearing. Each student is assigned to an ASL interpreter-mentor who reinforces and hones

the student's skills.

The students also spend one summer in Gallaudet University's residential ASL/deaf culture immersion program, which helps students gain experience with deaf language and culture, while helping members of the DHHC learn that they can proactively establish good working relationships with doctors.

Improving communication of health information to the deaf and hearing impaired is important both for clinical investigators and physicians treating individual patients, Sadler continues.

Marketing experts believe that between seven and 21 messages must be received in rapid succession before a message will be assimilated. Yet, most of the methods traditionally used to communicate health information to the hearing community are largely inaccessible to the deaf.

TV and radio advertisements are obviously not as useful and detailed patient information in print may also be difficult for the DHHC to understand.

One of the program's initiatives is developing alternative health message delivery strategies. And, at the same time, testing of these message strategies has enabled some members of the San Diego DHHC to gain experience with clinical research.

Sadler has designed small studies that survey the opinions and experience of different groups to find out what cancer prevention messages they have been exposed to and how effective these prevention messages have been.

Groups of deaf and hard of hearing people have helped researchers validate the survey tools for the deaf community. And participation in the small opinion studies has paved the way for involvement of hearing-impaired patients in clinical studies, she points out.

"In that way, they are exposed to the basic elements of clinical research and trial design," she says. "If they later decide to participate in a larger trial, they will know what the consent form will look like, what its purpose is, etc."

The task remains for investigators to better understand hearing-impaired patients and what techniques can improve their understanding of and willingness to participate in a clinical trial.

"If a deaf patient is referred to an investigator, then that investigator has to be prepared to have a conversation with that person," Sadler notes. "That may mean including the services of an interpreter and knowing how to interact with the patient and the interpreter."

There are a lot of cultural barriers to communication in addition to physical barriers, she adds.

Sadler says that many physicians don't realize that, for hearing impaired patients, they need to be sure that they face the patient the entire time they are speaking and look directly at them.

Or that when using an interpreter, the physician should speak to the patient, but realize that the patient needs to watch the interpreter in order to understand what has been said.

"Often the physician will end up just speaking directly to the interpreter, which can be seen as dismissive of the patient," she says. "You need to look at the person, even if they are not always looking at you."

Sadler's group has published different articles on the health information needs of the deaf and hearing-impaired. She hopes that this information can, in small ways, help other physicians do what the medical students in the deaf culture program are learning to do — provide better information, care, and access to treatments for members of a group that often is ignored.

For more information

• Sadler GR, Gunsauls DC, Huang J, et al. Bringing breast cancer education to deaf women. *J Cancer Ed* 2001; 16:225-228.

• Sadler GR, Huang JT, Padden CA, et al. Bringing health care information to the deaf community. *J Cancer Ed* 2001; 16: 105-108. ■

Adolescent research needs extra attention

Experts offer suggestions

The very idea of deciding when to waive parental permission or allow investigators to inquire into a teenager's sexual history and drug use may make some IRBs a little nervous.

But experts in socio-behavioral research involving adolescents say such situations are common and typically involve less than normal risk.

"Should adolescent assent for a minor be the only consent needed for a study?" asks **Cathryn Samples**, MD, MPH, principal investigator at the Boston Unit of the Adolescent Trials Network for HIV/AIDS Interventions and faculty member in the unit of adolescent/young adult medicine at Children's Hospital Boston in Boston.

"There seems to be universal agreement that if you're doing a study with substantial risk, greater

than normal risk, the waiver probably is not appropriate," Samples says. "But when doing a minimal risk study, which most socio-behavioral research is, then if the adolescents don't normally seek the parent's permission, a waiver is all right."

For example, adolescents typically do not seek a parent's permission to seek family planning information or to receive treatment for a sexually transmitted disease, so a waiver would be acceptable in those types of studies, Samples says.

In other cases, waivers of parental permission may not be appropriate, particularly if the study involves treatment, including treatment for substance abuse, says **Janet Brody**, PhD, research scientist and clinical director of the Center for Family and Adolescent Research at Oregon Research Institute in Albuquerque, NM.

"When it comes to treatment, which is what we do, I don't believe waivers are particularly useful and appropriate," she says.

An ethical dilemma might arise in states where adolescents are able to seek substance abuse treatment without parental consent. If the treatment also involves a research study and if the adolescent has been court-ordered to participate in the treatment program, the adolescents may believe that if they choose not to stay involved in the research project they will be put in jail, Brody notes.

"So one of the issues that comes up is that participation in the research can be coercive, and it's important that treatment alternatives are clearly available to kids," she says.

Brody and Samples offer these suggestions for how an IRB can handle the review of protocols involving adolescents in socio-behavioral research:

• **Protect anonymity with waiver of written consent.** Socio-behavioral research involving adolescents often involves questionnaires or audio-assisted self interviews in which the responses remain anonymous, Samples says.

"If you are doing research and the only thing connecting the young person to the study is the signature on the consent form then waiving that written consent is often a bigger protection for the young person," Samples says. "And sometimes the two are combined — waiver of parental permission and waiver of written consent."

In these cases the top part of the form would constitute the informed consent with instructions for the subject to skip any questions that make him or her uncomfortable and to make certain the subject's name is not on the questionnaire, Samples explains.

• **Offer teenage participants fact sheets that they can share with parents.** For teens in the 16- to 19-year-old age group, their parents often do not keep close tabs on their whereabouts after school, so it may be appropriate to waive parental permission and instead provide the teens with fact sheets they can use to discuss the study with their parents, if they choose, Samples says.

"The fact sheet doesn't mention details, such as that the teen participating in the study is sexually active and sexually transmitted disease screening is a part of the study," Samples notes. "We're not trying to keep the study secret, but we are keeping some portions of it confidential, and a young person isn't required to discuss it with parents, but we suggest it."

• **Be aware of legal risks to subjects.** Adolescent research sometimes involves study of teens who are admitted to substance abuse treatment programs. When these programs are offered free because of the research, this incentive alone might be coercive because the programs often are prohibitively expensive, Brody says.

The other issue is that sometimes the teens referred to such programs are young people who've gotten into legal trouble and who are on probation. If the study will require a urine test, it's possible the subject's probation officer will request to see the results of that test, she says.

"And if the urine test is positive, then there's a possibility that because the teenager participated in the research study that collected the urine then he or she will be put in jail," Brody says. "IRBs need to appreciate that there need to be greater protection that the teenager won't be harmed because of the release of information."

The other issue is that teen subjects who are aware that their study urine test could be used against them in court may fake the urine screening and ruin research data, she notes.

• **Pay close attention to privacy issues.** In most substance abuse treatment research, the teen subjects are enrolled because their parents brought them in, so parental permission is not an issue, Brody says.

But the subject's privacy can be jeopardized without appropriate protections in place, she notes.

For example, teen subjects may sign a release to allow their parents to see the results of their urine tests because they don't understand that marijuana can stay in their urine for a month, and this would be an unintended disclosure if the test returns positive, Brody explains.

"There are studies where parental involvement is not useful, and you can't get it, and there are

kids who want to be in research and get treatment and so it's not necessary to have the parent's permission," she says. "But this needs to be determined on a case-by-case basis."

Another privacy issue involves pregnancy testing, particularly in cases of research that requires this as criteria for inclusion, Samples notes.

While these studies often are biomedical, they also could be considered minimal risk for adults, whereas the issue of a pregnancy test disclosure could create privacy problems for adolescent subjects, she says.

"So we make sure the use of assent for the study is very clear around the rules of pregnancy testing and whether or not the adolescent's parents might find out if there's a pregnancy," Samples explains. "'We make sure the parental permission on the study clearly states that pregnancy testing may be done, and we may not be able to discuss the results of the pregnancy test without the child's permission."

However, if the study also states that a pregnancy would mean immediate withdrawal from the study and a teenage girl is suddenly taken out of the study without explanation, then her parents might deduce the reason, Samples notes.

• **Decide how parental permission would be sought.** In some studies that will require parental permission, the big question is whether the parent or child should be approached first, Samples says.

Perhaps investigators will not want to approach the parents first because then the adolescent might feel pressured to by the parent to participate in the study, she says.

In some cases, the parents and child will be seen together, so investigators can discuss the study with them simultaneously, Samples adds.

• **Consent must be maturity- and age-specific.** "The spectrum of kids from ages 13 to 19 have a developmental range in their capacity to understand what they're consenting to," Brody says. "So even if you go by state law that says kids have the opportunity to consent to treatment, there may be developmental reasons why they're not capable of doing that; for instance, if they are substance using and high or intoxicated."

The question IRBs need to consider are the ethical issues related to whether an adolescent is able to give informed consent based on the nature of the disorder, Brody says.

Even a study's inclusion of adolescents of different maturity levels can be a problem.

Sometimes an IRB might be concerned about the use of an adolescent focus group in which there is too much of an age gap between members, Samples notes.

"Our IRB would be unhappy if we were doing a focus group about condom use and had 13-year-olds in with 19-year-olds, but 15- and 16-year-olds together would be OK," Samples says.

Also, IRBs might consider whether a waiver of parental permission is appropriate for all adolescents in a study or only for adolescents who are ages 16 and older, Samples says.

"So the IRB may look at the study and say, 'We'll approve waiver of parental permission for these people, but not for those people,' or the investigator may propose it that way."

• **Look at definition of minimal risk from adolescents' perspective.** "We're finding differences in perspectives between adolescents and parents and the amount of risk in various kinds of procedures," Brody says. "So the adolescent perspective on the level of risk is an important and not a well-researched topic."

One example is the use of venipuncture in a study, which adolescents often view as a much riskier procedure than it's considered by parents, physicians, and IRBs, Brody says.

• **IRB should have expert member or consultant for this type of research.** "In my experience, it's been extremely helpful to the IRB to have an adolescent-trained person on the IRB or available for consultation when considering these issues," Samples says. "IRBs that deal only with adults get extremely nervous when dealing with adolescent research, and those that deal with research involving children tend to take the parent approach to everything."

Also, IRBs need to review recommendations by the Society for Adolescent Medicine (on web site: www.adolescenthealth.org) for how scientists and IRBs should handle human subjects issues regarding adolescent research, Samples says. ■

OHRP seeks feedback on registration form change

What was voluntary now is required

OHRP is seeking comments from IRB members and others about proposed changes to the agency's registration requirements, which apply to all IRBs that review human subjects research conducted or supported by HHS.

The comment period, which ends Oct. 4, 2004, is the next step before OHRP revises its proposal and, eventually, issues a final rule. The FDA also has published a proposed rule regarding IRB registration requirements for research subject to FDA regulations.

The chief difference in current practice and what OHRP has proposed, which can be found on the web site: www.hhs.gov/ohrp/news/irbnotice.pdf, is that IRBs now complete some of the registration information on a voluntary basis, and the proposed rule would make this same submission mandatory, says **Irene Stith-Coleman**, PhD, director of OHRP Division of Policy and Assurances in Rockville, MD.

"Some examples are the information on accreditation status of the IRB, as well as identifying the accrediting body," she says. "That's voluntary and would be required under the proposed rule."

Also, IRBs would be required to submit information about active, HHS-supported protocols that are under ongoing review by the IRB, Stith-Coleman says.

"One piece of information that's voluntarily submitted now that would not be required is active protocols that are under review, but which are supported by other departments and agencies than HHS," she explains. "That's voluntarily submitted currently, and that would not be included anymore as voluntary even — we would restrict it to HHS-conducted and supported research, as opposed to going outside of the department."

The change from voluntary to required submission probably will have little impact on many IRBs, since the majority of IRBs already submit both the voluntary and required information, Stith-Coleman notes.

Some of the feedback already received by OHRP asks for clarifications about how the submissions to both FDA and OHRP will be handled, she says. "We indicate FDA-covered IRBs would also be submitting information to our site, as well. The IRBs covered by the FDA would submit registration information to the same HHS site that OHRP-covered IRBs are submitting to, which is currently happening right now."

One point that OHRP wants to make perfectly clear is that the proposed rule is not a requirement for IRBs to register all human subjects trials, and there are no regulations that would make this a requirement, Stith-Coleman says.

"Our regulations would not allow us to adopt such a policy on the part of IRBs," she says.

The proposed change will update requirements to meet current regulations regarding OHRP's federalwide assurances.

"Regulations require institutions to designate their IRBs," Stith-Coleman says. "We need to know names and affiliation and additional information about IRB members themselves."

The agency also needs contact information on the IRB's chair and the IRB office.

OHRP officials issued the proposed rule in July 2004, after reviewing a report by the OIG, published in 2003, recommending that all IRBs register with the federal government on a regular basis, Stith-Coleman notes. "After reviewing that recommendation, OHRP concluded that registration of IRBs would enable it to be identify more precisely the IRBs covered under our regulations and to keep an accurate update of IRBs, and to send out educational information and other information to IRBs."

"It allows us to more precisely understand who we're covering and how to reach them in ways that would support improving health and welfare of subjects that are a part of research," Stith-Coleman adds.

Also, OHRP will be in a better position to determine whether IRBs have adequate staff and support, whether IRBs have kept their registration information up to date, including changes to member lists, Stith-Coleman says.

IRBs can register electronically, although signature pages need to be faxed to the agency. By the time the rule is made final, IRBs also should be able to provide updates electronically and the system may be capable of handling an electronic signature page, as well, Stith-Coleman says.

Until all comments are received and reviewed, OHRP can offer no estimate on when the rule will be made final, Stith-Coleman says. ■

NEWS BRIEF

Some journals fail to enforce disclosures

Several leading medical and science journals fail to enforce their own policies for disclosing financial conflicts of interest among contributing authors, according to a study released July 12 by

the nonprofit Center for Science in the Public Interest (CSPI).

The study examined 163 articles in the *New England Journal of Medicine (NEJM),* the *Journal of the American Medical Association (JAMA), Environmental Health Perspectives (EHP),* and *Toxicology and Applied Pharmacology.*[1] It identified at least 13 articles where authors did not disclose relevant conflicts of interest that should have been disclosed according to the journals' policies. CSPI found another 11 articles where there were undisclosed conflicts of interest that might not have directly related to the subject at hand, but should have been disclosed nevertheless.

"Published research that fails to disclose authors' ties to drug companies threatens the credibility of scientific journals and rightly undermines public confidence in studies about the safety or efficacy of various drugs or chemicals," said **Merrill Goozner**, director of the Integrity in Science Project at CSPI and the author of the study.

Nondisclosure of financial conflicts of interest was a problem at all four journals, the study found, but *JAMA* had the highest rate of nondisclosure of conflicts at 11.3% (six out of 53 articles). The undisclosed conflicts in *JAMA* ranged from consulting fees from companies immediately involved in the subject of the study to authors holding patents on technologies that may one day prove valuable because of information contained in the study.

Information not submitted

CSPI recommends that journal editors require authors to disclose any financial arrangements they have had with private firms within the past three years, regardless of whether those arrangements relate to the subject of the article, and that the conflicts be published if they are in any way related to the article's subject. CSPI also says that authors should be required to disclose any patent applications, or intentions to apply for any patents. To encourage authors to comply with journals' policies, CSPI also recommends that editors adopt strong sanctions for failing to disclose conflicts of interest, such as a three-year ban on publication imposed on authors who fail to make complete disclosures.

"Some of the blame for the failure to disclose these conflicts rests with the individual scientists, who clearly feel comfortable withholding fairly glaring conflicts," Goozner said. "But much of the blame must rest with the journal editors themselves, who, for the most part, have created disclosure policies that too narrowly define what conflicts are relevant."

When asked about the study, some journal editors said the CSPI report unfairly implied that prior corporate consulting relationships were an inherent conflict of interest and defended their monitoring of compliance.

Gregory Curfman, executive editor of *NEJM*, told *The Wall Street Journal* that the center's criticism levied against the two researchers in the journal was "underwhelming," noting that their article didn't involve assessments of any drugs or products. He added that, while the *NEJM's* disclosure policies may not be perfect, "we spend a lot of time on this."

Editors of some of the other journals covered, however, told the newspaper they welcomed the report. "We really rely upon scrutiny of these disclosure statements by other scientists and outside organizations," said **Tom Goehl**, editor-in-chief of *EHP*, who added that his editorial board plans to discuss whether to impose sanctions on researchers who fail to disclose conflicts.

Reference

1. Tomsho R. Report faults scientific journals on financial disclosures. *The Wall Street Journal,* July 12, 2004: p. 3/section D. ■

COMING IN FUTURE MONTHS

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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. 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.

9. Gene therapy protocols submitted to NIH's Office of Biotechnology Activities should include:
A. A scientific abstract.
B. The proposed clinical protocol with relevant manuscripts.
C. The proposed informed consent document.
D. All of the above

10. Which of the following is listed among problems IRBs might have with reviewing gene transfer research?
A. It's difficult to obtain the necessary expertise to review protocols in this new field of research.
B. Gene transfer research generally involves small populations and rare diseases, making it difficult to find consistency in the protocols and to put adverse events into context.
C. Because the research is so new, the risks largely are unknown and difficult to assess.
D. All of the above

11. Researchers conducting socio-behavioral studies involving adolescents generally agree that waivers for parental consent can be considered if the research is deemed minimal risk.
A. True
B. False

12. OHRP has proposed a rule that IRBs will be required to submit registration information on all active protocols supported by HHS. What is one feature of this proposal?
A. IRBs would need to continue to submit information on protocols that are supported by the Department of Defense and other non-HHS federal departments.
B. IRBs would need to submit information on the accreditation status of the IRB.
C. IRBs would need to submit information on all active protocols so that the government will have a list of protocols that were started but never published.
D. All of the above

Answers: 9-D; 10-D; 11-A; 12-B.