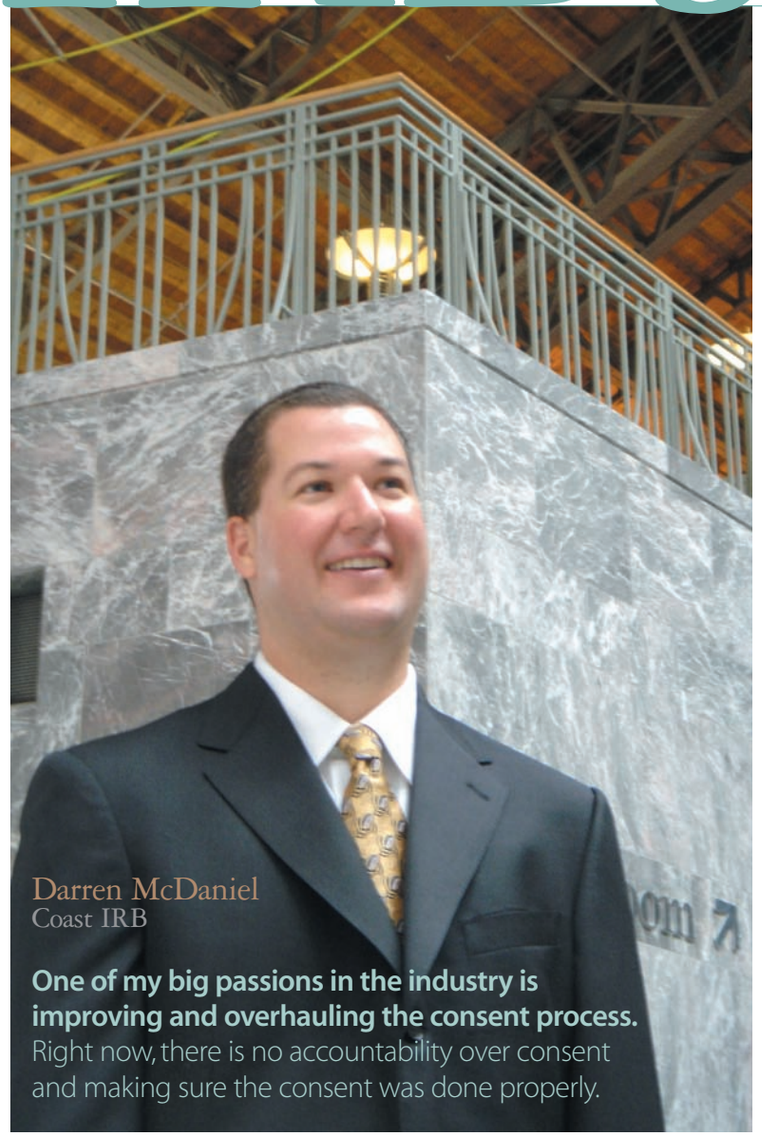
BY DENISE MYSHKO

Institutional Review Boards

IRBs The Safety Gatekeepers



Darren McDaniel
Coast IRB

One of my big passions in the industry is improving and overhauling the consent process. Right now, there is no accountability over consent and making sure the consent was done properly.

Current pressures to speed drugs to market have resulted in the increased use of independent, centralized institutional review boards as an alternative to academic IRBs, because they can offer faster and more efficient protocol reviews.

Institutional review boards, or IRBs, are an important piece of the clinical-trial puzzle. IRBs are the gatekeepers of ethical, regulatory, and policy concerns of human-subject research. And they take seriously their mandate of protecting the rights and welfare of study subjects to the best of their ability, as well as making sure those subjects are fully informed about the risks and benefits of participating in research.

"The IRB is accountable for the patient; IRBs make sure the patient is fully informed of the risks, the benefits, and the different aspects that are important in the trial," says Darren McDaniel, CEO and founder of Coast IRB LLC. "The IRB is accountable to make sure the consent discussion is done properly. The IRB also must make sure that the research site presents the research to a prospective patient in a way that allows the individual to make a yes-or-no decision without any undue influence."

The goal of IRBs should be to protect the rights and welfare of subjects to the best of their ability by fully informing them of the risks and benefits of the studies and giving them a good opportunity to discuss any questions or concerns that they have with the investigator before they make their informed choice, says Lynn A. Meyer, president and founder of IntegReview Ethical Review Board.

In the United States, IRBs are mandated by the Research Act of 1974, which defines IRBs and requires that they are part of all research that receives funding, directly or indirectly, from what was at the time the Department of Health, Education, and Welfare and is now the Department of Health and Human Services (HHS).

Over time, the research landscape has dramatically changed, allowing the emergence of independent IRBs. The Food and Drug Administration's recognition that IRBs need not be located in an institutional setting created the first gateway for the use of independent IRBs in the 1980s.

"Research was often being conducted by independent investigators not located in academic settings, and independent IRBs were born," says James Saunders, VP of New England Institutional Review Board.

"Back in 1989 when we got started, there were only a few commercial or independent IRBs," he continues. "The whole concept was novel. The independent IRBs had to develop their niche. But because of the regulatory environment, it took a while for sponsors to embrace the idea and the value that independent IRBs could provide."

The percentage of studies that now go to independent IRBs has increased over the years. Experts estimate that about half of all studies are reviewed by independent IRBs.

In 2002, there were about 60,000 clinical trials conducted and about half were government-funded studies, Mr. McDaniel says.

"Most government studies go through academic IRBs," he says. "Industry studies mostly go through central IRBs, but sponsors still use local IRBs because they want to reach certain opinion leaders within universities."

Mr. Saunders says sponsors have become more comfortable working directly with independent IRBs.

"Sponsors were hesitant to arrange for an independent IRB directly," he says. "Because of the way the regulations were worded, the conclusion was that it was inappropriate for sponsors to have a direct relationship with the IRB. Most of the language talked about a relationship between the investigator and the institutional review board. Just within the last year, the FDA published a guidance on centralized IRBs that says it is permissible for the sponsor and the independent IRB to work collaboratively."

In March 2006, the FDA issued the guidance document for using a centralized IRB for multicenter clinical trials. The guidance indicates that use of a centralized IRB review process is consistent with the requirements of existing IRB regulations, provided that the IRB is competent to understand the local context of the research. (See box on page 46 for more information.)

Institutional review boards, or IRBs, are an important piece of the clinical-trial puzzle. IRBs are the gatekeepers of ethical, regulatory, and policy concerns of human-subject research.

Industry leaders say central IRBs need to understand local community standards, which are important for clinical research and for protecting patients.

"The local IRBs have the advantage of knowing the nuances of the local site and in that sense may have consent forms that are better targeted toward the local population," says Judy Stone, M.D., an infectious disease physician and a principal investigator in private practice.

"For example, the local IRB would know if the consent forms need to be written at an 8th grade reading level or lower so that patients can understand them," Dr. Stone says.

John Isidor, CEO and founder of Schulman Associates Institutional Review Board Inc., says the FDA guidance provides the central IRB with several mechanisms to oversee community involvement.

For example, according to the FDA, a centralized IRB review process should include mechanisms to ensure meaningful consideration of relevant local factors.

Possible mechanisms include: provision of relevant local information to the central IRB in writing by individuals or organizations familiar with the local community, institution, and/or clinical research; participation of consultants with relevant expertise, or IRB members from the institution's own IRB, in the deliberations of the central IRB; and limited review of a central IRB-reviewed study by the institution's own IRB, with that limited review focusing on issues that are of concern to the local community.

Mr. Isidor says central IRBs will adopt a methodology of assessment of community attitudes, but every IRB interprets the FDA's guidance differently as to how to oversee the community attitudes process.

"We follow the guidances, which serve the best interest of anyone in research in the United States," he says.

Mare Ryan, director of clinical operations, Liberty IRB Inc., agrees.

"As a central IRB we have an obligation to find out what the community's needs are," she says. "We use consultants in various areas of the country so that we are familiar with what's going on in the centers in any part of the country. But if a study is in an area where there is a vulnerable population, such as native Americans, we would also be clued in to those nuances through our application. The same would be true if there was a large indigent population or populations that speak a certain language."

Mr. Isidor says another reason for the increased use of independent IRBs is that institutions are looking to outsource their industry-sponsored studies because of the volume of trials they are handling from federally funded institutions.

"Academic IRBs are under pressure to outsource," he says. "They're losing research opportunities because some of their academic centers are not as efficient as they could be. Outsourcing gives them more ways to apportion resources to manage internal studies."

Mr. McDaniel agrees that local IRBs are trying to develop partnerships with central IRBs because they are so overwhelmed with the volume of research.

"I don't think there is competition between the two IRB models," he says. "The local IRBs are contacting the central IRBs for assistance. There are about 5,000 local IRBs in the United States. I would say a growing percentage of local IRBs are embracing the concept of outsourcing to central IRBs."

Ms. Meyer says her organization also is being contacted by institutions that are evaluating the possibility of outsourcing their industry-sponsored studies.

"The volume of studies is increasing, and local IRBs just can't handle the volume they have with the resources they have," she says.

Experts say independent commercial IRBs have more frequent meetings, can have more resources than local IRBs, and have their sole organizational focus on providing review services.

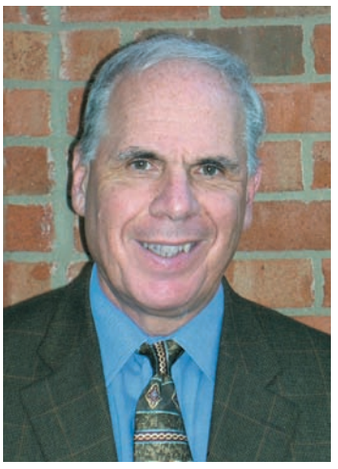
"An independent IRB simplifies the logistics of the clinical trial for whoever is managing the study at the sponsor or CRO level," Mr. Saunders says. "The basic utility of an independent IRB is that one review of the protocol is done for

James Saunders
New England Institutional Review Board

Because of the regulatory environment, it took a while for sponsors to embrace the idea and the value that independent IRBs could provide.

Lynn Meyer
IntegReview

Sponsors need to be more cognizant of the reading levels involved with informed consent and take into consideration that the literacy rate continues to decrease in the United States.



John Isidor
Schulman Associates

The first-rate central IRBs try to insulate the board members and create a wall so that the business considerations are not an issue with the board's decisions.

multiple investigators as opposed to multiple reviews of the protocol by many investigators. It's not totally clear that those multiple reviews would add much value to the protection of human subjects, which is what the IRBs do."

Central IRBs also can offer a faster turnaround of reviews and can be more flexible.

"If there is any type of change to the research for safety issues, commercial IRBs can convene on very short notice to address and respond accordingly," Mr. Isidor says.

Reviews happen much faster in a central IRB setting since this is their mission and focus, Ms. Ryan says.

"Many times, in a university setting, the reviewer is a part-time position," she says. "The hospital or university wants to maintain control of its studies and sets up the IRB, but there is a very different mentality. Generally, there are more administrative approvals required through the university or hospital. Hospitals always have a right to turn down a study even if the IRB has approved it."

Ethical Issues

Commercial IRBs can be perceived as having a conflict of interest, but experts say there are plenty of safeguards in place to avoid such an occurrence. Board members usually are independent and are compensated for their time. They are unaware of the business implications of their decisions and don't have any financial stake in the review.

"The first-rate central IRBs try to insulate the board members and create a wall so that the business considerations are not at issue with the board's decisions," Mr. Isidor says. "All of the major central IRBs have removed from their boards anyone who has a direct equity interest in the company."

Additionally, Mr. McDaniel says, company management should not be members of the review boards.

"Board members make the decisions, not the IRB's management," he says. "Different IRBs operate differently. The IRB pays board members a fee or stipend for their service, generally to attend the investigator meetings and do the review of the research. And because the board is independent and autonomous, members aren't paid by the pharmaceutical company. Hypothetically, there may be an ongoing trial that the board wants to halt because of increased risks to patients, so they halt the study. Does that have a financial impact on the IRB? Absolutely. But because the board is independent their decisions are outside management's control, which is appropriate and ethical."

Mr. Isidor says central IRBs know that if they are not doing a thorough and diligent review and a protocol or series of protocols implode, their review processes will be looked at under a microscope. Furthermore, if it is found that the IRB's processes do not meet regulatory guidelines, the company will be ruined.

Another issue that IRBs face is the potential for sponsors to "IRB shop."

"People think that IRB shopping comes from the motive that if the sponsor didn't get the right answer it will keep looking until it finds an IRB that will give it the answer it was looking for," Mr. Isidor says. "One IRB may believe that a study is inappropriate, and another may believe that it meets the standards. If the sponsor of the research reasonably believes that the research design is adequate, I don't think it's wrong to get a second opinion, in this case a second IRB to review the protocol. It's possible that the first IRB could be wrong."

Ms. Meyer agrees and recognizes that there are many different opinions among different boards and among different board members.

"One board may not agree with the decisions from a previous IRB, but it's hard to know whether that is bad or good," she says.

Generally, an IRB will ask the sponsor whether a study has ever been reviewed by another IRB, and if so if it had not been approved or had been withdrawn.

"If the answer from the sponsor is yes, the IRB may ask a series of questions regarding the design of the protocol," Mr. Isidor says. "Of course, if the IRB believes the trial design needs to be changed, it could become a nonstarter. If the sponsor has to substantially change its design, this could negate the whole research hypothesis."

In January 2006, the FDA concluded that IRB shopping either did not occur enough or

www.kendle.com

Photography: Salvador de Bahia, Brazil

Real people. Real results.®

Kendle

We see clinical development from a different viewpoint. Yours.

When you choose Kendle to deliver your Phase III trial you can be confident of success. By connecting our skills, energy and commitment around the world, we'll tailor-make an elite team that's focused on delivering your trial on time and with the highest quality results.

Together we'll deliver Phase III.

Phase

Accreditation Standards for IRBs

THE ASSOCIATION FOR THE ACCREDITATION OF HUMAN RESEARCH PROTECTION PROGRAMS INC. (AAHRPP) IS A NONPROFIT ORGANIZATION THAT OFFERS ACCREDITATION TO INSTITUTIONS ENGAGED IN RESEARCH INVOLVING HUMAN PARTICIPANTS.

AAHRPP has adopted nine principles for accreditation of human research protection programs. These nine principles serve as the foundation for the structure and content of AAHRPP's accreditation standards. The standards themselves are designed to help organizations consistently meet ethical principles and standards for protecting research participants, yet be flexible enough to account for the diverse institutional and cultural contexts in which research is conducted and reviewed.

WHAT AAHRPP EXPECTS FROM ORGANIZATIONS

1. Protecting the rights and welfare of research participants must be an organization's first priority. An organization should promote a research environment where ethical, productive investigation is valued.
2. Protecting research participants is the responsibility of everyone within an organization and is not limited to the Institutional Review Board (IRB). Accreditation examines whether the policies and procedures of the organization as a whole result in a coherent, effective system to protect research participants and that all individuals know their roles and responsibilities.
3. Striving to exceed the federal requirements and continually seeking new safeguards for protecting research participants while advancing scientific progress must be integrated into an organization's mission.

WHAT ORGANIZATIONS CAN EXPECT FROM AAHRPP

1. The standards for protecting participants in human research will be clear, specific, and applicable to research across the full range of settings (e.g., university-based biomedical, behavioral and social-science research, independent review boards, hospitals, government agencies, and others). Standards will address any special concerns (e.g., the use of vulnerable populations or heightened risk to privacy and confidentiality) that may arise in each setting.
2. The standards will identify outcome measures that organizations can use to assess and demonstrate quality improvement over time.
3. The standards will be performance-based, using objective criteria and measurable outcomes to evaluate whether a Human Research Protection Program effectively implements the standards. The evaluation will result in a grade of pass or fail for each standard and, where appropriate, will also include commendations or recommendations for meeting the standards.
4. The accreditation process will provide a clear, understandable pathway to accreditation, along with equally clear pathways for appeal and the remediation of identified shortcomings.
5. The accreditation process will be educational, involving collegial discussion and constructive feedback. The accreditation process will identify areas in which the Human Research Protection Program does not yet meet the standards and give organizations the opportunity to discuss potential program improvements.
6. The accreditation process will be responsive to changes in federal regulations and to standards that will evolve based on what AAHRPP learns from accrediting organizations from research settings.

Within a Human Research Protection Program, responsibilities must be delegated for providing ethical review and oversight of research. These responsibilities may be distributed differently in different organizations; in many organizations the IRB along with the support personnel and systems provide these functions. In more complex organizations, there might be multiple IRBs, a general oversight office, or individual organizational officials with oversight responsibilities.

The Human Research Protection Program must have mechanisms in place to ensure the independence of its ethical review and oversight functions from other units within the organization, particularly with respect to decision-making regarding the ethics of research involving human participants. IRB structure, composition, operations, and review standards are set forth in federal regulations.

A major IRB responsibility is to determine that the risks of the proposed research are reasonable in relation to the potential benefits to the participants and to society and that risks are minimized to the extent possible consistent with sound research design. In addition, the IRB must determine that the risks of research do not fall disproportionately on one group while the potential benefits accrue to another.

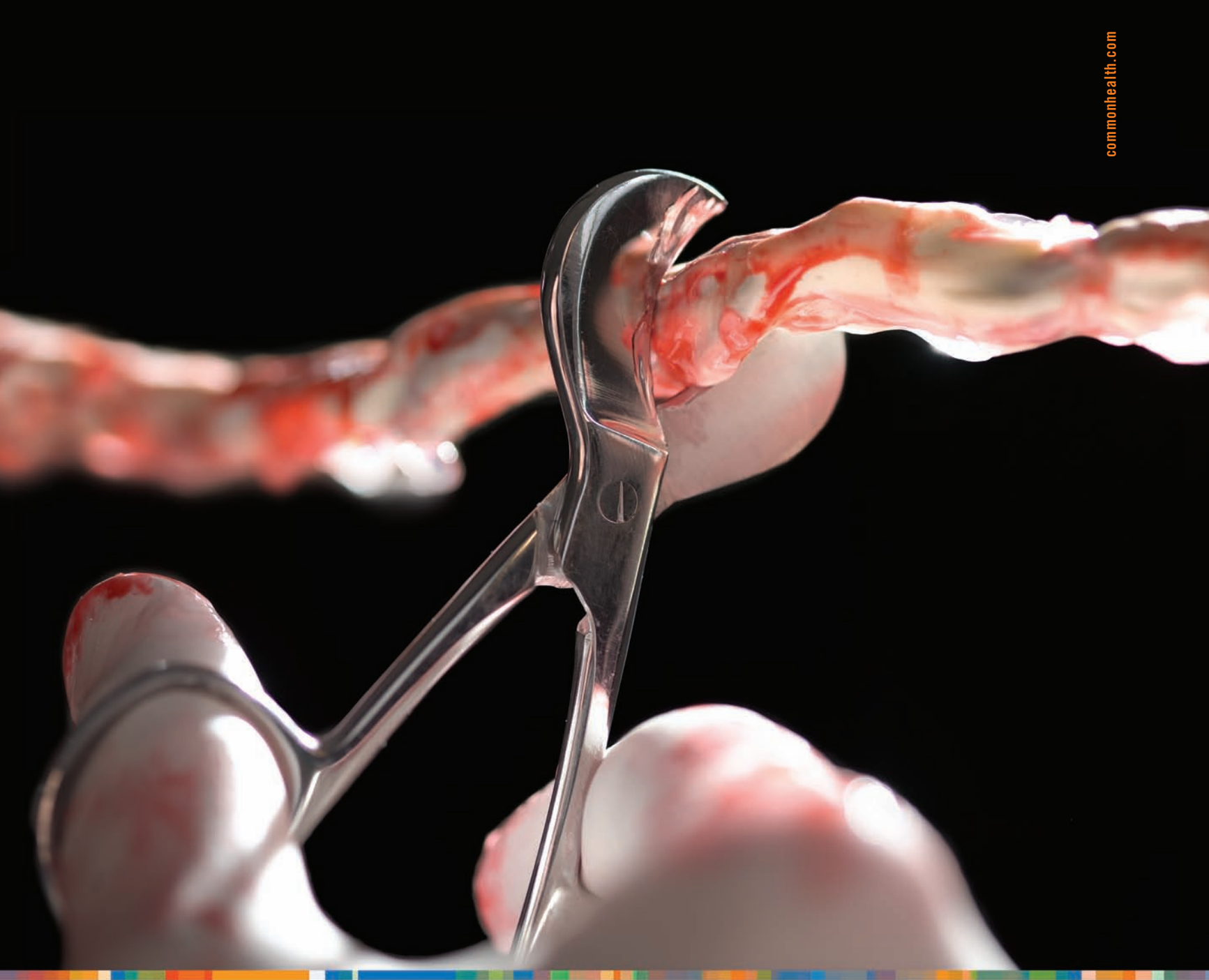
IRBs must approve a consent process that is voluntary and fully informs the prospective participant about the research study. Individuals who are particularly vulnerable or whose capacity to consent may be in doubt require additional protections.

IRBs must determine that the research is designed to respect individual privacy and preserve the confidentiality of identifiable information.

Finally, IRBs have ongoing responsibility for approved research to oversee that the welfare of the participants is protected and to determine that the risks and potential benefits remain reasonable.

In carrying out its obligations, an IRB may approve, disapprove, or require modifications to research protocols. It also may suspend or terminate its approval of ongoing (previously approved) research.

Source: Association for the Accreditation of Human Research Protection Programs (AAHRPP), Washington, D.C. For more information, visit aahrpp.org.



commonhealth.com

Real. Breathtaking.

Some moments are etched in your mind forever. A successful brand can have many of these; its first launch, next year's campaign, a new indication.

We'll make your brand unforgettable. By recording and analyzing hundreds of actual in-office visits, our proprietary method allows us to distill the wants and needs of physicians and patients. Because we've been doing this longer than anyone, we've compiled the largest library of its kind. We leverage this inside information to create reality-based, results-driven campaigns, ensuring your brand reaches its full potential.

You want to see real growth for your brand? Now is the moment.

CommonHealth® Collaborative Velocity℠

A WPP Company

There's nothing common about us.

Adient__Altum__Carbon__Conectics__Ferguson__HLS__MBS/Vox__Noesis__ProCom__Qi__Quantum__Solara__Xchange

didn't present a big enough problem to the extent that warranted rulemaking at the time.

Certification and Accreditation

The organization called Public Responsibility in Medicine and Research (PRIM&R) certifies board members and IRB staff. Begun as an initiative to help its members meet professional development goals, the Council for Certification of IRB Professionals (CCIP) was established in 1999.

The certification process is voluntary and individuals who satisfy the educational and employment requirements and pass the examination receive the designation of Certified IRB Professional (CIP).

The certification process evaluates and validates individuals' knowledge of ethical principles, historical events, regulatory requirements, and operational and functional issues relating to IRBs and human-subject protection programs.

PRIM&R also offers educational programs that cover the ethics, history, and federal regulations related to the conduct of biomedical and social science research on human subjects.

IRB accreditation is done through the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Originally incorporated in Massachusetts under the auspices of founding member PRIM&R, the association was later incorporated as a nonprofit organization in Maryland in 2001.

Accreditation involves a set of objective standards to evaluate the quality and level of protection that an organization provides research participants. AAHRPP accreditation is valid for three years. Accredited organizations submit annual reports to AAHRPP on the status of their human research protection programs.

Accreditation is a goal for most institutions, Ms. Meyer says.

"Our organization is in the process of obtaining accreditation now," she says. "It's a lengthy, time-consuming process, but once IRBs achieve the accreditation, they're telling the industry that they are going above and beyond the federal requirements for protecting subjects." ✦

FDA's View on Central IRBs

In March 2006, the Food and Drug Administration issued a guidance document for industry on using a centralized IRB for multicenter clinical trials. The guidance indicates that the use of a centralized IRB review process is consistent with the requirements of existing IRB regulations, provided that the IRB is competent to understand the local context of the research.

This would require sensitivity to community attitudes and the ability to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

The guidance states IRB review, through its membership, is intended to provide meaningful consideration of various local factors in assessing research activities, including the cultural backgrounds (e.g., ethnicity, educational level, religious affiliations) of the populations from which research subjects will be drawn, community attitudes about the nature of the proposed research, and the capacity of the institution to conduct or support the proposed research. The guidance says intercommunity differences could influence assessments of whether mechanisms of subject selection will be equitable, whether adequate provision is made to minimize risks to vulnerable populations, and the adequacy of the informed consent process.

Sponsors can initiate plans for use of a centralized IRB review process and facilitate agreements and other necessary communications among the parties involved.

The central IRB is the IRB that conducts reviews on behalf of all study sites that agree to participate in the centralized review process. For sites at institutions that have an IRB that would ordinarily review research conducted at the site, the central IRB should reach agreement with the individual institutions participating in centralized review and those institutions' IRBs about how to apportion the review responsibilities between local IRBs and the central IRB.

Source: Food and Drug Administration, Rockville, Md.
For more information, visit fda.gov/cder/guidance/OC2005201fnl.pdf.

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

To access a FREE Podcast on this topic, featuring Lynn Meyer, go to pharmavoice.com/podcasts.

Experts on this topic

JOHN ISIDOR. CEO and Founder, Schulman Associates Institutional Review Board Inc., Cincinnati; Shulman is an independent IRB that has more than 20 years of experience in reviewing research protocols and consent forms. For more information, visit sairb.com.

DARREN MCDANIEL. CEO and Founder, Coast IRB LLC, Lake Forest, Calif.; Coast IRB is an independent review board that provides ethical and thorough review with an internal focus on quality and exceptional service. For more information, visit coastirb.com.

LYNN A. MEYER. President and Founder, IntegReview Ethical Review Board, Austin, Texas; IntegReview reviews studies of medical devices, social and behavioral, as well as Phase I to Phase IV clinical studies. For more information, visit integreview.com.

MARE RYAN. Director of Clinical Operations, Liberty IRB Inc., DeLand, Fla.; Liberty Institutional Review Board is an independent, central IRB. For more information, visit libertyirb.com.

JAMES SAUNDERS. VP, New England Institutional Review Board (NEIRB), Wellesley, Mass.; NEIRB, a division of Thomson, serves as an independent institutional review board for multisite studies and individual researchers. For more information, visit neirb.com.

JUDY STONE, M.D. Physician and Principal Investigator in private practice, Memorial Hospital, Cumberland, Md. Dr. Stone is the author of "Conducting Clinical Trials: A Guide for Physicians, Nurses, Study Coordinators, and Investigators." For more information, e-mail jstone@conducting-clinical-research.com.