Carolyn Gretton

Remaking the RULES

Institutional review boards (IRBs) and research compliance offices remain at the forefront of providing responsible protection of human subjects within the research environment, but the differences in how each group interprets and implements these responsibilities can directly affect the function of both entities.

DR. SANJAY GURUNATHAN *Sanofi Pasteur*

"Before the start of any study, we provide the trial protocol, informed consent, and trial background to the investigators, who then provide them to their IRBs. After the trial starts, we have regular — usually monthly — communications with all investigators to share information on enrollment, procedures, trends, etc. to make sure that all are kept up to date on the program."

Federal regulations mandate independent review and approval of trial protocols by an IRB before studies that involve human research subjects may begin.

The review process is being complicated by evolving research involving biological targets, diagnostics, and combination products. Remaining in compliance with regulations while obtaining the appropriate data and using specimens for these research studies can present challenges for researchers and IRBs.

"As the sponsor of clinical trials, Sanofi Pasteur's primary priority is participant safety; since the IRB's role is to protect the patient, there really aren't any issues," says Sanjay Gurunathan, M.D., associate VP, clinical development, North America for Sanofi Pasteur. "As the investigators are the liaisons between the IRBs and trial sponsors, if there were any safety issues, we would directly inform the investigators, who in turn inform the IRBs."

According to a Rand Corporation study of IRBs released in the December 2011 issue of The Milbank Quarterly, Burdens on Research Imposed by Institutional Review Boards: The State of the Evidence and Its Implications for Regulatory Reform, although many researchers strongly support the need for IRB review, they contend that it often imposes costs that do not strengthen the protections afforded to research participants, and that this burden threatens the viability of research.

The Rand study notes that evidence from a total of 52 studies found that IRBs operate at different levels of efficiency; that waiting to obtain IRB approval has, in some instances, delayed project initiation; that IRBs presented with identical protocols sometimes asked for different and even competing revisions; and that some decisions made (and positions held) by IRBs are not in accord with federal policy guidance. However, the Rand study also acknowledges that the evidence gathered is too limited to allow for valid estimates of its overall magnitude or to serve as the basis for formulating policies on IRB reform, though it did find that in the area of multicenter research, review by several local IRBs is likely to be burdensome.

Powered-Up Protections

The evolving complexity of clinical trials has prompted the U.S. Department of Health and Human Services (HHS) to seek to overhaul the regulations governing IRBs. Last summer, HHS proposed changes designed to strengthen protections for human research subjects, publishing the changes under consideration in an Advance Notice of Proposed Rulemaking (ANPRM) and inviting the public to provide input on an array of issues related to the ethics, safety, and oversight of human research.

The so-called Common Rule guidelines governing human subject research were developed years ago when research was mainly conducted at universities and medical institutions, and each study generally took place at only a single site. The expansion of human subject research into many new scientific disciplines and venues, along with an increase in multisite studies, have highlighted ambiguities in the current rules and have led to questions about whether the current regulatory framework is keeping pace with the needs of researchers and research subjects.

"The adoption of the Common Rule two decades ago was a landmark event to ensure ethical practices and the safety of those individuals who participate in research," says Howard Koh, M.D., HHS assistant secretary for health. "The changes under consideration offer the promise of updating and enhancing those protections to keep pace with current challenges."

So far the ANPRM has received a large number of comments from a wide range of stakeholders, most of whom have applauded the HHS's efforts to clarify and update the existing human subject protection guidelines. In her October 2011 letter to OHRP Director Jerry Menikoff, M.D., Ann Bonham, Ph.D., chief scientific officer of the Association of American Medical Colleges (AAMC) called the ANPRM a "bold effort to bring the rules governing human subjects research into the 21st century.

"We hope that the focus remains on har-

monization, simplification, and protection of human subjects, as well as the advancement of research to improve the health and lives of all," Dr. Bonham said in the letter.

Marjorie Speers, Ph.D., president and CEO of The Association for the Accreditation of Human Research Protection Programs (AAHRPP), observes that one area of the ANPRM where there has been almost universal consensus is around single IRB review for multisite studies.

"I believe that the research community clearly understands the burden that's imposed when multiple IRBs review the same protocol," Dr. Speers says. "And while many have argued that multiple IRBs often find different important issues related to the protocol, most of the time that's not the case, and a single, well-informed, competent IRB can adequately protect human subjects."

Other government agencies also are participating in the Common Rule review. The Presidential Commission for the Study of Bioethical Issues issued a report in December 2011 that concluded the current rules and regulations provide adequate safeguards to mitigate risk. However, the report also recommended a number of changes to current practices to better protect research subjects and called on the federal government to improve its tracking of research programs supported with taxpayer dollars.

According to the commission's chair, Amy Gutmann, Ph.D., the report made it clear that improvements can be made to protect human subjects going forward.

"With the commission's recommendations, society will continue to benefit from advances in quality of life made possible by human subjects research and ensuring respect for the inherent dignity of individual research volunteers," Dr. Gutmann says.

"Many of the most important advances today are driven by research that involves human participants," adds Vice Chair James Wagner, Ph.D. "We must ensure that the way we conduct research involving human subjects protects, encourages, and makes fruitful the selfless practice of allowing oneself to become the subject of a medical or social study intended for the benefit of another."

Informed Consent

In February, the FDA issued a guidance document designed to help small businesses better understand the agency's new informed consent requirements for clinical research established in 2011. These amended regulations require that informed consent documents and processes for applicable drug and biological products and device clinical trials include a specific statement that clinical trial information will be entered into a clinical trial registry databank maintained by the National Institutes of Health/National Library of Medicine (NIH/NLM).

Dr. Speers says more guidance in these areas can be helpful, but that she would like to witness greater consensus from the ethicists who weigh in on the issue of informed consent in cases where it isn't clearly known whether the submitted substances or data might be used in future studies.

For his company's part, Dr. Gurunathan says Sanofi Pasteur conducts investigator meetings to review and discuss the procedures of all clinical programs to ensure a clear understanding of the science and procedures required for participating in the company's clinical studies.

"Before the start of any study, we provide the trial protocol, informed consent, and trial background to the investigators, who then provide them to their IRBs," Dr. Gurunathan says. "After the trial starts, we have regular —usually monthly — communications to all investigators to share information on enrollment, procedures, trends, etc. to make sure that all are kept up to date on the program."

With regard to the ANPRM, Dr. Speers stresses that it's important for IRBs and regulators to realize that guidance is not the same as law.

"That's always an important point to remember; it's something that can lead IRBs to be risk-averse, because they worry that an FDA inspector might come in and cite them for something that's actually under guidance, not a violation of regulations," she explains. "I think it's really important to know what's a rule, what's a law, and what's guidance, and where these all apply."

One area of informed consent that Dr. Speers considers both interesting and not well-understood is the use of specimens and data for future research.

"We started from a very conservative per-

VIEWPOINTS

MATT BAKER
Compass IRB

Creating Clear Communications

Clear lines of communication begin and end with listening. When two institutions begin to collaborate and work together each must listen to the other to truly have effective communication. It doesn't matter how good you are at telling the other side what you want or need. It doesn't matter if you are able to set your expectations or lay out each of your demands and requirements with exact clarity. If one side is not willing to truly listen to the needs of the other, a breakdown will occur. Listening develops trust and trust develops partnerships. Partnerships lead to success.

LYNN A. MEYER
CCRP
Managing Partner
IntegReview Ethical Review Board

Creating a Bond of Trust

When promoting clear lines of communications between different institutions, I believe the best practices are to take time to fully understand the expectations, experience, and environment of each entity. When this effort is successful, a bond of trust is created and relationships will thrive to the benefit of all parties.

GRETCHEN MILLER BOWKER
Chief Operating Officer
Pearl Pathways

Keeping Up with Regulations

Both the Office of Human Research Protection (OHRP) and the Food and Drug Administration (FDA) have made an effort to help clarify the guidance and expectations for use of previously collected specimens for research.

A good example is the YouTube video that explains OHRP thinking with specific examples. As clinical research becomes more complex, both pharmaceutical sponsors and IRBs need to beef up their regulatory knowledge through training and research.

spective where unless the researchers can say exactly how the specimen is going to be used, they can't get consent," she says. "In other words, we have to be able to tell a subject that we want to do X, Y, and Z with that subject's specimen in the future in order for the subject to provide consent.

"We've learned over the years that there are gradations, where we might say, 'we want to be able to use your specimens in future research on diabetes, or on cancer, or whatever, and we won't use it for other things,'" Dr. Speers continues. "In that case, we haven't specified exactly what the study will be, but at least we've narrowed it down, and that's been acceptable to IRBs. I think that the challenge is how much do we have to know about future use in order to make an IRB comfortable to approve the study, and make the subjects feel they have been informed well enough that they can give their consent for use of the specimens. My sense is that this is an area that continues to evolve and will continue to evolve, particularly as we know more and more about genetic makeup, and we're moving more and more toward personalized medicine." PV

EXPERTS

ANN BONHAM, PH.D. Chief Scientific Officer, the Association of American Medical Colleges (AAMC), a nonprofit association representing all 137 accredited U.S. and 17 accredited Canadian medical schools; almost 400 major teaching hospitals and health systems, including 62 Department of Veterans Affairs medical centers; and 93 academic and scientific societies. For more information, visit aamc.org.

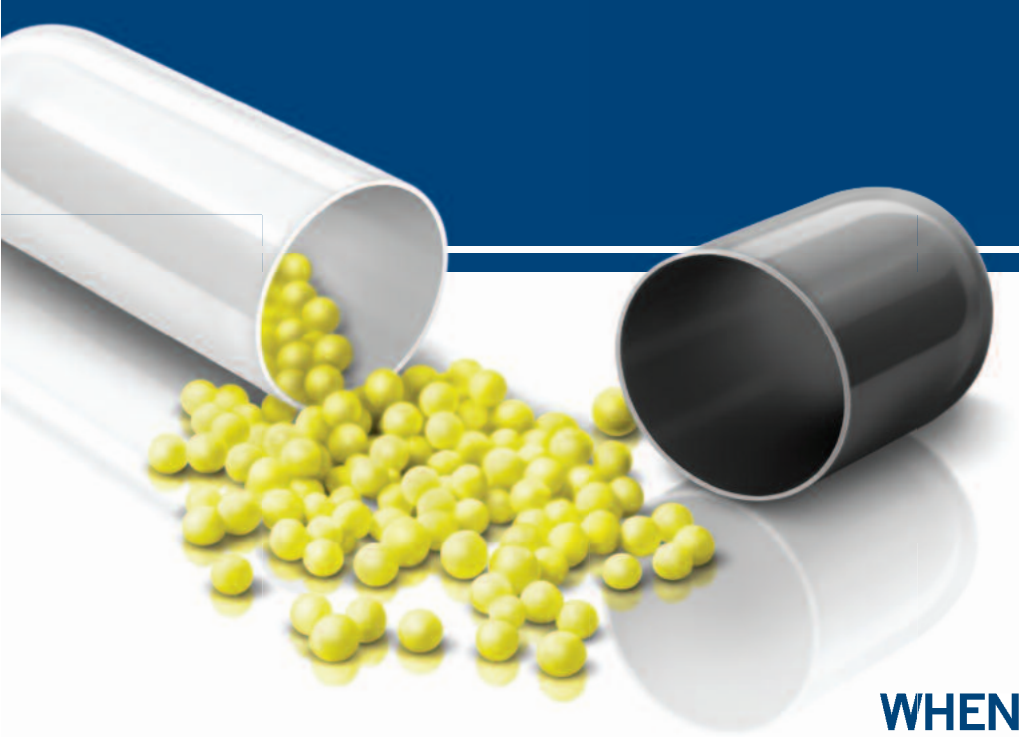
SANJAY GURUNATHAN, M.D. Associate VP, Clinical Development, North America, Sanofi Pasteur, the vaccines division of Sanofi. For more information, visit sanofipasteur.com.

AMY GUTMANN, PH.D. Chair, the Presidential Commission for the Study of Bioethical Issues, an advisory panel to the U.S. President focused on bioethical issues arising from advances in biomedicine and related areas of science and technology. For more information, visit bioethics.gov.

HOWARD KOH, M.D. Assistant Secretary for Health, the U.S. Department of Health and Human Services, the principal agency for protecting the health of all Americans. For more information, visit hhs.gov.

MARJORIE SPEERS, PH.D. President and CEO, the Association for the Accreditation of Human Research Protection Programs Inc. (AAHRPP), a nonprofit body that offers voluntary, peer-driven, educational accreditation to human research protection programs. For more information, visit aahrpp.org.

JAMES WAGNER, PH.D. Vice Chair, the Presidential Commission for the Study of Bioethical Issues, an advisory panel to the U.S. President focused on bioethical issues arising from advances in biomedicine and related areas of science and technology. For more information, visit bioethics.gov.



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