IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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IN THIS ISSUE

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Historians, OHRP and IRBs looking for common ground on oral history projects

Is IRB review necessary? Historians say 'no,' OHRP says 'maybe'

Add one more discipline to the list of those that have issues with IRB review: Oral historians, who maintain that they should not be required to seek review for their interviews with participants.

Oral history involves gathering interviews, in written or recorded form, from participants in past events in an effort to help understand the events or past ways of life. Historians argue that these types of interviews, which participants usually agree to store in archives in an identifiable way, don't conform to a definition of research that would require the review of an IRB. OHRP, asked to weigh in on the matter three years ago, agreed that "oral history activities in general [italics added] do not involve research as defined by the HHS regulations."

But some oral historians say that other OHRP guidelines on the issue have been vague and potentially contradictory, and that IRBs have been using them as a pretext to unnecessarily require IRB review of their work. **Linda Shopes**, MA, who works as a public historian at the Pennsylvania Historical and Museum Commission in Harrisburg and has represented the American Historical Association (AHA) in discussions with OHRP on the issue, says IRB involvement in oral history proposals has had a chilling effect on some projects.

One professor, Shopes says, was told by an IRB that he couldn't conduct interviews about race relations in a Texas community because the results could embarrass the community. She says other historians have been warned not to ask about potentially criminal behavior — even civil disobedience within the civil rights movement that may have resulted in criminal charges.

"In many cases, it's just an annoyance and on some level, it's an insulting annoyance," she says. "But beyond that kind of annoyance, there is a real threat to free inquiry implicit in a lot of IRB actions."

One IRB that has grappled with the issue say it's possible to craft a policy that is sensitive to the needs of oral historians and which also sensitizes historians to the requirements to protect the people they interview.

"We're an interdisciplinary committee and there are no historians on

our committee, so you have to understand a different field of study and what their scholarship is all about," says **Nancy Fishwick**, PhD, FNP, associate professor of nursing and chair of the human subjects review committee at the University of Maine in Orono. "The human subjects committee has to be educated about history as a field of study and oral history as their scholarly method. But you also have to educate the history department about what the spirit or the intent is for human subjects protection. So it's a two-way street."

Confidentiality, psychological harm

Shopes says the controversy over IRBs and oral history first came to her attention in 1997, when she was president-elect of the Oral History Association, an international professional organization of oral historians. She says the organization began to receive reports from members about incidents such as dissertations being refused because the author had failed to seek an IRB review for an oral history project, or IRBs issuing requirements that were at odds with the general practice of oral history.

Shopes says there are two areas in which IRBs and oral historians tend to clash: confidentiality and psychological harm. In biomedical or social-behavioral research, participants are assured that their privacy will be protected and that personally identifiable information about them won't be revealed to others. But in oral history, Shopes says, participants' statements are usually included in archives with identifying information.

"A fundamental practice in oral history is to secure a signed release form from a narrator [participant] which dictates the terms in which the interview can be used," she says. "Oral history interviews are understood as copyrightable documents owned by the narrator and until the narrator signs over a release, we can't use them.

"That would seem would obviate any concern about confidentiality," Shopes says. "The narrator determines whether he or she wishes to remain confidential. They can close part of an interview. They can say, 'I'm sorry, you can't use any of this interview.' They can request anonymity. We don't like them to do that, but that's their right."

In regards to psychological harm, Shopes says some IRBs are concerned that speaking with a participant about a traumatic event may cause some type of psychological harm.

"That is a slippery slope and it is an undocumented slippery slope," she says. "There's good evidence, both anecdotal and scientific, that discussion of sensitive topics does not harm people, but in fact is often salutary. But there is excessive concern about psychological harm."

She says the deeper point of contention between IRBs and oral historians is a difference

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in focus. "There is a presumption in the regulations that the individual is to be protected at all costs — that is the primary concern. That is not the primary concern of historians," Shopes says. "Our job is to follow the evidence, not to protect people from their past actions or from where the evidence leads."

Shopes says oral historians, through their professional organization, do promote good judgment and practices, including giving narrators their full rights. "But our fundamental job is to follow the evidence, not necessarily to protect individuals."

OHRP enters the debate

In a September 2003 letter to Shopes, **Michael Carome**, MD, OHRP's associate director for regulatory affairs, stated that because oral history activities in general are not designed to contribute to generalizable knowledge, they do not involve research as defined by regulations (45 CFR 46.102) and don't require IRB review.

"Although the HHS regulations do not define 'generalizable knowledge,' it is reasonable to assume that the term does not simply mean knowledge that lends itself to generalizations, which characterizes every form of scholarly inquiry and human communication," he wrote. "While historians reach for meaning that goes beyond the specific subject of their inquiry, unlike researchers in the biomedical and behavioral sciences, they do not reach for generalizable principles of historical or social development, nor do they seek underlying principles or laws of nature that have predictive value and can be applied to other circumstances for the purpose of controlling outcomes."

Carome noted that oral history participants are not anonymous or chosen randomly. Questions tend to be open-ended rather than a standardized questionnaire. He did note that if an investigator conducting true research used oral history methods in obtaining data, that would require IRB review.

Later that year, in response to questions from IRBs asking for further clarification of its position, Carome included some OHRP recommendations for evaluating whether a project required review:

— Oral history activities that *only* document a specific historical event or the experiences of individuals, without the intention of drawing conclusions or generalizing findings, would *not* constitute research, or require IRB review.

An example cited was an oral history recording of interviews with Holocaust survivors created for viewing in the Holocaust Museum. The sole purpose of the recording is to create a historical record and provide an outlet for survivors' stories, not to draw conclusions, so it would not be considered research for HHS purposes.

— On the other hand, systematic investigations using open-ended interviews "designed to contribute to generalizable knowledge," for example, to draw conclusions or to inform policy, *would* be considered research under the HHS guidelines, and would require review.

An example OHRP cited would be interviews with Gulf War veterans to document their experiences and draw conclusions about those experiences, inform policy or generalize findings. That project which would be considered research for HHS purposes.

— If oral historians seek to create an archive of interviews for the purpose of providing a resource for others to do research later, the project itself *would* be considered research and be subject to IRB review.

The example cited would be someone seeking to interview surviving Negro League baseball players to create an archive for future research. That would itself be considered research under OHRP's interpretation and would require IRB review.

Shopes says that OHRP's various comments on the topic have given IRBs a means by which they claim authority over much of the oral history work being undertaken at their institutions.

She points to an AHA survey conducted last year of IRB policies regarding oral history. AHA staffers surveyed policies posted on the web sites of 152 research universities with history PhD programs, as well as sites from a random sample of 100 other four-year colleges and universities.

They found that on almost 95% of the sites, there was little guidance to faculty or students about oral histories, except for a passing reference to oral history as one research method subject to expedited review by IRBs. Few explicitly stated that oral histories were generally excluded from review.

In November, **Ron Rosenzweig**, vice president for research for the American Historical Association, wrote to OHRP Director Bernard Schwetz to reiterate their concerns about OHRP's various statements on the subject of oral histories, and asking for further clarification.

Shopes says that to date, OHRP has not responded. Her organization now is working to

advise its members on how best to answer concerns by IRBs, and is preparing a pamphlet and supporting documents that can be used in discussion with boards.

Fostering a collegial relationship

At the University of Maine, **Gayle Anderson**, special assistant for research administration in the Office of Research and Sponsored Programs, says her office met with the head of with the university's Folklife Center several times over the past few years to discuss the issue of how to handle oral histories.

"It was an issue we grappled with, so we decided to try to come to a conclusion about whether they required review or didn't require review," she says.

Fishwick notes that traditionally, historians haven't believed that their work required IRB review. "They haven't considered their work to be research by the strict definition of research, systematic data collection and analysis, and so forth," she says.

"They seemed to believe that anything they did didn't need to come through the human subjects review committee, but upon rare occasion there is something that probably should. It may be judged exempt, but nevertheless, someone else should be making that decision besides the researcher."

The university's guidelines hew closely to the OHRP recommendations, and oral historians are usually directed to read those recommendations carefully when deciding whether to submit proposals for review.

Anderson and Fishwick agree that the guidelines themselves aren't definitive.

"It kind of gives the spirit of the intent of the process, but they can't be terribly specific, because it really is a case-by-case basis in that particular field of study," Fishwick says.

"Is this going to be systematic data collection that's going to be used for any kind of generalizable conclusion? Sometimes maybe it doesn't quite meet that definition, but they're planning on publication in peer-reviewed journals or presentations at large conferences," she adds. "And more and more journals are expecting people to have gone through a human subjects process."

Fishwick says that to the best of her recollection, her board has never asked for changes in a proposed oral history project that has been submitted for review. She notes that most are very low-risk activities that don't involve sensitive subjects.

Anderson and Fishwick say they don't know of any continuing controversy over the issue with historians at the University of Maine.

But Fishwick says that this issue, like others involving the limits of IRB review, is bound to come up again. She says the key is to maintain collegial relationships with departments to ease the process.

"Gayle Anderson fields questions every day from people in all the different departments on campus," Fishwick says. "If you have a central place and a knowledgeable and cordial person who will answer people's questions, then you don't end up with tension. We'd rather have them ask the questions and to submit extra applications for consideration than to not be doing that."

To view the University of Maine's guidance on when oral history activities require IRB review (including OHRP statements on the issue), visit http://orspdocs.umesp.maine.edu/Ethical/oralhistory.htm. ■

De-identification software for researchers and IRBs

Software creates safe researcher playground

Editor's note: In this issue of IRB Advisor is a continuation of a series on how IRBs can use software programs to improve their operations. This month we profile De-ID de-identification software.

As IRBs deal with the privacy provisions of HIPAA, they often must decide whether researchers are allowed to waive individual authorization for use of patients' data.

One way to exempt research from the requirements of HIPAA is for a researcher to show that data has been sufficiently de-identified — stripped of the 18 individual identifiers named in the privacy rule.

Often, IRBs must wade through the researchers' de-identification plans to ensure that patient privacy is protected. Some IRBs, however, are naming de-identification tools as their own institutional standard, in order to make the process more efficient, says **Steven Merahn**, MD, chief medical officer of De-ID Data Corp. in Philadelphia, which markets De-ID de-identification software.

"It removes a barrier to clinical research at every institution," Merahn says. "So the researchers now only have to think about the research, they don't have to worry about building into their research project the de-identification part of it."

He says that when an IRB incorporates his company's software as a compliance tool, it ensures consistency across projects and gives the IRB confidence that the de-identification is being done properly.

"You know that regardless of the researcher, they're using the same exact method," he says. "It's the same tool, a tool you know is developed and supported. It streamlines the compliance process, it enhances the productivity both of the IRB and of the researchers themselves, as well as maintaining a certain level of quality of de-identification."

He says there are even broader and potentially more exciting uses of the software that IRBs can glean by using them on an institutional level.

Merahn says he's currently speaking with a potential IRB client who wants to de-identify large numbers of medical files to provide to researchers as a de-identified database with which to do various types of research.

"It allows for a lot more creativity and exploration on the part of the researchers," he says.

Developed at Pittsburgh

De-ID was developed at the University of Pittsburgh about five years ago, Merahn says, to solve the problem of reliability and consistency of de-identification across the institution's various research projects.

"They said, 'We've got all these people coming in, presenting research projects to the IRB,'" Merahn says.

"They've got to certify a de-identification method as part of their IRB application. And yet we're not looking at the cross-project consistency of these schemes. So the informatics group at Pittsburgh said maybe there's a way through automation that we can increase the reliability and consistency of de-identification."

Once the software was developed and used at Pittsburgh, and its reliability and validity was studied, it became the de-identification standard for the IRB at the University of Pittsburgh Medical Center, Merahn says.

When Merahn and his partner were doing work on informatics and research, he says they came to realize that de-identification was a huge barrier to fuller progress in their fields. So when they came across the University of Pittsburgh's De-ID software, they saw its value and made a deal with the university to commercialize the software.

Kim C. Coley, PharmD, an associate professor of pharmacy and therapeutics at the University of Pittsburgh School of Pharmacy, uses De-ID frequently in her work. She jokingly calls herself a "guinea pig" for the earlier versions of the software as it was developed at the university.

"When the software first came out, we would notice that something might be stripped that shouldn't have been stripped — for instance, a dosage of a drug, because they thought it was an address, or something like that," she says. "And we'd tell them, and they'd go back and fix the software."

She says the bugs all were worked out of the software long before it got to the commercialized version of De-ID, and she no longer sees these types of problems.

Her work involves using existing clinical data retrospectively, after having it de-identified to meet HIPAA guidelines.

For example, she might design a study to look at the possible effect of anemia on the likelihood of a patient fall, using the risk management database of falls and comparing them to lab records of blood draws.

In order to avoid privacy concerns, Coley uses a so-called honest broker — a person who can collect the necessary files and then de-identify them before the researcher sees them. It is that person who actually runs the software.

Coley says De-ID has been useful not only in working with formatted reports such as pharmacy reports but with full text files as well, searching for the identifiers and stripping them out.

"We couldn't do what we do here at our center without this software, and still meet the [HIPAA guidelines]," she says. "We frequently submit our research to the IRB as exempt from informed consent. This enables us to meet those criteria."

Merahn describes De-ID as a plug and play system, which can run as a freestanding program on a laptop, if necessary. The operator can have De-ID call up the application where data files are stored, input the files and automatically de-identify a pool of records. The process creates an entirely separate, de-identified record, while not changing the original record.

Instead of simply eliminating some of the

identifiers, the software can be programmed to instead provide proxies and offsets to increase the files' research value, Merahn says.

For example, it can use proxies for doctors' names (Dr. A, Dr. B, Dr. C) or use an age range in place of a specific age. The software's dictionary can be edited to include common location names and acronyms at the institution.

Researchers' playground

Last year, the National Cancer Institute licensed De-ID for the de-identification component of some of the applications in its Cancer Biomedical Infor-matics Grid (CaBIG).

"They're building a 50-hospital content repository for pathology data and they're using De-ID software as their HIPAA/patient privacy compliance tool for the entire grid," Merahn says. "Every one of the hospitals that participates has De-ID on site as the de-identification tool that allows the record to leave the hospital and be put in to the content repository."

Merahn says he's excited by De-ID's potential for use by IRBs to create safe databases of de-identified files as a so-called playground for researchers.

"Some IRBs are saying in order to facilitate research at their organization, they're going to en masse, de-identify 10,000 records," he says. "They're going to put them in a de-identified database, and they're going to let their researchers have that as a playground.

"Normally, you wouldn't be able to do that — that would be a massive investment," Merahn says. "It wouldn't be possible without automated de-identification. That's the big difference that De-ID can make to a lot of institutions."

He says he's currently in negotiations with an IRB to acquire De-ID for that purpose.

"The IRB is incredibly excited about it because they don't have to see every project now; it's a batch that has been approved so that the IRB can comfortably allow research to take place."

Merahn says the annual cost of the software contract varies based on the size of the institution — anywhere from single projects at an academic medical center to network-level pricing. The cost includes regular updates.

"I can tell you it's very reasonable for medical centers and researchers," he says. "We are pricing this to make it usable."

For more information on De-ID, visit De-ID Data Corp. website at www.de-id.com ■

NIH's ethical framework wins award for excellence

Ethical guide applies to international research, also

Guidelines and regulations related to research ethics often are conflicting and difficult to follow, so IRBs are left with a multitude of ways to interpret human subjects research issues that arise during the protocol review process.

The NIH now offers IRBs and researchers some help with this dilemma. NIH has developed a framework that provides a systematic approach to deciding whether a particular research protocol is ethical.

The NIH project, called the Framework and Benchmarks for Evaluation of Research, recently received the 2005 Award for Excellence in Human Research Protection by the Health Improvement Institute of Bethesda, MD.

The first framework was published in the *Journal of the American Medicine Association* in 2000 and established the seven principles on which the framework is based, says **Christine Grady**, PhD, RN, head of the section on human subjects research in the department of clinical bioethics at the Clinical Center at NIH.

In 2004, NIH published in the *Journal of Infectious Diseases* (*JID*) a second article on the benchmarks, focusing on what makes clinical research in developing countries ethical.[1]

"This system of seven principles ideally is supposed to be followed sequentially, and they're meant to be comprehensive, systematic, and universal in terms of different kinds of research," Grady says. (**See story on seven principles, p. 32**.)

IRBs will find that the guidelines are very familiar and that they synthesize existing guidance, Grady notes.

"We've made these in a more systematic fashion, and it's had a lot of resonance with people who have found the framework helps them think through the ethics of research," Grady says. "It's worked so well that some IRBs around the world have adopted it as their mode of reviewing research."

In the *JID* article, which is available in the public domain on-line at the *JID* website, the focus is on the debate about ethics in developing countries and the three main issues of standard of care, reasonable availability of interventions, and the quality of informed consent.

In the framework Grady and co-authors presented for this issue, the first principle is minimizing exploitation, which is greater in developing nations than it is in resource-wealthy nations. While individuals or communities in developing countries assume the risks of research, most of the benefits may accrue to people in developed countries, the article states.

One way investigators and IRBs can prevent exploitation from taking place is to follow a blueprint to ethical principles and benchmarks, which the authors created and published, as follows:

• **Collaborative partnership:**

— Develop partnerships with researchers, makers of health policies, and the community.

— Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health care system.

— Respect the community's values, culture, traditions, and social practices.

— Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise.

— Ensure that recruited participants and communities receive benefits from the conduct and results of research.

— Share fairly financial and other rewards of the research.

• **Social value:**

— Specify the beneficiaries of the research.

— Assess the importance of the health problems being investigated and the prospective value of the research for each of the beneficiaries.

• **Enhance the value of the research for each of the beneficiaries through dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements.**

— Prevent supplanting the extant health system infrastructure and services.

• **Scientific validity:**

— Ensure the scientific design of the research realizes social value for the primary beneficiaries.

— Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the health care interventions to which they are entitled.

— Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health care and physical infrastructure.

• **Fair selection of study population:**

— Select the study population to ensure scientific validity of the research.

— Select the study population to minimize the risks of the research and to enhance other principles, especially collaborative partnership and social values.

— Identify and protect vulnerable populations.

• **Favorable risk-benefit ratio:**

— Assess the potential risks and benefits of the research to the study population in the context of its health risks.

— Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations.

• **Independent review:**

— Ensure public accountability through reviews mandated by laws and regulations.

— Ensure public accountability through transparency and reviews by other international and nongovernmental bodies, as appropriate.

— Ensure independence and competence of the reviews.

• **Informed consent:**

— Involve the community in establishing recruitment procedures and incentives.

— Disclose information in culturally and linguistically appropriate formats.

— Implement supplementary community and familial consent procedures where culturally appropriate.

— Obtain consent in culturally and linguistically appropriate formats.

— Ensure the freedom to refuse or withdraw.

• **Respect for recruited participants and study communities:**

— Develop and implement procedures to protect the confidentiality of recruited and enrolled participants.

— Ensure that participants know they can withdraw without penalty.

— Provide enrolled participants with information that arises in the course of the research study.

— Monitor and develop interventions for medical conditions, including research-related injuries, for enrolled participants at least as good as existing local norms.

— Inform participants and the study community of the results of the research. ■

Reference:

1. Emanuel EJ, Wendler D, Killen J, Grady, C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *JID*. 2004;189:930-937.

NIH's 7 principles relating to clinical research ethics

Use these benchmarks during review process

The NIH has created a framework and benchmarks program for evaluating research ethics. **Christine Grady**, PhD, RN, head of the section on human subjects research in the department of clinical bioethics at NIH, provides these insights into the seven principles outlined in the framework:

1. Value or social value: "The simplest way of understanding it is to ask whether this research question has any value either socially, scientifically, or clinically, and whether it's worth answering," Grady says.

For example, a research ethics expert once told Grady about a nightmare he had in which he was in the hallway of an institution where a colleague described having successfully transplanted an appendix into a research participant, Grady recalls.

The question is whether this transplantation was an ethical thing to do, Grady says.

The colleague answers that question by saying he received informed consent, but that's not proof of research value, Grady notes.

"Unless there is a good valid reason to understand what a transplanted appendix would do then this is not an ethical study," Grady says. "There is no value to this intervention unless you have a hypothesis about it."

Another example of research that might be put into the questionable value category is me-too studies in which there already has been conclusive investigation into the research question, she says.

"If you already have answers to a question, how valuable is it to answer the question again or to answer it in a slightly different way?" Grady asks.

2. Validity: Once an IRB has established that the research has value, then the next question is whether the proposed study has an acceptable scientific design, statistical methodology, implementation strategy, and feasibility so that the research question can be answered and interpreted, Grady explains.

"If the question is worth asking you have to ask it in a way that you can interpret the answer," Grady says. "If you can't design the project in a way that will get you an understandable answer, then the question is not worth asking anyone to assign any kind of risk in order to answer it."

For example, in the 1990s, there was a great deal of discussion about the effectiveness of giving antiretroviral treatment to health care workers who had been stuck with a needle that might have been contaminated with HIV. Post-exposure prophylaxis was the term used for this type of treatment.

"It's an important question to answer, but the design of such a study seemed to be impossible because the incidence of transmission was so low that you would need an enormous number of people to answer the question," Grady says. "And you would never have enough of a sample to get the power needed to answer the question in a vigorous way."

So a randomized control trial was never conducted, and instead public health officials relied on data from case reports, she adds.

3. Fair subject selection: "This is basically the notion that people should be selected to participate based on a scientific question and not for other reasons, such as favor or disfavor or ease of manipulation," Grady says.

"Once scientifically appropriate participants are identified there still needs to be consideration of vulnerability and risk and benefit, and so you balance the need to fairly select people with the need to minimize risks with the people who are selected," Grady says.

An obvious example of an unfair subject selection would be the research work done historically in orphanages, Grady says. While an orphanage has an easy-to-contain population, it's not a good population for any study, she says.

A more contemporary research subject selection issue involves who can be justifiably excluded from a study, Grady says.

"I think that's a very interesting issue," Grady says. "I have a colleague who talks about how everyone should have a fair chance to participate in research, and the onus should be on how well you can justify your reasons to exclude people based on whether it's inappropriate."

For instance, some populations or people might be placed at a risk in a particular study and there wouldn't be any means for alleviating, overcoming, or compensating for that risk, Grady explains.

"They're so vulnerable that you can't compensate for that vulnerability in some way," Grady says.

4. Risk/benefit: This principle is more complicated than its label, Grady says.

"The notion is that even after you've got a valuable question and a rigorous design that will answer it and a fair subject selection process and a goal, there still is more that can be done to minimize risk and to maximize benefits to the participants in this study," Grady says.

"Minimizing risks and maximizing benefits should be done all the time," Grady says. "But there's an interesting reality that maximizing benefits does not mean the people participating in the study are going to benefit from the study."

Some studies will provide no benefits to subjects, and these can be perfectly ethical, Grady notes. "However there are lot of things people can do within the context of the study to minimize the risks," Grady says.

For example, some straightforward changes could be to make sure that the number of procedures required of participants are precisely what are necessary to obtain useful data, Grady says.

So if there are four MRIs proposed, but three MRIs would be adequate for obtaining the necessary data, then the study should have three MRIs instead of the four, she explains.

"Similarly, minimizing risks means making sure that interventions, procedures are done when clinically indicated," Grady says.

For instance, when a research study requires a tube of blood for a research assay, it's better to have that blood drawn at the same time the patient is providing blood for clinical care so the person doesn't have to undergo two blood draws, Grady says.

"Some of these changes are very detailed, but they can make a huge difference in terms of the risks people are exposed to," Grady says.

"Certainly the IRB makes the judgment about whether the risks you can't take out and can't minimize are justified by the value of doing the study."

5. Independent review: While this is a procedural requirement, it is one that has other benefits, such as public accountability, Grady notes. "It's a way to check both enthusiasm and potential conflicts on the part of investigators," she says.

"Understandably and actually in a very positive way, people who do research are often enthusiastic about the research they're doing," Grady explains. "Enthusiasm without careful methodology could lead one to their own conclusions, so an independent review of the proposal and methodology and statistical analysis plan serves to check that kind of enthusiasm that could lead to the wrong conclusion."

Independent review is a hot button issue right now, Grady notes. "The IRB system has been widely adopted not only in our country, but in many places around the world," Grady says. "It makes a lot of sense on one level, but people have argued, and there is a case to be made that it was based on research that was done at an institutional level."

IRBs worked most effectively for smaller, institutional research, but the complexity of the multi-site and multi-national research of today has raised questions about whether the current system is the correct one, Grady says.

"One example that people talk about all the time is the multi-site study that has 64 different sites, for instance," Grady says. "Under the current system many of those studies will have to go through 64 IRBs, and the time table for each might be different, and the exact things an IRB wants changed or altered might not coincide across the 64, and it creates a huge lag in doing the research."

While the FDA allows for a central review with one IRB of record as long as all sites accept that IRB, this isn't done as often as it probably should be done, Grady says.

6. Informed consent: Some investigators and IRB members might question why informed consent is in the sixth position instead of being placed earlier in the framework since it's typically considered one of the most important ethical issues, Grady notes.

"But if we're right about this framework, you would never get to the informed consent unless other things are satisfied," Grady says. "If you don't justify the risks and benefits then you never ask people to participate, so while informed consent is an important part of doing research and a universal requirement, it's not where you start."

Informed consent is based on people's ability to make their own decisions, and they need the right amount of information to make this decision, Grady says.

"I guess one point I would make to reviewers of research proposals is there seems to be a lot of attention paid to the details of the information written into a consent document," Grady says. "Whereas, I think it's pretty clear that the process around giving information and helping people understand it is so much more important."

A study could have a pristine consent document, but people might not read it, so the focus should be on what people are told and the context and slant of this discussion, Grady says.

"That's much more important to the ethical evaluation of the study than what the words say on the paper," Grady says.

7. Respect for enrolled participants: "This category reflects the notion that even after you have carefully designed a study and individuals have consented to participate voluntarily, there still are things one needs to do to show respect for the individuals who have chosen to participate," Grady says.

"It includes monitoring the well-being of the individuals in the study, protecting their confidentiality, making relevant information available that people would need to know to make a relevant decision about continuing participation, and they need to be reminded they have the right to withdrawal if they want to," Grady says. "There are a host of things one needs to do to show respect to individuals in a study."

An infamous example of research that lacked the ethical respect for participants was the Tuskegee study in which African American men were enrolled as part of a study of the symptoms of syphilis.

When the study began antibiotics were not a proven treatment for syphilis, but as participation in the study continued over decades, the research participants could have received antibiotic treatment but were not informed of its availability.

"I think Tuskegee is a good example of a lack of respect for enrolled subjects because as information became available over the course of many years, it was relevant to their well being, but it wasn't shared with the participants," Grady says. ■

Think far beyond ethical requirements set in regs

IRB's need more intuition, compassion

One of the drawbacks for research conducted in this age of checklists and strong regulatory oversight is that IRBs and research institutions do what they're required to do and sometimes neglect to address the bigger picture, an ethics expert says.

"I think that research with human subjects is governed by regulations, which set the bare minimum for conversations that need to happen," says **Nancy Neveloff Dubler**, LLB, director of the division of bioethics and vice chair of the Montefiore Medical Center IRB, department of epidemiology and population health, at Montefiore Medical Center in Bronx, NY. Dubler also is a professor of bioethics in the Albert Einstein College of Medicine in Bronx, NY.

"In addition to regulatory steps, an IRB needs to be thoughtful, intuitive, compassionate, and learned about the population in its area, so it can learn about vulnerable populations," Dubler says. "These processes all are facilitated by the regulations. The regulations provide a platform, but they don't in fact demand that you go into these directions, which I think are ethically required."

Dubler has co-written a new book on research ethics titled *The Ethics and Regulation of Research with Human Subjects*, published in 2005 by LexisNexis Group in Newark, NJ.

The goal of ethical consideration is to delve deeper into issues and considerations before approving a particular research project, Dubler says.

A first step to a more thoughtful and intuitive IRB review is for the IRB member to read the protocol carefully and think about who the stakeholders are in the proposal and what their interests are, Dubler suggests. "Then step back and ask, 'Who are the people being asked to become research subjects?"

Other questions to ask are:

- Are they insured or uninsured?
- Are they rich or poor?
- Are they in the community or in nursing homes?
- What is the situation of the possible human subjects?
- What could that situation mean for the quality of independent consideration of the protocol and for quality of the consent process?

IRB members can apply compassion to their review work by thinking about what it would be like to be a person in the place of this possible research subject, Dubler says.

These questions to ask oneself are as follows:

- What would you want to know?
- How might you want to be protected?
- What information would you want shared?
- How might the protocol change your life?

"So I think that what this requires is an in-depth, thoughtful exploration of who these possible research subjects are and what might be important to them," Dubler says.

For example, if an IRB is considering approval of a research project involving children, the

regulations will require the board to address the various situations in which the children will find themselves during the study, as well as the nature of the research and the possible risks and benefits of the research, Dubler says.

"I would argue that you then have to step back and think, 'What is the quality of parental permission that we would require to enroll a child?'" Dubler says.

Other ethical questions to consider in this example are these:

- Is it possible that parents will enroll their children as a way to gain access to care?
- Does that change how we think about the consent process?
- How might economic or social factors play on the willingness of parents to agree?
- How does the system for delivering care that forms the background of the protocol interact with this protocol?

"Those are not issues that naturally come to the fore when you read the regulations," Dubler says.

"You need to think about what are the larger sets of issues that we should be concerned with since it's clear that the regulations do provide a minimum basic framework," Dubler adds. "But then the research must be considered by the IRB in light of all the conditions that are in effect in the community in which the IRB sits."

Also, IRB members should give thoughtful consideration to the terms assent and consent when applied to research involving children, Dubler suggests.

Researchers need both permission from the parent and assent from the child who is capable of providing assent, she says. "Those two ingredients are necessary, but I'm suggesting they are not ethically sufficient," Dubler says.

When research issues involving consent and assent are considered beyond the regulatory box, it's more likely an IRB will avoid approving some of the research that later becomes controversial or the subject of lawsuits.

For instance, in the *Grimes v. Kennedy Krieger Institute Inc.* case in Maryland, a research institute created a non-therapeutic trial in which different levels of lead abatement modifications were performed in homes with children, Dubler says. The families involved were mainly poor and African American, and investigators placed their children at risk for lead poisoning without clearly indicating the dangers to them, Dubler explains.

"They wanted to find out what was the cheapest level of lead abatement that would give them a safe home setting," Dubler says. "The critics of the research were parents who sued, and the court was very critical. All of this could have been avoided by having greater sensitivity to the children, the setting, the family, and the issues."

Authors of the recent ethics book state: "Moreover, in our view, parents, whether improperly enticed by trinkets, food stamps, money or other items, have no more right to intentionally and unnecessarily place children in potentially hazardous non-therapeutic research surroundings, than do researchers. In such cases, parental consent, no matter how informed, is insufficient."[1]

"There are a lot of IRBs who think their job is to protect human subjects and that their obligation is completed if they respond to issues in the regulations," Dubler says.

The problem is that most IRB members probably don't really know the regulations, Dubler notes. "So they use a sort of shorthand for quoting the risk-benefit ratio without most members of the IRB actually having grappled with the actual language of the regulations," she says.

To make changes in an IRB so that it will more fully consider ethical issues, there will have to be a strong commitment on the part of the IRB chair and administrator, Dubler says.

"They have to find and educate nonaffiliated members of IRBs and give them the real education and tools they'll need to move forward," Dubler says. ■

Reference

1. Coleman CH, Menikoff JA, Goldner JA, Dubler NN. *The Ethics and Regulation of Research with Human Subjects.* LexisNexis Group; Newark, NJ. 2005:1-746.

COMING IN FUTURE MONTHS

- Improve compliance between IRB and research institution
- Here's how IRBs can handle (or not handle) QI activities
- Expert offers guide to evidence-based ethics
- Ensuring that research registries protect online participants

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*

9. Which of the following would not be an oral history project that would constitute research under HHS guidelines?
A. Recorded interviews with Holocaust survivors intended to be played at a Holocaust museum.
B. Interviews with Gulf War soldiers intended to collect information to inform retention policy.
C. Interviews with surviving Negro League baseball players intended for a database to be used for future research projects.
D. None of the above

10. De-identification software allows IRBs to create de-identified databases of patient records for research that would be exempt from HIPAA requirements.
A. True
B. False

11. Which of the following is not a good strategy for ensuring optimal informed consent during research trials conducted in developing nations?
A. Involve the community in establishing recruitment procedures and incentives.
B. Disclose information in culturally and linguistically appropriate formats.
C. Implement supplementary community and familial consent procedures where culturally appropriate.
D. All of the above

12. Questions that should be asked during an ethical review of a protocol include:
A. What would you want to know?
B. How might you want to be protected?
C. How might the protocol change your life?
D. All of the above

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