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IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Special Series: Assessing Risks/Benefits

Assessing a clinical trial's risks and benefits requires closer IRB attention

Research proposals often need work in this area

Here's a scenario that's all too common: A federally funded research proposal that would involve a medically vulnerable patient population in a multicenter trial includes a discussion of risks and benefits that is summarized as "Informed consent will be required."

Instead of a thorough and ethical discussion of a trial's risks of harm and potential for benefit, the research proposal dismisses the issue in a stock statement about informed consent.

"The thing that gives me the most concern is that IRBs are often not presented with enough information to make a realistic risk or benefit assessment," says **Dale Hammerschmidt**, MD, FACP, associate professor of medicine at the University of Minnesota Medical School in Minneapolis. He is a member of one of the university's IRBs and has chaired IRBs for a decade.

Hammerschmidt recently reviewed a research proposal that included the above statement about informed consent in lieu of offering a risk-benefit assessment. The patient population of this project would include intensive care unit patients, some of whom would not be able to give their own informed consent and, therefore, would require surrogates to decide whether they would participate in the trial.

"The protocol had no discussion of vulnerability or the implications of using a surrogate or why there was a benefit in the protocol to using people who couldn't give consent," he says. "This information was only available if members of an IRB had the expertise to bring it to bear."

And yet, IRBs reviewing this protocol were expected to form some sort of rational judgment on whether the risks and benefits were in balance and would justify using subjects who were unable to make their own informed consent, Hammerschmidt adds.

"The generic underlying problem is when people are crafting protocols

they are spending a lot of time and attention on designing the protocol for the highest resolution of scientific question, but the ethical implications of the study seem to be delegated to someone else and are an afterthought in the protocol, as well," he says.

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Editorial Questions

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"There are all types of risks in research such as physical, economic, legal, social, confidentiality and psychological," says **John Isidor**, JD, CEO of Schulman Associates IRB of Cincinnati and *IRB Advisor* editorial board member.

"Examples of physical risk are the risks of the study product or comparison product. Also, there may be risks from the study design such as a washout risk or placebo. There are also risks from the study procedures such as surgery, scopes, biopsies, X-rays, etc. Economic risks may include the costs of the research, particularly in device research where the subject pays the cost of the product and lost compensation for the time it takes to participate in research," he explains.

"Social and psychological risks could emanate from the social or psychological harm of the research. Illustrations could include research into activities such as sexual behavior, alcohol or drug abuse or psychological types of research. Legal risks include research involving illegal activities such as drug abuse, violence, etc., which could expose the participant to arrest if their identity is disclosed," Isidor concludes. "I think IRBs should establish categories of risk so they can review the risks involved in the research. I think a review outline or checklist identifying categories of risks is helpful for reviewers. Our IRB utilizes this approach."

All types of risks exist

Researchers and IRBs often do not devote enough attention to assessing risks and benefits in clinical trials, says **Paul B. Gold**, PhD, an assistant professor of psychiatry at the Medical University of South Carolina in Charleston. Gold also is a member and an associate vice chair for an IRB at the university.

"There are many different dimensions of risk and benefit, and these are often dimensions that don't get much consideration," he says. "There's an overall global risk and benefit that people tend to view for their study. Unfortunately, that oversimplifies it."

Too often researchers and IRBs do not consider the various kinds of risks of harm and the probability of these occurring, he says.

Likewise, many researchers fail to address the concept of benefit and do not provide the IRB with an assessment of the probability and magnitude of a benefit that's being considered, Gold adds.

Hammerschmidt, Gold, and other experts say that the entire issue of assessing risks and benefits is poorly addressed and misunderstood by

many researchers, study subjects, and even IRBs. This misunderstanding sometimes leads to the unrealistic expectations on the part of trial participants that they will personally benefit from their participation in a study, even in cases where this potential direct benefit is very unlikely.

"I believe this is the case, particularly in the context of phase 1 clinical trials," says **Howard Mann**, MD, program associate in the Division of Medical Ethics at the University of Utah School of Medicine in Salt Lake City. Mann, a radiologist with the university hospital and clinics in Salt Lake City, developed the ASSERT statement that represents an explanation of the requirements for the ethical conduct of human subjects research in the form of randomized controlled clinical trials. **(See story on ASSERT in the November issue of *IRB Advisor.)***

What about benefits?

"IRBs, in my view, do not pay sufficient attention to this when comparing the trial's protocol with what is stated in the consent document," Mann says. "In contradistinction, investigators do not mention the benefits associated with trial participation, per se."

While study protocols often do discuss risks of harm, there is very little discussion about potential for benefit, notes **Nancy M.P. King**, JD, professor of social medicine at the University of North Carolina-Chapel Hill.

"IRBs are used to looking at consent forms with a great deal of detail about the risk, including likelihood and magnitude," she says. "But that doesn't happen very much with benefit."

Even the most conscientious investigators may simply state that a participant may or may not benefit, a vague statement that leaves its meaning up to the subject's imagination, King says.

The subject is left to guess the answers to these questions: "Is it a cure? Is it a temporary change in some kind of measure of illness? How long will it last? How likely is it? What are your chances?" she asserts.

"There is an assumption that taken to an extreme is a therapeutic misconception and it is that there is a potential for benefit because the person has a disease and the potential, down-the-road treatment is being tested," King says.

Despite the fact that investigators are not accustomed to thinking in terms of describing potential benefit, this can be and should be done, she states.

"It's possible to be somewhat specific because we're somewhat specific about the risks of harm all the time, even from animal studies," King says. "So one of the things I think is it's important for investigators to become accustomed to providing potential subjects with more information about how 'If everything goes the way we envision it, here's what we expect, and if not, here's what is likely to happen.'"

One of the more controversial issues has to do with the IRB's role in conducting or ensuring an adequate scientific review of a protocol.

"IRBs for a variety of reasons really do have to do a scientific review of a protocol," King says. "They have to be able to make their own judgment about whether the risk for harm and potential for benefit calculus has been done with enough information."

Potential social and scientific value should be considered in relation to what is already known about the medical issue, Mann says. "This should be assessed in relation to a systematic review of the relevant medical literature."

It's a matter of resources

At major medical academic centers IRBs see many protocols that have thorough scientific reviews because the studies have been through a National Institutes of Health review or were reviewed as part of a pharmaceutical industry sponsorship. But the problem may lie with small IRBs at community hospitals, start-up companies, and homegrown studies, where the IRB may be the only body that is capable of doing a scientific review of the protocol, King explains.

"I think ultimately what IRBs may not do enough of, especially small IRBs without resources, is to say, 'We cannot evaluate the science of this and are worried about it,' and then leave it at that and make the investigator figure out what to do to make a persuasive case," she says.

Even when a protocol contains a scientific review, it should be assessed for bias.

Research applications typically contain an investigator's or sponsor's narrative review, but the relevance of these may be biased by selective literature citations, Mann says.

One example of an instance where reference to a systematic review of the literature may result in the decision that the proposed study does not meet an IRB's requirements pertains to a placebo-controlled trial of an intervention, he says.

"A literature review may show that many previous placebo-controlled trials have been completed, and that the research question has already been answered: The intervention is

The Belmont Report

ETHICAL PRINCIPLES	PRACTICAL APPLICATIONS
Respect for People	***Informed Consent***
• Requirement to Acknowledge Autonomy • Requirement to Protect People with Diminished Autonomy	• Information • Comprehension • Voluntariness (No Coercion)
Beneficence	***Assessment of Risks and Benefits***
• Do No Harm • Maximize Possible Benefits and Minimize Possible Harms	• Careful Arrayal of Relevant Information • Nature and Scope of Risks & Benefits • Systemic Assessment of Risks & Benefits
Social Justice	***Selection of Subjects***
• Justice • Injustice • Departures from Equal Distributions • Selection of Research Subjects	• Individual Justice • Social Justice • Burdened Classes • Vulnerable Subjects

Source: Medical University of South Carolina, Charleston.

efficacious," Mann says. "Randomization of participants to a placebo arm is unethical when effective treatment exists."

Risk-benefit tools

Although the idea hasn't caught on universally, there is at least one strategy IRBs might use to make sure risks and benefits have been adequately addressed. This would be to require investigators to include a risk-benefit ratio tool with their protocol proposals.

A number of these tools exist, and one example is a risk-benefit matrix that Gold developed from the Belmont Report for his own research. The tool is a simple chart that includes columns on ethical principles and practical applications. **(See risk-benefit chart, above.)**

"What I do in my work is I lay out the possible harms, and I always try to think in terms of parallel construction of use of terms because one of the things that's devastating to people in the world of medicine and science and life is that we use words like 'risk' and 'benefit' and interpret the meaning of those words differently," Gold explains. **(See story on developing and using a risk-benefit matrix, p. 113.)**

The term risk equals a probability, and the term benefit equals an outcome, Gold says. "Thus, a risk/benefit assessment is a bit of a misnomer because a probability is compared with an outcome."

A better strategy is to frame risks as probability and magnitude of potential harms and, in parallel, to frame benefits as probability and magnitude of gain, Gold adds.

"Then it may be possible to array harms and benefits to make a determination about whether benefits exceed harms and thus argue that a study ought to go forward," Gold says. "This approach assumes that other criteria necessary to justify a study are clearly met."

This type of thoughtful assessment of risks and benefits could be a gold standard that IRBs expect from investigators, but this often isn't the case.

"IRBs are put into the awkward position of being perceived as a real barrier to research if they say, 'You haven't given us enough information.' They're seen as obstructionist," Hammerschmidt says.

"But if researchers have included the ethical questions in the planning of their research, then they probably would have known what to say in those parts of the protocol, and it would have been very clear," he adds. "The fact that it's not there makes me think it hasn't been thought about in a clear way." ■

A risk-benefit matrix should ask the right questions

Here is how to develop an effective tool

Simply asking investigators to provide a thorough discussion of a proposed study's probability of risk and potential benefits may not always result in an effective analysis that can be used by IRBs to assess a protocol.

This is why it's a good strategy to ask investigators to use a risk-benefit tool, such as a matrix, in analyzing their protocols.

"The burden is on investigators to demonstrate what the risks of harm are," says **Paul B. Gold**, PhD, an assistant professor of psychiatry at the Medical University of South Carolina in Charleston. He also is an associate vice chair for one of the university's three IRBs, and has been a principal investigator for studies in which he has submitted to an IRB his own risk-benefit matrix as part of the protocols.

Research problems have been highlighted in the popular media so often in recent years that it's incumbent upon investigators and IRBs to help reverse the trend of low respect for medical research, he says.

"We have a task in front of us, and we do have to gain credibility," Gold says. "Through being transparent and showing what we do and being honest with what we know and what we don't know, we'll get the credibility back."

With this objective in mind, Gold has developed a risk-benefit matrix for harm assessment. This matrix forces an investigator to take a clear and honest look at the proposed study's probability and magnitude of harm, and it provides a blueprint for information that will be disclosed to potential subjects in the informed consent discussion and document. It also makes it very easy for an IRB to assess a protocol in terms of the balance between risks and benefits.

"When I set up a matrix for harm assessment, I'm also thinking statistically," Gold explains. "So I'm looking at things from four perspectives simultaneously: One is the ethical approach, another is statistical, third is from the perspective of the provider of care, and the fourth is as a patient."

Gold then asks himself what a federal scientific reviewer would think about this protocol and whether an IRB would be comfortable approving it.

Here's how Gold developed the matrix:

• **Keep in mind the three major ethical principles:** "In my matrix for beneficence, I have an assessment of risks and benefits," Gold explains.

The three major principles are:

— Respect for people;

— Beneficence;

— Social justice.

• **Understand the various types of benefits:** In assessing a protocol in terms of the ethical principles, it's important to consider that there are three levels of benefits, including direct benefit, collateral benefit, and societal benefit, views taken by the National Bioethics Advisory Commission and Nancy M.P. King, JD, professor of social medicine at the University of North Carolina-Chapel Hill.

A particular study may have all three benefits, or perhaps only one of the three. But if the investigator hasn't given this area some thought, it's possible that both the investigator and subjects will misunderstand the potential benefits.

"Direct benefit means the individual participant will gain personally from participating in the study," Gold says. "That's a rigorous definition and extremely difficult to meet and hard to estimate."

A collateral or indirect benefit is a benefit that occurs as a result of the person's participation in a study, but it was not the goal or intention of the study to produce this benefit.

The societal benefit may include solving a problem therapeutically or increasing the scientific community's knowledge of a process in hopes that this information will one day lead to developing a new therapy.

• **Estimate probability of direct benefit:** Before researchers can say that a particular study may provide a direct benefit to participants, they should analyze the probability and magnitude of such an outcome, he says.

"The direct benefit generally is going to be very low for the individual, but that doesn't nullify the value of a study," Gold says. "That just means participants should be aware of that fact, so they don't fall victim to the therapeutic misconception."

It's also important for investigators to be aware of their own therapeutic misconceptions, especially if they recruit volunteers from their clinical case loads and take on the dual role of provider and investigator, he says.

As an example, Gold has calculated that a particular study he reviewed for his IRB would have a one-in-eight likelihood of direct benefit, based on a randomization scheme, the study's anticipated results, and other information included in the protocol. "I was making a guess, and we do

that all the time anyway," he says. "Just like with harms, the probability and magnitude of benefits should be determined, even though it is tougher with a benefit."

• **Provide practical applications analysis:** Gold's matrix includes three practical applications, which are:

— Informed consent;

— Assessment of risks and benefits;

— Selection of subjects.

The informed consent discussion, for example, would include information about the study, an attempt to make certain the information easily can be understood, and an effort to show how subjects volunteered without any coercion.

• **Look at risks of all facets of harm:** Gold typically will begin to assess a study with regard to all of the possible harms, including psychological, social, economic, and physiological.

"Physiological gets most of the attention because those harms often carry a probability for severe injury, possibly even death," he says, "whereas the others may carry humiliation, loss of job, or loss of insurance."

For instance, suppose an insurance company learns from a research study that a particular client suffers from clinical depression and has a problem with alcohol abuse.

"The insurance company may say that the person drinks alcohol, which is a voluntary behavior, and therefore the company won't insure the person for major medical problems," Gold says. "Researchers take care to preserve confidentiality, but there still are potential harms, and I lay these out along with specific harms, such as psychological discomfort in an interview."

Economic harms might include job loss and other things that occur in people's daily lives, but are accentuated because of a study.

• **Predict harm probability and magnitude:** With each potential harm identified for a particular study, Gold will look try to determine the probability or likelihood of this harm occurring and the magnitude or how damaging it would be if it did occur.

"You may have the probability of one in 10,000 for a harmful reaction to a medication, and that may not require as much attention to protect research volunteers as the probability of one in 10 that someone's HIV status gets communicated to the wrong people," Gold explains. "So that [latter] harm needs more attention so you can protect subjects against the breach of confidentiality."

"In my matrix of harm, probability, and magnitude, I also have a column of what we're going to do to minimize a harm," Gold adds.

As part of the process of completing a harm-benefit matrix, investigators should list all of the measures they will take to minimize the potential for harm. These may include the following:

— How information will be collected, stored, and protected.

— How closely adverse events will be monitored and the likelihood of these occurring.

— How frequently subjects will be contacted.

— Whether participants have mechanisms for contacting investigators.

— Whether participants will be given written explanations of the potential adverse events, and whether they can remember what these are.

— Who is going to be in charge of coordinating this investigator-subject communication.

"I find it hard to get that level of specificity from investigators submitting protocols to the IRB, but it's necessary," Gold says. "Having someone volunteer in your study is a privilege and not somebody's right."

Volunteers are heroes, Gold adds. "If they were perceived as heroes for going into research, we'd all be very careful." ■

Does anybody really know what HIPAA is?

The Privacy Rule is not as restrictive as anticipated

The Health Information Portability and Accountability Act (HIPAA) of 1996 contained a provision for protecting patients' privacy by protecting their health information. The final rule was published in August, and though most health care professionals have heard of HIPAA, most have only a vague notion of what it is and how it will impact day-to-day interactions with patients.

On the IRB Forum web site (www.irbforum.org), those talking about HIPAA are asking for clarification. "How does the revision affect the functioning of IRBs?" asked **Susan C. Gusy**, AS, executive administrative support staff for the Eastern Connecticut Health Network Institutional Review Committee in Manchester. "I am currently struggling with the HIPAA issue and have not received any real clarifications at this

(Continued on page 116)

Frequently Asked Questions about HIPAA

Q: What does this regulation do?

A: The Privacy Rule became effective April 14, 2001. Most health plans and health care providers that are covered by the new rule must comply with the new requirements by April 2003.

The Privacy Rule for the first time creates national standards to protect individuals' medical records and other personal health information.

- It gives patients more control over their health information.
- It sets boundaries on the use and release of health records.
- It establishes appropriate safeguards that health care providers and others must achieve to protect the privacy of health information.
- It holds violators accountable, with civil and criminal penalties that can be imposed if they violate patients' privacy rights.
- And it strikes a balance when public responsibility requires disclosure of some forms of data — for example, to protect public health.

Q: What does this regulation require the average provider or health plan to do?

A: For the average health care provider or health plan, the Privacy Rule requires activities, such as:

- providing information to patients about their privacy rights and how their information can be used;
- adopting clear privacy procedures for its practice, hospital, or plan;
- training employees so that they understand the privacy procedures;
- designating an individual to be responsible for seeing that the privacy procedures are adopted and followed;
- securing patient records containing individually identifiable health information so that they are not readily available to those who do not need them.

Q: What is the difference between "consent" and "authorization" under the Privacy Rule?

A: A consent is a general document that gives health care providers, which have a direct treatment relationship with a patient, permission to use and disclose all personal health information (PHI) for treatment, payment, or health care operations (TPO). It gives permission only to that provider, not to any other person.

An authorization is a more customized document that gives covered entities permission to use specified personal health information for specified purposes, which are generally other than TPO, or to disclose PHI to a third party specified by the individual. An authorization is more detailed and specific than consent. It covers only the uses and disclosures and only the PHI stipulated in the authorization; it has an expiration date; and, in some cases, it also states the purpose for which the information may be used or disclosed.

Q: Will the rule hinder medical research by making doctors and others less willing and/or able to share information about individual patients?

A: We do not believe that the Privacy Rule will hinder medical research. Indeed, patients and health plan members should be more willing to participate in research when they know their information is protected. For example, in genetic studies at the National Institutes of Health (NIH), nearly 32% of eligible people offered a test for breast cancer risk decline to take it. The overwhelming majority of those who refuse cite concerns about health insurance discrimination and loss of privacy as the reason.

Q: Are some of the criteria so subjective that inconsistent determinations may be made by IRBs and Privacy Boards reviewing similar or identical research projects?

A: Under the Privacy Rule, IRBs and Privacy Boards need to use their judgment as to whether the waiver criteria have been satisfied. Several of the waiver criteria are closely modeled on the Common Rule's criteria for the waiver of informed consent and for the approval of a research study. Thus, it is anticipated that IRBs already have experience in making the necessarily subjective assessments of risks and benefits. For multisite research that requires PHI from two or more covered entities, the Privacy Rule permits covered entities to accept documentation of IRB or Privacy Board approval from a single IRB or Privacy Board.

Q: Does the Privacy Rule prohibit researchers from conditioning participation in a clinical trial on an authorization to use/disclose existing PHI?

A: No. The Privacy Rule does not address conditions for enrollment in a research study. Therefore, the Privacy Rule in no way prohibits researchers from conditioning enrollment in a research study on the execution of an authorization for the use of pre-existing health information.

Q: Does the Privacy Rule permit the creation of a database for research purposes through an IRB or Privacy Board waiver of individual authorization?

A: Yes. A covered entity may use or disclose PHI without individuals' authorizations for the creation of a research database, provided the covered entity obtains documentation that an IRB or Privacy Board has determined that the specified waiver criteria were satisfied.

Q: Will IRBs be able to handle the additional responsibilities imposed by the Privacy Rule?

A: Recognizing that some institutions may not have IRBs, or that some IRBs may not have the expertise needed to review research that requires consideration of risks to privacy, the Privacy Rule

permits the covered entity to accept documentation of waiver of authorization from an alternative body called a Privacy Board, which could have fewer members and members with different expertise than IRBs.

In addition, for research that is determined to be of no more than minimal risk, IRBs and Privacy Boards could use an expedited review process that permits covered entities to accept documentation when only one or more members of the IRB or Privacy Board have conducted the review.

Q: By establishing new waiver criteria and authorization requirements, hasn't the Privacy Rule, in effect, modified the Common Rule?

A: No. Where both the Privacy Rule and the Common Rule apply, both regulations must be followed. The Privacy Rule regulates only the content and conditions of the documentation that covered entities must obtain before using or disclosing PHI for research purposes.

Q: Is documentation of IRB *and* Privacy Board approval required before a covered entity would be permitted to disclose PHI for research purposes without an individual's authorization?

A: No. The Privacy Rule requires documentation of waiver approval by either an IRB *or* a Privacy Board, not both.

Q: Does a covered entity need to create an IRB or Privacy Board before using or disclosing PHI for research?

A: No. The IRB or Privacy Board could be created by the covered entity or the recipient researcher, or it could be an independent board.

Q: What does the Privacy Rule say about a research participant's right of access to research records or results?

A: With few exceptions, the Privacy Rule gives patients the right to inspect and obtain a copy of health information about themselves that is maintained in a "designated record set." A designated record set is basically a group of records which a covered entity uses to make decisions about individuals, and includes a health care provider's medical records and billing records, and a health plan's enrollment, payment, claims adjudication, and case or medical management record systems. Research records or results maintained in a designated record set are accessible to research participants unless one of the Privacy Rule's permitted exceptions applies.

One of the permitted exceptions applies to PHI created or obtained by a covered health care provider/researcher for a clinical trial. The Privacy Rule permits the individual's access rights in these cases to be suspended *while the clinical trial is in progress*, provided the research participant agreed to this denial of access when consenting to participate in the clinical trial. In addition, the health care provider/researcher must inform the research participant that the right to access PHI will be reinstated at the conclusion of the clinical trial.

Q: Are the Privacy Rule's requirements regarding patient access in harmony with the Clinical Laboratory Improvements Amendments of 1988 (CLIA)?

A: Yes. The Privacy Rule does not require clinical laboratories that are also covered health care providers to provide an individual access to information if CLIA prohibits them from doing so. CLIA permits clinical laboratories to provide clinical laboratory test records and reports only to authorized persons, as defined primarily by state law. The individual who is the subject of the information is not always included as an authorized person. Therefore, the Privacy Rule includes an exception to individuals' general right to access PHI about themselves if providing an individual such access would be in conflict with CLIA.

In addition, for certain research laboratories that are exempt from the CLIA regulations, the Privacy Rule does not require such research laboratories if they are also a covered health care provider to provide individuals with access to PHI because doing so may result in the research laboratory losing its CLIA exemption.

Q: Do the Privacy Rule's requirements for authorization and the Common Rule's requirements for informed consent differ?

A: Yes. Under the Privacy Rule, a patient's authorization will be used for the use and disclosure of PHI for research purposes. In contrast, an individual's informed consent as required by the Common Rule and FDA's human subjects regulations is a consent to participate in the research study as a whole, not simply a consent for the research use or disclosure of PHI. For this reason, there are important differences between the Privacy Rule's requirements for individual authorization, and the Common Rule's and FDA's requirements for informed consent. Where the Privacy Rule, the Common Rule, and/or FDA's human subjects regulations are applicable, each of the applicable regulations will need to be followed.

Source: Department of Health and Human Services, Office for Civil Rights, Washington, DC. Web: www.os.dhhs.gov/ocr/hipaa/finalmaster.html.

time," she told *IRB Advisor*.

The questions posed on the Forum included the role of Privacy Boards, the impact the provision will have on informed consent, and how information can be used in reporting results. **(See "Frequently Asked Questions about HIPAA," p. 115.)**

"To the extent that there is confusion, it likely involves areas where HIPAA and the Common Rule contain similar, but not identical, concepts, such as de-identified or anonymous data and the

HIPAA authorization waiver criteria vs. the Common Rule's considerations for waiver of informed consent," says **Clinton D. Hermes**, JD, a lawyer with the Boston firm of Ropes & Gray.

A layman's version of the rule appearing on the Department of Health and Human Services' (HHS) Office of Civil Rights web site explains the rule thusly, "Where research is concerned, the Privacy Rule protects the privacy of individually identifiable health information, while at the same time, ensuring that researchers continue to have access to medical information necessary to conduct vital research. In the course of conducting research, researchers may create, use, and/or disclose individually identifiable health information with individual authorization, or without individual authorization under limited circumstances."

Those limited circumstances include:

• "Documentation that an alteration or waiver of research participants' authorization for use/disclosure of information about them for research purposes has been approved by an Institutional Review Board or a Privacy Board. This provision of the Privacy Rule might be used, for example, to conduct records research, when researchers are unable to use de-identified information and it is not practicable to obtain research participants' authorization.

• "Representations from the researcher, either in writing or orally, that the use or disclosure of the personal health information is solely to prepare a research protocol. This provision might be used, for example, to design a research study or to assess the feasibility of conducting a study.

• "Representations from the researcher, either in writing or orally, that the use or disclosure being sought is solely for research on the personal health information of decedents, that information being sought is necessary for the research *and,* at the request of the covered entity, documentation of the death of the individuals about whom information is being sought."

When an authorization waiver is requested, the IRB or Privacy board will have to determine the following, explains **Ralph L. Glover II**, JD, an attorney with the Chicago law firm Michael Best and Friedrich:

• whether the use or disclosure of protected health information for the research study involves no more than a minimal risk to the privacy of the participants;

• that the research could not practicably be performed without the waver or alteration;

• that the research could not practicably be conducted without the protected health information.

"IRBs need to be aware of the authorization and waiver requirements and of the limited data set requirements," Glover says. "The limited data set is protected health information stripped of 16 identifiers about the individual, their relatives, household members, and their employers." Data sets can be used for research, public health or health care operations, he explains, but before a limited data set is disclosed, a data-use agreement must be in place with the recipient of the limited data set."

Records reviews or disclosure of personal health information can be used for subject recruiting, however, IRBs should be aware that HHS has guidelines regarding this practice. According to Glover, "The Privacy Rule permits a hospital to disclose personal health information to a researcher at the hospital's premises if the researcher states, either in writing or orally, that 1) the use or disclosure is sought solely to review protected health information as necessary to prepare a research protocol or for similar purposes preparatory to research; 2) no protected health information is to be removed from the hospital by the researcher in the course of the review; and 3) the protected health information for which use or access is sought is necessary for the research purposes. If the researcher intends on removing protected health information from the hospital, the hospital must obtain an authorization for this disclosure. "

"The Privacy Rule is not going to significantly change the way hospitals use or disclose protected health information because presumably, they already comply with applicable federal laws relating to privacy of medical information, including the Common Rule," he says. "Most uses and disclosures of an individual's protected health information for research will be conducted with the authorization of the individual. In these cases, the research authorization can be attached to the informed consent document." ■

Beyond HIPAA: Protect sensitive information

Certificates of Confidentiality keep out prying eyes

The National Institutes of Health (NIH) issues Certificates of Confidentiality when it is necessary to provide better protection to research subjects' privacy, but there have been questions

recently about whether these are being used appropriately.

Essentially, the certificates allow investigators to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceeding at the federal, state, and local levels. This protection can be a powerful aid when investigators are dealing with sensitive information, such as genetic, psychological, and substance abuse data.

But do investigators and IRBs understand when and how to seek a certificate? Some institutions may use these too much and others too little, which is a problem that has prompted the NIH to issue some recent guidelines, addressing the issue.

How much is too much?

According to Certificates of Confidentiality experts at the National Institute of Mental Health (NIMH) in Bethesda, MD, there is some variability in familiarity with Certificates of Confidentiality across investigators and IRBs, depending on their history of past use, the kinds of research conducted at the local institution, and other factors.

This is why NIH created a Certificate of Confidentiality Kiosk at the web site: http://grants1.nih.gov/grants/policy/coc/index.htm. The kiosk provides background information and instructions about applications, and it provides a list of NIH contacts who can answer questions.

However, should an IRB or investigator err on the side of caution or expediency?

Researchers at the Washington University School of Medicine in St. Louis have been using Certificates of Confidentiality for years, although NIH officials sometimes tell them that they use these too frequently, says **Patricia Scannell**, BA, CIP, director of the Human Studies Committee.

"Evidently, many institutions do not use Certificates of Confidentiality to the extent that we do," she says. "We use them for sensitive, behavioral research, as well as research that screens for HIV/AIDS, and other sexually transmitted diseases [STDs]."

Investigators benefit because their subjects are provided an additional level of protection to assure them that their confidential information will not be disclosed, Scannell adds.

Several years ago, an investigator at Washington University School of Medicine was served with a warrant from a local law enforcement agency, seeking the whereabouts of a particular research subject. This experience brought home the value of having a Certificate of Confidentiality, Scannell notes.

"We have many research proposals that focus on substance abuse and involve information that could be used against a subject should the information be brought to court or discovered outside the research realm," she says. "Likewise, HIV testing is frequently part of studies, and this information could cause significant harm to a subject should it become known outside of the research."

It may be difficult for investigators to recruit potential subjects without providing them this additional security, Scannell says.

It's appropriate to use Certificates of Confidentiality for research involving HIV, however STD and HIV disclosures may be made to public health authorities as voluntary reports, and subjects should be informed of this possibility in the informed consent, NIMH officials say.

Some IRB members and research experts may be concerned that research sponsors and investigators could misuse the certificates, particularly if these are rarely used by others involved in similar research.

For instance, an IRB at North Memorial Healthcare in Robinsdale, MN, reviewed a research project involving a clinical trial of two drugs, and a Certificate of Confidentiality had been sought, says **Mark Hochhauser**, PhD, of Readability Consultant in Golden Valley, MN. Hochhauser is the community representative of the IRB.

"I couldn't figure out why these were in a clinical trial of two drugs," he says. "I asked the researcher who presented it before our committee why there was a Certificate of Confidentiality for this kind of research because there was no sensitive information and nothing illegal."

The investigator told the IRB that the company was doing research in prisons, and this was the consent they were using there and it probably just got attached as the same consent form for every site, Hochhauser recalled.

"But I'm still a little troubled because of the implications of a Certificate of Confidentiality," he says. "I was cynical enough to think this is a way for the sponsor to avoid disclosing information in a court setting."

While Hochhauser raises a valid point, the rules regarding Certificate of Confidentiality should protect subjects from these being used abusively. Researchers and research institutions cannot use the certificates if the subject requests disclosure of his research information, NIMH officials say.

That restriction is imposed to prevent precisely the sort of scenario Hochhauser envisioned of a

researcher or institution using the certificate to evade responsibility in the event a subject chooses to file a lawsuit, NIMH officials say.

Should the IRB require a certificate?

Sometimes it's the IRB that will ask investigators to apply for a Certificate of Confidentiality when IRB members believe the information is highly sensitive and that extra protection is warranted.

However, investigators sometimes balk at this request. "Investigators say, 'You're asking us to do all this paperwork in order to put an extra blanket of protection on something we're scrupulously protecting to begin with,'" Scannell says. "I guarantee that with all the hoops investigators go through they are not happy when IRBs ask them for additional paperwork."

Plus, NIH asks that Certificates of Confidentiality be submitted three months before research subjects are enrolled, and this could tie up some studies.

So it's up to the IRB to weigh the risk of disclosure of subject's private information vs the investigator's need to proceed on schedule with the study, Scannell says.

HIPAA may impact use

Sometimes the IRB may decide that the protocol cannot be approved without the certificate, while in other instances the IRB may say that if the investigator can destroy all links to the private information, that would be protection enough, she adds.

Also, with the Health Insurance Portability and Accountability Act (HIPAA) privacy regulations, it's possible that these will diminish the need for Certificates of Confidentiality. **(See related story, p. 114.)**

This is a development that NIH is in the process of analyzing, although, so far, it appears that HIPAA will not seriously affect the usefulness of Certificates of Confidentiality, NIMH officials say.

Here are some of the basic NIH guidelines pertaining to applications for Certificates of Confidentiality:

- These can be used for biomedical, behavioral, clinical, or other types of research that is sensitive, which means that the disclosure of identifying information could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.
- Sensitive research activities may include genetic information; information on subjects' psychological well-being; information on subjects' sexual attitudes, preferences, or practices; substance abuse data; information on illegal risk behaviors; and studies where subjects may be involved in litigation related to medical, environmental, or occupational exposures.
- Projects that are not eligible for a certificate include projects that are not research; where personally identifiable information is not collected; where studies are not reviewed or approved by an IRB; or where the collection of information would not significantly harm or damage a participant if it were disclosed.
- Certificates protect against involuntary disclosure, but subjects may voluntarily disclose their research data or information to physicians or third parties, and they may authorize in writing for investigators to release the information. Investigators may not use the certificate to refuse disclosure when authorized by the subject.
- Certificates do not prevent researchers from disclosing child abuse, reportable communicable diseases, or a subject's threatened violence to self or others.
- A Certificate of Confidentiality protects identifiable information about subjects in perpetuity, so long as identifiable data about that subject was maintained in study records while the certificate is in effect.
- A certificate is issued by the NIH based on a principal investigator's (PI) application for a specific research project, and it's granted to the researcher's institution. When a study is a multisite project, the PI may apply on behalf of all sites. ■

COMING IN FUTURE MONTHS

- IRB director offers advice about handling an accreditation survey
- Tweak and improve your conflict-of-interest policy
- Give as much attention to benefits as you do with risks in informed-consent discussions
- International human research protection effort

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;
- understand 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;
- have an understanding of the potential for conflict of financial interests involving human subject research;
- understand reporting adverse events during research. ■

CME*questions*

CME subscribers: Please save your monthly issues in order to take the CME semester tests in June and December. A Scantron will be inserted, but the questions will not be repeated.

13. In assessing probability and magnitude of benefit for the purpose of doing a risk-benefit analysis, which is not considered one of the potential levels of benefits?
A. Direct benefit, which means the individual participant will gain personally from participating in the study.
B. Familial benefit, which is when a subject's close family or friends receive an indirect benefit from the subject's participation in the research.
C. Collateral benefit, which is a benefit that occurs as a result of the person's participation in the study, but which was not the goal or intention of the study.
D. Societal benefit, which is a benefit that includes increased knowledge or therapeutic means that eventually may lead to better out comes in treating patients with particular diseases or problems.

14. Which of the following are considered sensitive research activities for the purposes of applying for a Certificate of Confidentiality?
A. Genetic information
B. Information on a subject's psychological well-being
C. Information on a subject's sexual attitudes, preferences, or practices
D. All of the above

15. The Privacy Rule:
A. Gives patients more control over their health information.
B. Sets boundaries on the use and release of health records.
C. Establishes appropriate safeguards that health care providers and others must achieve to protect the privacy of health information.
D. All of the above

16. HIPAA compliance in the research community will require:
A. Patient authorization
B. Patient informed consent
C. Informed consent waiver
D. None of the above