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Collecting extra tissue samples should be a no-go without consent

Add-on gene studies pose special concerns for IRBs

In recent years, it has become a common practice for sponsors of clinical trials to collect extra blood and tissue samples from subjects for genetic analysis and possible later use in future research projects. However, trial coordinators should be aware that these types of arrangements — known as add-on studies or tag-on studies — are drawing increasing scrutiny from institutional review boards.

"When industry sponsors propose to add on a genetics study to a traditional clinical trial, this may be viewed as suspicious and potentially create a substantial risk [to subjects] due to the lack of specificity inherent in the protocol," says **Barbara Handelin**, the CEO of Kenna Technologies Inc., a drug discovery company in West Chester, PA.

In 2000, Handelin, a trained geneticist, helped conduct a research study funded by the U.S. Department of Energy that evaluated the challenges IRBs faced when reviewing genetic studies. In her studies, add-on genetic research was of particular concern for many IRB members.

Two main characteristics of such studies can be troubling for IRBs, she says. One, the potential for unknown future use of the clinical specimens and the afterthought nature of how the consent to participate in the add-on protocol may be presented to potential subjects.

"It is a different approach to conducting research," she notes. "It is a cataloging process more than being hypothesis driven."

With traditional research protocols, investigators have a hypothesis in mind and seek evidence to either support the hypothesis or disprove it.

Now that the human genome has been mapped, however, researchers often simply want to collect and examine the DNA of large populations of people in the hopes that some genetic mutation may be observed and subsequently linked either to a particular disease or condition or a resistance to it.

Lack of specificity troubling

Add-on studies have quickly become very common, particularly in clinical drug trials, says **Daryl Pullman**, MD, associate professor of

medical ethics at Memorial University of Newfoundland in St. Johns.

"Just within the last five years or so, almost every clinical trial has a genetic add-on," says Pullman, who sits on the university's research ethics board (REB), the Canadian counterpart to U.S. IRBs. "If there is a clinical trial, they often want to ask if they can take another blood sample, telling the subject, 'Your DNA may be valuable for research purposes and we'd like for you to give us another sample.'"

The problem, he says, is that investigators themselves don't know what kinds of studies might be performed on the samples in the future, what information might be sought, and how the information will be used. Therefore, they can't truly inform the subjects about the possible risks and benefits to participation.

Certainly, in many cases, participants in genetic studies can expect to see no individual benefit.

"For example, there is a family that has a high prevalence of a kind of neuropathy that gives them chronic insensitivity to pain," he says. "So there is real interest, from a genetics perspective, in finding out what is the genetic problem that makes these people insensitive to pain. But the interest isn't in treating the condition so they can become pain sensitive. The interest is in finding out what the genetic link is. There can be all kinds of implications — e.g., developing new analgesics, etc. — so, none of the benefits of the specific research would ever go back to this family. They are just interesting research subjects."

Investigators must be up front in their consent documents and explain the unknown nature of the future research and specify how the subjects' DNA will be maintained, whether it will be identifiable and how participants may withdraw their consent at a later time, if they so decide, Pullman says.

At Memorial, the REB has prohibited add-on protocols that simply want to collect DNA for any type of future cataloging, he says. Investigators must stipulate that the samples collected will be used for studying a condition related to the subject of current study.

"For example, if the subjects are participating in the trial of a psoriasis drug, the future studies would have to be related in some way to the study of psoriasis — they couldn't just collect the samples for any purpose," he notes.

Consent is not one-time event

If the samples taken are going to remain linked in any way to the subject's identifying information, then the subject must also be given information about how his or her privacy will be maintained, where the information will be stored, and provide

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a way for the subjects to withhold or withdraw their consent, Pullman adds.

"We are very concerned about blanket consent to allow the researchers to do anything they want with the samples," he continues. "If it is de-identified, that is one thing — but oftentimes they want to maintain some kind of linkage with the patient record because that is what is important about the information. In addition, when you obtain consent to use samples for research purpose afterwards, you can't just use it for any research approved by an IRB; you can only use it for research that is related to rheumatoid arthritis or whatever. And you have to give the subject the option of saying, 'No, at the end of the study I want my sample destroyed,' and provide a way for them to ask, if they change their minds later, that their identifiable sample be removed and destroyed."

If the samples will be de-identified early on, potential participants should also be informed of that and informed at what point they will no longer be able to withdraw consent, because the sample will be de-linked and investigators won't be able to determine which sample belonged to which person.

Separate document required

Memorial's REB also requires investigators proposing add-on studies to put information about that study in a separate informed consent document, rather than buried within the current study consent form, Pullman says.

"Informed consent documents tend to be overly burdensome in terms of the level of detail and the kinds of information presented; it is difficult sometimes to comprehend what is being proposed. If somebody has cancer or arthritis, we already have enough problems getting them to understand that this is not clinical care that we are proposing, this is research," he explains.

"We don't think that in the midst of all of that there should be two lines that say, 'Oh yeah, we'd like to take some additional samples for future use and you're signing away all rights in the event that we find something that might be of clinical or economic use.' We have actually required that those kinds of statements be taken out of the informed consent document for the trial. We now require a separate consent form for genetic add-on studies."

The issue of telling subjects they will not be entitled to share in the financial rewards should the study of their DNA yield valuable information is a tricky one, Pullman adds.

Memorial's REB does not allow informed consent documents to make statements that seem to prohibit subjects from seeking to share in the benefits of the research, but many institutions do, he notes. **(See story on exculpatory language, p. 41.)**

"More commonly, consent documents have to at least admit they are looking for something that may have commercial marketability and that might make a profit. They are required to at least be up front and say that might happen, but then they might say, 'We are not going to pay anything to you in the event that should happen, and that way people know ahead of time."

Pullman and colleagues at the university and in Newfoundland's provincial government are exploring ways to get sponsors of genetic research to work out separate benefit-sharing arrangements with communities before permitting add-on studies to take place in a certain locale.

In that way, subjects would be able to gather some benefit for participation whether or not their genetic information led to some breakthrough treatment. Such proposals are controversial, however, and legal determinations of who owns human DNA have not been clearly worked out anywhere, he notes.

"But without that process in place, we at least require any statements about the add-on studies to be taken out of the information about the current clinical trial that is taking place and be placed in a separate document," he says. "So the participant considers whether they want to participate in the clinical trial, and then, separately, consider whether they are willing to have their samples saved for later use." ■

Are research subject advocates the future?

NCRR created position, but roles vary

There is a new kid on the block, helping to oversee human subject protections at some institutions and providing some assistance to overtaxed IRBs: the research subject advocate (RSA).

The National Center for Research Resources (NCRR) of Bethesda, MD, decided several years

ago that researchers and IRBs needed additional resources when it comes to human subject protection, so NCRR created the RSA position to assist 82 General Clinical Research Centers (GCRCs) that receive funding from five-year National Institutes of Health (NIH) grants.

"I wasn't at NCRR when the decision was made, but I think from my discussions here that the thought was that RSAs were not to take the place of the IRB or human subject protection offices at institutions, but to help GCRC nurses, participants, lab staff, and principal investigators to understand what was needed," says **Elaine Collier**, MD, assistant director for clinical research at NCRR.

"The RSA's task is to represent the voice of the human subject on GCRC, because that's a voice that's not there," she adds. "So this is a person who thinks about how the participant would view the study when discussions are made of that study."

Many RSAs work closely with IRBs, and some are members of IRBs. This gives them an insight into what the IRB expects and needs from investigators, and they'll pass that information on to the investigators often before the protocols are submitted.

"Also, if they have concerns about a protocol they can profess those to the IRB, too," Collier says. "It's a two-way street."

Although RSAs now are only available at GCRCs, the model could be useful at other institutions, she notes.

Industry-sponsored and other government-sponsored trials could benefit from having an RSA involved, Collier says. "We don't envision right now moving in that direction, although we see how it would be useful."

Here's how the position works:

• **RSAs vary widely in their duties, but there should be little or no duplication with what IRBs do.** "IRBs have an actual statutory responsibility for human research subject protection. We try to assist investigators in meeting IRB criteria," says **Theresa O'Lonergan**, MA, research subject advocate at the Pediatric General Clinical Research Center at the University of Colorado Health Sciences Center and a biomedical ethicist at the Children's Hospital in Denver. She also is the president of the Society for Research Subjects Advocates.

"I work with the IRB, and we share a database that they have generously allowed me to access. If I see that an investigator's [paperwork] is about to expire, I can contact the investigator," O'Lonergan says. "I don't take on the IRB's work; I just make sure our principal investigators are doing what they're supposed to be doing."

Wajeeh Bajwa, PhD, a research subject advocate and regulatory consultant at Duke University Medical Center in Durham, NC, has provided RSA-type services to his institution since 1998, and the RSA model was developed based on his work.

The idea of having a separate regulatory consultant or RSA is that IRBs spend a great deal of resources in handling paperwork related to compliance and consent forms and have little time for hands-on oversight, Bajwa says.

The idea of having a separate regulatory consultant or RSA is that IRBs spend a great deal of resources in handling paperwork related to compliance and consent forms and have little time for hands-on oversight.

"There's very little in terms of oversight of manufacturing aspects or clinical trials in terms of doing orders and looking at documentation that each investigator has at his site," he explains. "At Duke, we started providing this service for investigators so they could request a regulatory consultant to help them become fully compliant with good manufacturing practices and good clinical practices."

Once Bajwa began the work, the response from investigators was tremendously positive, he says. "Usually investigators do not have the funds to hire an outside consultant."

Likewise, the Duke IRB was supportive of the role and has always been mutually cooperative, Bajwa says.

"I am a member of the IRB, and some protocols are assigned to me to review, and they are not necessarily related to GCRC," Bajwa adds. "I can stay abreast of what new things the IRB has to cope with, like when they had to modify all consent forms using HIPAA [Health Insurance Portability and Accountability Act] language."

In creating the RSA model, NCRR made the position flexible by giving institutions leeway to turn this into whatever worked best for them. For example, some GCRCs have full-time RSAs, while others may have several people providing part-time RSA work. The people working as RSAs have a variety of degrees and experience, and while some serve on IRBs, others do not because they feel it would be a conflict of interest.

"As you can imagine, we're an extremely

diverse group of people," says **Susan Margitic**, MS, GCRC research subject advocate for Wake Forest University School of Medicine in Winston-Salem, NC. "Some of us are ethicists, some are clinicians, and some are researchers."

• **RSAs often work directly with investigators and research staff.** One of the big advantages to having an RSA is that the RSA can work one on one with investigators, both in terms of providing input for the protocol as it's developed and helping to monitor the safety status of the study, Margitic says.

"Whereas our IRB is responsible for over 1,000 active protocols, our RSA office oversees the safety of about 100 protocols," she adds.

RSAs educate and work closely with investigators as they develop protocols, providing them with suggestions that will ease their application process.

"The main role of the RSA is the training and education of the investigators," Bajwa says. "The IRB is more of a monitoring board, and RSAs can fulfill this role of training and education and answering investigators' questions on a day-by-day basis."

O'Lonergan typically works with investigators for about four months before they're ready to submit their protocol to the IRB. "If I help them with the protocol, they typically go through the IRB review with fewer problems, and our review has fewer problems," she says. "I work with them on research design and human subjects protection."

Some RSAs, including O'Lonergan, are involved in the GCRC approval process, and investigators will make changes per the RSA's suggestions, she notes. "I have a good relationship with investigators; and if I bring up concerns, they know I'm not the only one who has them."

Once a protocol is approved by both the GCRC and the IRB, the RSA still may provide assistance through data safety monitoring, providing guidance during the informed consent or assent process, and training research staff, O'Lonergan says.

"If it's a problematic protocol I might suggest that I come in and help with the first month or so," she says. "I meet with them at protocol initiation, make sure nurses have no problems in recruiting and know what they are supposed to do."

RSAs may also assist experienced investigators by letting them know when protocol changes need IRB approval and providing some assistance with meeting HIPAA privacy regulations, O'Lonergan says.

"At first, you're always worried that investigators will think, 'Why is she bothering me?'" she says. "But I've had the good fortune to have investigators say, 'I didn't know you could do this — come on over.'"

Basically, RSAs provide investigators with assurance that their protocol applications are submitted properly and that their research meets all regulatory standards.

"The other thing that RSAs do is provide a friendly audit of trials for investigators at GCRCs," Collier says. "So if there are things that need to be improved, the RSA can talk with the investigator about them, and it's not a compliance audit."

• **RSAs may also work directly with research subjects.** Bajwa sometimes meets with research subjects to make certain that they understand the informed consent form.

Particularly in the cases of high-risk studies, he will make certain subjects understand all of the risks involved in the study, and he'll sit down with investigators when they are explaining consent to subjects.

"I monitor how the consent is being given and provided to the research subject, and in one study that can take up to 3½ to four hours," Bajwa reports.

Margitic also observes investigators as they provide informed consent, watching to make certain they engage the person in a dialogue and encourage the person to ask questions.

"We don't want to see any signs of coercion," Margitic says. "The consenter should take time and not give any indication that they're rushed."

The whole idea of having an extra person observing and monitoring research projects in a hands-on manner is one that might become a model for many institutions, Margitic says.

"My sense is we are really paving the way," Margitic says. "The RSA serves as a role model that is first of its kind and it may be a pilot for what could be done institutionwide, although we have the luxury of doing the work for a core group of protocols." ■

It's what you say that could create liability

Consent forms shouldn't waive rights

Federal laws governing research on human beings prohibit research institutions and sponsors from requiring subjects to sign documents that waive or appear to waive any of their legal

rights. However, researchers are also required to inform potential participants whether the sponsors intend to pay for medical care in the event a subject is injured as a result of participation.

In some cases, legal experts warn, sponsors' efforts to inform subjects about payment policies are crossing the line and may actually be interpreted as the waivers that the Common Rule prohibits.

"What you see, almost constantly, are sponsors, investigators and institutions attempting to inject into the consent document language that supports a particular view," explains **Thomas K. Dalglish**, JD, PhD, former director of the Office of Research Integrity at the University of Louisville (KY). "They will try to push the envelope. You see phrases like, 'I specifically understand that the sponsor is not liable for any . . .' or 'We will pay *only* for medical expenses related to the research study.'"

Such phrases attempt to make subjects believe that their options, in the event that injury occurs, are limited by the policies of the respective research sponsors when that, by law, is not the case, he says.

For example, injured subjects can sue if they believe they were injured as a result of an investigator's negligence. Subjects also may have rights to the information collected about them during the course of the trial.

Language in the consent form should inform subjects of things that the sponsor will provide (e.g., payments for medical care), but be careful not to imply that consent or acceptance of the terms limits the subjects' options at a later time.

"The point is, you should not write language that serves as a discouragement or disincentive — 'We will only pay,' for example, or 'I understand that I will only be entitled to . . .,'" Dalglish explains. "Those statements are not true. No matter what the policy of the institution or sponsor, subjects should be under no illusion and the sponsors should be under no illusion, that such policies limit what is available under the law."

What the rules say

Section 45 CFR Section 46.116 covers informed consent (as does similar language in the regulations of the U.S. Food and Drug Administration at 21 CFR Sections 50.20 and 50.25), says **Janet M. Lis**, Esq., a health care attorney practicing in Media, PA.

The introductory paragraphs of Section 46.116 state:

"No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence."

Section (a)(6) then states:

"For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained."

This can be fulfilled by stating what the sponsor on institution does plan to pay for or has set funds aside for should injuries occur, Lis says.

"The issue becomes that of stating what will or will not be provided clearly, and not stating or implying that rights have been given up [as prohibited by the introductory section noted above]. These statements should not make the subject think that he is releasing anyone involved in the research from liability for negligence or giving up rights that would otherwise exist," says Lis.

The federal Office for Human Research Protections (OHRP) has provided guidance as to what language they think is and is not appropriate, she adds **(see box, p. 43)**.

Assumption of risk does not apply

An argument often made is that, by signing the consent forms, subjects have assumed responsibility for the risks of the research, says Dalglish.

However, this is a legal concept that applies under contracts between specific individual parties that have equal power in their interaction, he explains.

"The relationship between investigators and subjects is inherently one of unequal power," he says. "Individual subjects cannot write individualized or customized consent documents. There is a certain rigidity in the posture that investigators bring to subjects — they screen them in, they have set exclusion criteria, and they tell all of the subjects the same thing, etc. The assumption of risk is not an appropriate doctrine in this context because it is in the nature of the activity that there are an enormous amount of risks that are unknown. You are not going to get a court to say that the person with the lesser power agreed to assume all of the risks in all of the experimental treatment — that is just not ethical."

A research protocol is not individualized

What to Say, What Not to Say

Examples of Exculpatory Language:

- By agreeing to this use, you should understand that you will give up all claim to personal benefit from commercial or other use of these substances.
- I voluntarily and freely donate any and all blood, urine, and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items.
- By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.
- I waive any possibility of compensation for injuries that I may receive as a result of participation in this research.

Examples of Acceptable Language

- Tissue obtained from you in this research may be used to establish a cell line that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.
- By consenting to participate, you authorize the use of your bodily fluids and tissue samples for the research described above.
- This hospital is not able to offer financial compensation nor to absorb the costs of medical treatment should you be injured as a result of participating in this research.
- This hospital makes no commitment to provide free medical care or payment for any unfavorable outcomes resulting from participation in this research. Medical services will be offered at the usual charge.

Source: Office for Protection from Research Risks. Cooperative Oncology Group Chairpersons Meeting. Nov. 15, 1996, "Exculpatory Language" in Informed Consent.

treatment that can be varied according to treatment needs; it is a set protocol where changes are limited to those within the protocol itself, agrees Lis.

"A potential subject is faced with wanting to participate in a clinical trial but finds that some of the pieces of the trial which may be negotiable, such as payment for injuries sustained, may not be to his liking," she continues. "As a research subject, he may feel that he has little bargaining position. Even if this is not true, and the sponsor would be open to negotiation with regard to the terms outside of the protocol itself, the unequal bargaining position (i.e., being presented with a form consent with set terms) is likely to make the subject feel that this is not the case. And, of course, if the information regarding what will or will not be paid for is not clearly stated in the consent, the subject does not even know what he could be paying for."

What should be said?

Dalglish believes researchers should include statements in informed consent documents that thoroughly explain what policies the sponsor or institution has regarding potential injuries to participants during trials. But, he says, they should also clearly state that the subject also might have other rights and include language informing them where they can go to find more information.

"You don't have to go into an exhaustive discourse, but you can say, 'You may have rights for damages allowable under the laws of this state.' And, I think it would be a good idea to say, 'Call X number,' which could be the human subjects' office, which would then be duty-bound to be straight about it."

Above all, informed consents documents must be truthful, adds Lis.

"So consent documents should include the things that will be covered, such as where the sponsor offers to pay for study-related injuries. This is often very finely parsed out; i.e., payment for medical treatment vs. emergency medical treatment, so it is important to make it clear to subjects," she says. "Also, even where payment is offered by a sponsor, it may be difficult to determine whether the injury is study-related or not."

If costs for medical care for injuries are not covered by anyone related to the study, she adds, it also seems fair to state how they will be billed. According to Lis, consent language could be something such as:

"Medical care for injuries related to the study is available. [Sponsor/Institution] has set aside funds to reimburse you for costs for medical or other injuries related to the study. This will be determined by [state how determined and by whom]. Costs for medical care for any injury not deemed study-related will be billed as usual. For more information, and if you think you have been injured, call [name and local telephone number].

"Nothing in this consent is meant to limit any of your legal rights"; or

"Medical care for injuries related to the study is available. However, no funds have been set aside, and there are no plans to pay you for costs

for any injuries related to the study. Costs for medical care for study-related injuries will be billed as usual. For more information and if you think you have been injured call [name and local telephone number].

"Nothing in this consent is meant to limit any of your legal rights."

It's also important to note that most people will think of injuries in terms of physical injury, but this is not necessarily the case. Participants may legally pursue compensation for other non-physical injuries and this should also be reflected in the informed consent. ■

NIH creates roadmap for clinical research

Focus on ethics is 21st century goal

The National Institutes of Health (NIH) in the early fall announced plans to transform the nation's medical research enterprises and expedite turning research discoveries into practical improvements.

Calling its goals the NIH Roadmap for Medical Research, the agency's vision coincides with shifts in public attitudes about research and with some transformations that already are under way.

"NIH's leadership now challenges all of us to think how research enterprise needs to be re-engineered," says **Debra R. Lappin**, JD, president of Princeton Partners Ltd. in Englewood, CO. Lappin also is an adjunct professor in the graduate program of clinical sciences at the University of Colorado Health Sciences Center in Denver, and she is the past national chair of the Arthritis Foundation, based in Atlanta.

The NIH has developed this new vision for clinical research, partly out of necessity as clinical research has gradually shifted away from the traditional setting in academic medical centers, Lappin says.

More than two-thirds of today's clinical trials research can be found in places other than academic medical centers, and these other places often are small clinical practices in which research and ethical training and experience are limited, she notes.

"What NIH is trying to suggest for the nation is a new clinical research network in which investigators in these new settings have been trained, " says Lappin. "This is a huge challenge and it allows us to rethink the enterprise and the system."

Lappin is an inaugural and four-year member of the NIH Director's Council of Public Representatives and had chaired the working group on human research protections, an assignment that ended in April. She will speak about this new paradigm for clinical research at a conference called Contemporary Issues in Human Research Protections, Nov. 17, 2003, at Iowa Methodist Medical Center in Des Moines.

The NIH roadmap, which can be found on the NIH web site at www.nih.gov, has a theme of Re-engineering the Clinical Research Enterprise. It will promote better integration of clinical research networks, and NIH has established implementation groups in these areas:

- Harmonization of clinical research regulatory requirements.
- Integration of clinical research networks.
- Enhance clinical research work force training.
- Clinical research informatics: National Electronic Clinical Trials and Research Network.
- Translational research core services.
- Regional translational research centers.
- Enabling technologies for improved assessment of clinical outcomes.

As NIH pushes for recognition of the changes that have taken place in clinical research and works to provide its roadmap for future courses, there are some important ethical questions that should be examined under the lens of a new public partnership, Lappin suggests.

These include the following:

- **Therapeutic misconception:** "The public partnership is based on the evolution of relationships with science, and it has moved from paternalism to an era of autonomy," Lappin says.

As such, the therapeutic misconception that has both investigators and subjects viewing clinical trials as therapeutic and falling under the physician-patient relationship should be acknowledged as an ethical distortion, she says.

Surveys have shown that more than half the people who participate in a clinical trial believe they are going to be finding some relief from their medical problem, Lappin adds.

"We're all a part of this misconception," she says. "Clinicians who recruit for trials do so with the honest thought that patients will find some relief; and we all have hope, and no one wants to remove hope from a patient's life."

Confronting this therapeutic misconception head-on might require changes to the informed consent process and viewing research from a

participant's point of view.

"Make sure differences from the standard of care treatment are well expressed in the informed consent," Lappin says. "These differences need to be suggested with ethical clarity about randomization, flexibility in dosing levels, and measuring outcomes that we don't normally use."

The NIH roadmap promotes the idea of expediting the clinical research trial process and moving trials into new communities where investigators can find clients, and this will create more challenges in educating research participants, she notes.

"Most clients are not going to be going to academic medical centers," Lappin says. "They'll be participating in private practices."

The fraternal approach of treating human subjects as though the physician/investigator knows what's best for them will no longer work, and researchers will have to adapt to the new approach that views research in the light of what best serves the public, she says.

"We need to conduct more practical or pragmatic clinical trials," Lappin says. "We must promise the public in the new partnership that if they participate in trials not only will we gain new treatments, but we'll gain answers to policy questions of what works in a real practice setting and what works with people with multiple chronic diseases."

• **Generalizable knowledge:** Investigators and IRBs need to consider their obligations in promising generalizable knowledge to research participants, as well as to the public, she says.

"I want to challenge all of us to think about how to draft industry relationships that do not compromise the promise of generalizable knowledge," Lappin says. "If we are asking a participant to give us tissue samples that will go to an industry partner and may be used in a way over which we have no control, what is our ethical responsibility?"

Questions to consider include, she adds:

— Do we have any control over the study design in our industry contract?

— What have you promised me as a member of the public?

— Do I presume that you have access to all the data-sites vs. the single data-sites of where the study is being conducted, if it's a multisite study?

— Do I presume that if there are negative findings that these will be published and that they will be of obvious value so that this science is not repeated in the future, if it in fact has rendered negative results?

"The failure of a system to publish negative trial results is a very big issue," Lappin says.

This is a big issue that could significantly impact an institution's reputation, she adds. "If you are an institution that has a valuable patient base with a particular disease, this has very valuable data but it may be a question of disclosure."

For example, the ethical way to handle this situation may be to disclose to participants that the investigators are requesting tissue samples that will be given to an industry partner, who may use it. But the investigator has no control over whether there will be any generalizable knowledge gained from its use, Lappin says.

• **Cultural and translational blocks across agencies:** "I think the public is holding clinical research enterprise and the federal government and agencies conducting clinical research to a new level of responsibility for addressing translational blocks," Lappin says.

Clinical research needs to move through the system with an effective translation from NIH to proof-of-concept clinical trials, Lappin says.

If clinical trials in very early stages do not show any biological signal of success, then bring that information into clinical practice and translate what has been learned, Lappin says.

This information could help inform public policy with regard to health care reimbursement, for instance.

"If we're going to have a Medicare reimbursement policy, then what do we reimburse?" Lappin says. "We need comparative clinical trials that compare old standards with far more expensive new drugs, and these trials are ones that the industry has no motivation to conduct."

There have been examples of where these types of comparisons were conducted and researchers discovered that the inexpensive, old treatment works best, Lappin says.

"It's so easy to believe the newest and most expensive [drug/device/procedure] is dramatically better, and therefore the public may feel that they've been let down by reimbursement policies and not getting the newest and latest medication," Lappin explains. "Whereas, there have been a couple of very recent areas in which we've seen that what we demanded and thought we needed as the public was in fact not the best treatment — hormone replacement therapy comes to mind."

• **Informed consent and conflicts of interest:** Investigators and IRBs need to keep in mind that informed consent should be informed participation, and it's a process — not an event, Lappin says.

"Perhaps we need new technology that allows informed participation to continue throughout the trial," she suggests. "It's not a static event."

Also, it would be advisable to have a third-party advocate who has access to clinical trial information and can advise participants, Lappin urges.

"The most important point is that there should be a layered approach that allows the participant to get increasingly important information," she says. "And the participant in the trial should know the outcome of the study irrespective of publication."

A good question for investigators and IRBs to consider is at which point they disclose recruitment bonuses. Major medical associations have suggested that the IRB has the responsibility of knowing this information, Lappin says.

IRBs will have to decide whether this information should be in an informed consent, she adds.

"I honestly think there is a way to disclose the financial underpinnings of the trial in a way that does not overwhelm a participant, but gives a participant the rationale sense that trials cost money," Lappin says. "Institutions will have to look long and hard at how it will look if participants aren't advised and something goes wrong."

Institutions and investigators should ask themselves, "Will this pass the *60 Minutes* [television show] test?" she says. ■

Keep up with new regs, know existing ones

Experts offer regulatory advice

Sometimes there are just too many acronyms, but it's important for research professionals to learn the regulatory power wielded by the big three: OHRP (Office for Human Research Protections), FDA (Food and Drug Administration), and NIH (National Institutes of Health).

Judith Brooks, MS, public health analyst with the division of education and development at OHRP in Rockville, MD, often speaks to the research community about the regulatory relationship between the three agencies.

"I use a diagram that shows how the FDA has regulatory authority over certain parts of research, and how we at OHRP have regulatory authority over HHS research," Brooks says. "And if you have an FDA-regulated product and get government money, then you have the two regulatory bodies."

Also, it can be a full-time job keeping up with the new regulations and guidance issued by the various federal agencies. For instance, the Secretary's Advisory Committee, which met for the first time in July 2003, is expected to issue a report within the next year, and this could change the way investigators look at many aspects of research.

One issue under study is adverse event reporting and how to clarify reporting requirements to satisfy both FDA and Department of Health and Human Services (DHHS) regulations, Brooks says.

One reason DHHS is working toward better educating the research community and better explaining regulations is because of the trend of greater public scrutiny paid to human subjects research.

"The modern approach and modern sensitivity have been driven by several very unfortunate incidents in which research subjects enrolled in clinical trials have either been seriously injured or, in some cases, died," says **Robert Bienkowski**, PhD, executive director of research at Iowa Health-Des Moines.

"An investigation and a very extensive evaluation of what happened has revealed many cases of shortcomings in the process," he says. "The institutions are not following their own policies and procedures or are not following or observing the requirements of federal regulations for protection of research subjects."

Add to the mix the Health Insurance Portability and Accountability Act (HIPAA), and the regulatory protections given to human subjects research may seem a bit overwhelming. However, research institutions and investigators can improve their own protocols and clinical trial system by making certain regulatory changes a priority and becoming educated about others.

Brooks and Bienkowski offer this advice:

• **Be careful how you add HIPAA language to an informed consent document.** When investigators merge HIPAA language into an informed consent document, they need to pay attention to several areas that are outlined in the NIH guidance document, Brooks says.

Also, keep in mind that if there is a HIPAA template that is inserted into the existing document, then this addition can be reviewed in an expedited way, Brooks says.

"When HIPAA came into effect, there were all

of these existing protocols with existing consent forms, and some institutions wrote their own authorization form, while others wanted to revise forms and put HIPAA language in it," Brooks explains. "OHRP said that as long as it was HIPAA-specific language that you inserted in every form it can be done in an expedited way."

Alternately, any consent form that is protocol-specific and if there are consent form revisions then it has to be reviewed by the full IRB, Brooks adds.

• **Learn when HIPAA waivers can be used.** HIPAA only applies to covered entities, such as health care providers, hospitals, physicians, etc. Any person who falls under HIPAA's umbrella has to receive authorization from patients to do anything with their medical records, Brooks says.

"In certain situations under HIPAA you can waive that authorization, such as if you're a hospital and are doing a research study or collecting information from patient records," Brooks says.

"And if it meets the definition of human subject research, you may be able to waive HIPAA requirements," Brooks adds. "But you can't waive the regulations that require informed consent unless it meets our waiver requirements."

• **Know all of the identifiable information and then think up some more.** HIPAA regulations provide a list of identifiable information that cannot be used, but OHRP also emphasizes that anything else that would make someone identifiable, should be avoided. This may include cases with a very rare disease, for example, Brooks says.

"We say it extends to any information that would reveal a subject's identity," Brooks explains. "If you live in a small community, and there's one person with leukemia in town then that person would be easily identifiable."

The regulations prevent investigators from revealing any such information that could be used to identify a person, including personal characteristics, Brooks says.

If an investigator has some question about this factor in a protocol, then it's best to send it to the full IRB for review, Brooks adds.

• **Create a research subject advocate position.** Iowa Health-Des Moines completely revised its own policies and procedures in 2002 to more clearly reflect federal and state regulations, Bienkowski says.

Another major change was that the institution has invested in a new position, called research subject advocate, he notes.

"The person appointed to the job is our director of corporate ethics, and she serves as the associate chair of the IRB and is a nurse by training with a master's degree in ethics," Bienkowski says.

"This position developed because we felt as part of our institutional commitment to the program of human subject research protection that it would be important to embody that role in one person, an ombudsman if you will," he says.

"This is someone who has no ties to the research and would be devoid of any possible conflict of interest," Bienkowski adds. "So if he research subject has any question, complaint, or concern then this would be yet another person the subject could turn to for advice, counseling, and to learn of the rights of research subjects." ■

CE/CME objectives

The CE/CME objectives for *Clinical Trials Administrator* are to help physicians and nurses be able to:

- review pertinent regulatory mandates;
- develop practical clinical trial oversight strategies;
- review best practices shared by facilities that successfully conduct clinical trials. ■

COMING IN FUTURE MONTHS

■ How software can help with compliance

■ Improving recruitment rates

■ Ethics and community consent

■ Has HIPAA had a negative impact on research?

CE/CME instructions

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*

13. What type of language is prohibited by federal regulations governing human subjects research?
A. Exculpatory language — statements that ask or appear to ask participants to waive their legal rights.
B. Language that informs participants what the sponsors' or investigators' policies are regarding payment for medical treatment for injuries incurred due to research participation.
C. Information about potential injuries that might occur during the course of the research protocol.
D. None of the above

14. It is recommended that consent information about add-on studies be taken out of the consent document covering the original study and be placed in a separate document.
A. True
B. False

15. The National Institutes of Health's Roadmap for Medical Research is designed to:
A. Expedite research that provides medical benefits.
B. Address research issues and problems that have risen from the shift of clinical trials from academic medical centers to smaller, community provider settings.
C. Both A & B
D. None of the above

16. Federal regulations under the Health Insurance Portability and Accountability Act (HIPAA) give specific details about how informed consent forms may be changed to include HIPAA disclosure. The regulations state:
A. If a HIPAA template is inserted into an existing informed consent document, then it must receive full IRB review.
B. Investigators may insert protocol-specific HIPAA language into their existing protocols and then apply for an expedited review.
C. Any informed consent form that is protocol-specific and has revisions with HIPAA language must be reviewed by the full IRB.
D. None of the above

Answers: 13. A; 14. A; 15. C; 16. C.