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Your Practical Guide To Institutional Review Board Management

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IN THIS ISSUE

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Successful accreditation process requires close attention to details

Small committee and IRB chairs' cooperation are key

The very first step to becoming accredited is to collect all of your institution's policies and procedures related to the human research protection program in a searchable electronic format, an expert advises.

"I highly recommend taking that first step because it makes it easier to see which policies apply to which elements in the AAHRPP Evaluation Instrument," says **Lisa R. Ballance**, MA, a special assistant to the vice president for research at Virginia Commonwealth University in Richmond, VA. Ballance helped steer her institution through a research accreditation process, and she's spoken on this topic at national conferences.

Virginia Commonwealth began the accreditation process with the Association for the Accreditation of Human Research Protection Programs (AAHRPP) of Washington, DC, in early 2005 by initiating a self-assessment process. The institution submitted the full application for accreditation in December, 2006, and received full accreditation in June, 2007, Ballance says.

"We had a core team of three people working on accreditation, with each of us taking the lead on one or more of the five AAHRPP domains — the organization, the research review unit, investigators, sponsored research, and participant outreach," Ballance says.

"Each of the domains is divided into standards and then elements," she notes. "We each had elements that we took the lead on for evaluation against AAHRPP standards."

The team then developed a matrix or map of the AAHRPP elements and standards, by domain. This was cross referenced with applicable policies, procedures, guidance, and forms, Ballance says.

"We noted where standards had been met, where clarifications were needed, and what our priorities were as we planned to implement changes," she says. "You need a point person who keeps track of the progress along the way."

Ballance suggests organizations also take these steps to improve their accreditation process:

1. Identify priority areas or concerns.

An accreditation committee can identify the areas that will need the most attention or involve institutional approvals or educational efforts, Ballance says.

"You need to identify those issues that will be protracted or require an additional layer of approval," she adds. "And you should get those projects started first."

For Virginia Commonwealth University, one such issue involved an institutional conflict of interest policy.

"We didn't have a written policy on the institutional side," Ballance says. "The IRB had a policy, but the institution didn't, so we needed to bring that to the attention of the upper administration to initiate that process."

2. Look for changes that won't need decisions from the top.

There are some policies that might be changed through simple wording changes or by adding references, Ballance says.

"So what kind of changes can you make without having to go through a large committee or process?" she says. "You should streamline the pathway to change, where possible."

For instance, Ballance noted that their committee negotiated approval to make procedural changes to written policies and to add clarifying information early in the process.

"This greatly reduces the 'noise' that can be created with change after change, and allowed us to focus our attention on changes that impacted how we carried out our human research protection program, in a more direct way.

"That saved us a lot of time," Ballance says. "Streamlining the pathway to change is very important when you're getting started in this process.

"The AAHRPP was instrumental in assisting us with defining our processes and procedures," Ballance says.

3. Work with IRBs.

"Our IRB is set up in five different panels," Ballance says. "So we needed to take procedural changes to all chairpersons so they could discuss these with us."

For instance, if there would be a change in the adverse event or unanticipated problems language in policies, the chairs would take a look at what was proposed, and their input would be incorporated into the changes.

"We'd take changes to the chairperson's committee that meets once a month," Ballance says. "It was always beneficial to us to be present during the discussion."

This was an efficient use of time for both the accreditation committee and the IRB chairs, she notes.

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"We knew this process would put us in the direction we needed to be," Ballance says.

Since not everyone agreed on each suggested change and revision, it meant discussion and revision before the changes were finalized, Ballance notes.

"Don't be afraid to make small changes even if these are not exactly what you think you'd like it to be or where you'd like it to be if you were accredited," she suggests. "Making change toward progress might be what you need to do in order to clarify concerns and focus on the real issues."

Plus, the AAHRPP supports and assists with even small changes in the right direction, she adds.

4. Show accrediting organization a mock-up of changes.

"We found that AAHRPP was very receptive to seeing a mock-up of materials, as long as we had identified it as a mock-up and noted timelines for planned education or implementation," Ballance says.

Although VCU's policies are not saved in an MS Word format, the mock-up was created in MS Word so that the program's track change and text highlight features could be used, she notes.

"It helped greatly to use highlight or track changes, as needed, to reference the specific area of a policy where an element was addressed," Ballance explains. "In fact, this helped us as well."

The application itself is sent in a pdf format, she adds.

"I found that submitting a pdf version to AAHRPP was useful for us," Ballance says. "We were able to use the same pdf version we sent to review their comments and plan for our next steps for implementation of changes."

5. Ask for help when needed.

"There were a couple of areas where we felt we needed clarity on the best way to approach a particular change," Ballance says. "It is possible to adopt a procedure that doesn't work for your program and which would possibly lead you into noncompliance."

So a change should not be made haphazardly, she adds.

When in doubt, Ballance recommends sending an e-mail to AAHRPP and asking questions.

"We'd say, 'We have some questions about this policy,' and then we'd review the specific area in question and outline the issues," Ballance says. "From the AAHRPP we always received very thorough responses and insightful comments or suggestions for developing procedures that were not only compliant, but also flexible, functional, and efficient." ■

The right to withdraw: What does it really mean?

Review withdrawal procedures, language in consent

Every study participant has seen some variation of this assurance in informed consent documents: "You are free to participate in this research or to withdraw at any time without penalty or loss of benefits you are entitled to receive."

That notice, and the underlying right to withdraw from research, is required by federal regulations. But what happens at the point when a participant decides to invoke that right? What can and should researchers say to participants about the decision? Is it permissible to ask a departing research subject to submit to some final tests for their own good, or for the good of the study?

Marjorie Speers, PhD, executive director of the Association for the Accreditation of Human Research Protection Programs (AAHRPP), says that the regulations are less clear on these questions.

"I would say it's not fully addressed in the federal regulations, so it's an area where it's really important for IRBs and researchers to think through these issues and to make an ethical decision," Speers says.

Elisa Gordon, PhD, MPH, an associate professor of medicine at Alden March Bioethics Institute in Albany, NY, has studied the language of informed consent documents to see how they address the issue of withdrawing from studies. She says that while documents always contain the required statement about a right to withdraw from studies, other important aspects of withdrawal are often left out or vaguely worded.

For example, a review of 114 consent forms from one Midwestern academic center found that 30 forms asked participants to submit to additional activities before withdrawing from a study. Only four forms cited safety as the reason for an additional visit or test.

"The language in the consent forms I saw was

really ambiguous," Gordon says. "They said things like, 'we encourage,' 'we recommend,' or 'we expect' something or other. That doesn't say whether someone is required to do it, but it also conveys a kind of power language. A study participant trusts the doctor and will probably want to do what the doctor says, given that ambiguous language.

"People should be told up front, very clearly: You have this right to withdraw, there are risks you should know of, and it would be great if you could come in so that we can make sure the drug testing went safely. Just be transparent about it."

Gordon says investigators may be resistant to the idea of discussing withdrawal in detail in consent forms. "They don't want subjects to have that in mind," she says. "But that just raises the whole point of voluntariness."

Detailing consequences

Federal regulations require that where appropriate an informed consent document must spell out the potential consequences on a patient's health or well-being of withdrawing from a study early.

Gordon says that in her review of consent documents she found none that addressed that issue.

"It's an area where we can make a lot of headway," she says. "We need to state explicitly what the consequences on the patient's health are, if it's the kind of study that's therapeutic and would have some bearing on their health. It's important for the consent form to articulate what the risks of withdrawing are, just as we inform people what the risks of participating are."

Speers notes that the regulations only require this type of disclosure when it's appropriate. In many studies, it wouldn't be necessary to bring it up.

"Say you're doing an hour-long survey and halfway through the survey, the individual says, 'I just don't want to continue.' In that situation, I can't imagine any consequences of discontinuing participation," she says.

"But let's say you're doing a clinical trial, where the individual is scheduled to receive an intervention — whatever it is, standard arm or experimental treatment arm. If they decide to discontinue in the study, there can be consequences," including having to seek the standard treatment from another source or having to be monitored for safety reasons.

"In that case, it would be ethically appropriate and really the obligation of the researcher to spell out the consequences of discontinuing the study," Speers says.

What can we do to keep you in?

Once a person has decided to withdraw from a study, the issue arises of how far investigators can go to try to persuade the subject to reconsider.

Some attempts could be considered benign — helping a subject find child care in order to continue to attend study visits, for example. But others could be seen as coercive.

Gordon says the power differential between a subject and patient makes walking this line particularly tricky.

"Even among those subjects who have high socioeconomic status and high education, it might be hard psychologically to withdraw if someone is trying to sell you to stay in," she says. "I'm cautious and not settled about the issue of people asking, 'What can we do to keep you in?'"

For her own part, when someone wishes to withdraw from her studies, Gordon is careful even when asking the subject's reason for withdrawing.

"On the one hand, I feel comfortable asking [why] for the sake of tracking, so that the study investigators can do a better job in the future with retention," she says. "I'll say, 'I track the reasons people don't want to participate, may I ask you' — I first ask if I can ask — 'what your reasons are?' They have the option to say no, they don't want to respond.

"I try to make it as transparent and open to people as possible."

Speers says it's ethical to ask the participant the reason for withdrawal, because it could be in the best interest of the subject to resolve the issue.

"If it's in a clinical study where there's an intervention, because we don't know the outcome of the study, we also don't know the outcome if someone drops out of the study early," she says. "So if they drop out, we don't have a way to follow them and monitor them. If they stay in the study we have a way to do that.

"It can be in their best interest to potentially stay in the study and [for the researcher to] explore with the individual why they want to

drop out in a non-coercive manner."

Gordon and Speers agree that if a subject is determined to leave the study, that right must be respected.

Gordon says subjects should not be asked to participate in additional visits or testing only to aid in the collection of data for the study.

"If somebody says they want to leave, you

Withdrawing from a biobank brings special challenges

Consent must spell out limitations

The growing field of biobanking has added new wrinkles to issues of withdrawal from research. Withdrawing from participation in a biobank or a large cohort study is a very different matter from withdrawing from a clinical trial. Because of the technology involved, it may not be possible to completely remove one's information from the research.

However, there's a consensus among researchers in this field that a strong right to withdraw still exists, says **Timothy Caulfield**, LLM, FRSC, a professor of biotechnology law and research director of the Health Law Institute at the University of Alberta in Edmonton, Alberta.

"I just did a survey of all the policy documents around the world for biobanking and large cohort studies," Caulfield says. "The right to withdraw endures, despite all the practical challenges associated with that and it should endure right up until the point where it can't be operationalized in a realistic way."

He says there has been a lot of discussion about how to preserve the right in a time of fast moving technology. A person who no longer wishes to participate in a biobank can ask that his or her tissue sample be destroyed, but that's only the beginning of the process.

"A lot of scholars have noted that that's a little bit of a smokescreen because it's not really the sample, the actual physical tissue that's important, but the personal information that it represents," Caulfield says. "Once you participate in a research project and information about you has been generated, information that's been aggregated and distributed, it becomes really difficult to pull it back."

He says a more complete withdrawal from a biobank also would include no further generation of information from the sample and most importantly, the severing of any linkages between the data already generated and information about the subject.

"A lot of biobanks and cohort studies that are emerging now are really about tying together various streams of information — health information, genetic information, socioeconomic information. So what you can do with a withdrawal is sever all those ties."

Because a biobank itself is not a single study but a research platform for a variety of studies, Caulfield says it's important to keep study participants informed about the research being conducted, so that they can choose to withdraw if they are uncomfortable with the type of research being done through the biobank.

"There has to be that ability to continually inform research participants of the kind of research that's going on, through research updates," he says. "That's the huge challenge around biobanks — at the consent stage, you cannot inform the research participants of all the potential research projects that are going to happen. We just don't know at the beginning."

He says consent forms need to be clear about the limitations on withdrawal.

"Where it becomes challenging is explaining in a digestible manner, the limits of that right as a result of the nature of that research," Caulfield says. "Once information is distributed, it's very difficult to pull it back in. The consent form has to be frank about that, because some people might not feel comfortable with that reality."

He says some ethicists argue that a protocol should be structured in a way that maximizes the ability of subjects to withdraw more completely from a biobank. For example, linkages to personal information actually could be maintained longer in the process, so that when a person wants to withdraw, the information can be more easily traced and removed. But Caulfield notes that such an approach would raise its own ethical issues related to privacy.

"The counterargument is that if the research participant is aware of the limits to the right to withdraw and goes in fully informed, you don't have that obligation," he says. ■

should let them leave," Gordon says. "If the rationale given for asking people to undergo a further study visit is to collect additional scientific data, that's not ethical."

Speers says such a request could be made, but would have to be handled very carefully, to ensure the subject doesn't feel coerced.

Keeping withdrawal in mind

IRBs should examine protocols with withdrawal issues in mind, say Gordon and Speers.

While it's not possible to anticipate all the reasons a person might want to drop out, Speers says an IRB should ask whether the researcher anticipates an attrition rate, and then discuss the possible consequences of withdrawal for the subjects.

"If there are negative consequences, then those need to be described in the consent process. You would be looking in the protocol for those consequences, some type of harm," she says. "Also, if there need to be procedures in place for terminating or discontinuing in the study, to spell out what those procedures will be."

In the case of unexpected withdrawals, Speers says the investigator should go back to the IRB to seek guidance on how to proceed.

Gordon says IRBs should be particularly rigorous in examining consent forms for withdrawal language.

"I think there should be more attention to any barriers to withdrawal that are in the consent forms — manifested, for example, in that kind of ambiguous language I mentioned."

She says that if study participants are asked in consent forms to undergo further testing or visits after withdrawing, the rationale should be stated clearly.

"I think it requires just a little bit more attentiveness," she says. "I know that's hard in this day and age, where IRB reviews take a long time, but this is an issue that deserves some attention." ■

NIH working group to help IRBs assess risk properly

NIH bioethicist cites lack of consistency

Two or more IRBs reviewing the same study might reach strikingly different conclusions about the study's risks and suitability for human subjects.

This shouldn't happen, says an expert from the National Institutes of Health (NIH) department of bioethics in Bethesda, MD.

"One thing we've discovered is there is a widespread variation about different ways IRBs evaluate things, such as a survey involving sexual activity or a CT scan, and it seems to me that is not justifiable," says **Ezekiel J. Emanuel**, MD, PhD, chair of the department of bioethics at NIH.

"There should be more efforts at standardization," Emanuel says.

The fact that IRBs can come to different conclusions when reviewing one protocol raises many questions about how the government could create more coherent standards about risk, he adds.

"I think one of our problems in the IRB world is we tend to have a lot of gut reaction to studies and not a lot of standardization," Emanuel says.

"It's a little unfair to present one's protocol and get very different evaluations in different places when all of the IRBs are supposed to be using the same standards," he says. "If all other things are equal, you should have the same judgment."

To standardize IRB review requires data on risk for the various procedures and tasks required of research participants, he says.

"We need to come up with numbers of how risky it is for subjects to come in for an MRI, how risky it is for subjects to receive 10 blood draws a day," Emanuel says.

The NIH is undertaking a project to standardize IRB risk assessment and reviews, with plans to hold a working group meeting in January, 2009, he notes.

The goal will be to find a systematic approach to quantifying the risks to research participation.

"We're trying to get a consensus agreement from a wide variety of people," Emanuel says. "We'll have IRB members, administrators, researchers, patient advocates, and ethicists."

Part of the systematic approach will include classifying actual interventions according to how risky they are.

"You shouldn't have this big disagreement about whether the MRI scan is really risky or not really risky," Emanuel says. "Our goal is to have the numbers and make decisions based on data about risk."

One of the problems of the current system in which IRBs operate is that there are no numbers

available to help IRBs determine risks, he adds.

"We rely on people's gut reactions, which tend to not be very reliable," Emanuel says.

The widespread variation in IRB decisions suggests that there's a problem with the system, he notes.

"So our goal is to bring order, rationality, and systemization to these things, and that's why we're doing it," Emanuel says.

When IRBs disagree on the risks of research procedures, there's a problem with inconsistency.

The way things work at present, there are two dangers, Emanuel suggests.

"We may be inhibiting research that is quite legitimate, and we may be permitting risky interventions we shouldn't because we don't have the right standards," Emanuel says. "My general feeling is it's probably the former — that we're being way too cautious, but the latter is possible too." ■

Ethics Corner

When is an inducement 'undue?' Is a payment ever coercive?

Expert suggests IRBs pay closer attention

From a bioethical perspective, payments to research participants are complicated, an expert says.

"Partly because a lot of people are used to how clinical medicine works, the idea of paying people to participate in clinical studies, particularly when they involve risk, makes people very uncomfortable," says **Neal Dickert**, PhD, MD, a resident at Johns Hopkins Hospital in Baltimore, MD.

"That's the fundamental issue," Dickert says.

Other ethical concerns involve the notion that segments of the population who are economically disadvantaged and, perhaps, vulnerable, are more likely than others to be attracted by offers of money, he says.

"The fundamental issue of paying people to be involved in research, that it might be harmful leads to significant worry about preying on people's vulnerability," Dickert explains.

One possible solution is to standardize participant payments according to a model or models that the research industry would agree upon, Dickert says. **(See article on payment models, p. 105.)**

Dickert has published research on payment policies for study participants, and he and co-investigators have found that phase I studies often are well-designed with regard to participant payments.[1,2]

"We found from talking to chief executive officers at drug companies that phase I units often have the most well-worked-out and defined payment schedules," Dickert says.

Here are the three main reasons why payments to participants are a significant issue to investigators and IRBs:

1. Is a payment too much?

"Paying people too much money might invalidate their ability to give informed consent," Dickert suggests. "Like deer in the headlights, they might pay too much attention to the money and not enough to the risk."

2. Will it force a bad decision?

Another argument is that payments for research participation discourage potential participants from thinking carefully about the risks and benefits, Dickert says.

"Making money hijacks their judgment, and they might make bad decisions," he explains. "These are the kinds of arguments people advance."

There are no data to support this argument, but it has not been studied well, he adds.

"People take money into account all the time in making lots of different decisions, and we don't normally say they're unable to make those decisions because money is involved," Dickert says.

3. Is payment coercive?

People in the research community experience great discomfort around the idea of paying people to participate in clinical trials, Dickert says.

"The subset of arguments about payments is that it invalidates consent," he explains.

However, the word "coercive" should not be applied to clinical research, Dickert says.

"One thing I've tried to argue over the years is that a payment for research participation cannot

be considered coercive because coercion involves the presence of a threat," he says. "If someone mugs you and puts a gun to your head and says, 'If you don't give me your money I'm going to shoot you,' that's coercive."

But asking people to participate in clinical research is not the same as making a threat, Dickert says.

"No one is threatening to make you worse off if you don't do what they offer," he says. "If you were offered $1 million to participate in a research study, and you say, 'No,' then there's no harm that comes to you."

On the other hand, this doesn't mean that all offers of payment for participation are okay, Dickert says.

"It's a semantic decision, but I think it's important that we be straight when we say what we mean by coercion," he says. "In general, coercion is defined by the presence of harm if one doesn't do what the person wants them to do."

The more proper term is "undue inducements," Dickert notes.

"That, more properly, is the concern that most people have," he says. "It's a concern that is hard for people to define."

Research regulations and guidance documents provide lots of different ways to think about how to define undue inducement.

"There are so many different concepts of what undue inducement might be that there's little in the way of clear guidance out there," Dickert says.

From an ethical standpoint, there is nothing inherently wrong with providing inducements to research participation, he says.

One study found no evidence that commonly used payment levels represent undue inducement.[3]

"There are inducements all around us, such as whether we take a job we like or shop at a sale at a store," Dickert says. "All those things are designed to induce us to do things we might not necessarily do, but we don't say they're bad."

Likewise, inducements in research are not problematic.

"An inducement could be anything as simple as offering to pay for a person's parking because the person might not participate if he has to pay for his own parking," Dickert explains. "But we don't think there's anything wrong with that."

Concern over undue inducement is properly raised in settings where large amounts of some compensation are involved and where the research might cause some people to have significant value-based objections or concerns, Dickert says.

For example, suppose there's a clinical trial studying different ways of delivering blood transfusions, and the participant pool is composed of people who are Jehovah's Witnesses, who clearly object to blood transfusions, Dickert says.

"Most of us would think there's something wrong with going to this population to say, 'How much do we have to offer you to get you to participate in this study?'" he adds. "The problem with this is you're using large amounts of money to overcome important values that people hold."

Another concern is when participants are paid large amounts of money in studies that fall toward the risky end of the approvable spectrum, Dickert notes.

Dickert's own research has shown that the dollar amounts research participants are paid vary widely, and the variation is unexplained.[1]

One study showed that 11 IRBs approved 467 study protocols that paid participants from $5 to $2,000 with an overall median of $155. These payments were described in the consent forms 94.4% of the time.[1]

The variation occurred even among the same study at multiple sites and among similar studies.[1]

The findings suggest that there is little logic to the amount of money research participants are paid.

By the same token, the amount of money it would take to induce someone to become involved in a study they otherwise might avoid also varies.

"IRBs cannot be expected to approve protocols that fit everybody's risk threshold, because otherwise no study would ever be approved since there will be something in every study that someone objects to," Dickert says.

"The worry becomes greater when you're offering money to overcome certain concerns about risks," he adds. ■

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Expert offers suggestions for standardizing subject payments

Wage-payment model might work well

Ethicists and others continue to find it troubling that payments to research participants are part of the recruitment process.

"I think a lot of the talk about undue inducement is about compromising someone's judgment," says **Neal Dickert**, PhD, MD, a resident at Johns Hopkins Hospital in Baltimore, MD. Dickert has been studying research participant payments for more than a decade.

"It's not that people are making involuntary decisions," Dickert adds. "But when we think about the role of the human subjects research enterprise, it's disturbing that we would allow unrestricted amounts of money that would encourage people to override certain values that they hold."

For instance, the role of an excessive payment changes according to the study's type and risk.

"Imagine a study where you're doing a fingerstick blood glucose test, which diabetics do all the time," Dickert says. "If you want to pay people $5 million to take the glucose test, it's hard for me to say something other than 'That's a terrible use of resources.'"

But if the same payment is being made to subjects who are participating in a study that involves significant risk in a product that never before has been tested in humans and where there is a very real concern about toxicity, then that's where IRBs and ethicists will worry a little bit more about the potential impact of money, Dickert explains.

A possible solution to the ethical dilemma of undue inducement for study participation is to standardize how research subjects are paid.

Dickert has studied several models for how payments to participants could be made, and his research has described three types.

Market model

According to this model, participants would be paid according to the potential for benefit and the degree of risk in a study. So if the chance for a benefit is nonexistent and the potential risk is great, then they would receive a greater payment. Alternately, if they might be motivated to participate because they could be receiving a new drug for their disease, and the risk is proportional to not receiving the treatment, then they might be expected to participate as an unpaid volunteer.[1]

This model could lead to charges of undue inducement, and this model also could provide enough incentive for some people to become professional research participants.

"There are no data that this is happening, but some people have a gut level reaction that people might become professional research subjects," Dickert says.

Even if this were to happen, it might not be ethically misguided unless participants are lying about conditions to meet eligibility or are ignoring adverse events after enrolling so that they might stay in a study, he notes.

"We don't have good evidence to suggest that either of those kinds of things are happening," Dickert says. "This would be a separate kind of issue, if that's the case, where people are distorting their medical history to continue to receive payments."

Another problem with the market model is that it could drive up fees for participants and encourage recruitment for the wrong reasons, he notes.

"By that I mean the studies that happen to have a lot of money to pay subjects will have the best ability to recruit," Dickert says. "It would be unfortunate to have studies compete based on payment."

Wage-payment model

This model suggests that research participation does not require skills, but does require time, endurance, and effort. It has an egalitarian viewpoint that all subjects performing similar functions should be paid similarly.[1]

This would lead to a standardized, low hourly wage with some additional payments to augment the more uncomfortable or burdensome procedures and a completion bonus that is not disproportionately large.[1]

"The amount is calibrated to the typical amount of payment for relatively unskilled labor in the market where the project is being conducted," Dickert says. "I think this is the best way to think through this issue."

Although the amount subjects are paid would be increased for any inconvenience they

experience, it would not be tied to the study's potential risk, he adds.

"You would pay people in a way that appropriately recognizes the kind of job or service that research participants are providing," Dickert says.

"I like the idea of this type of standardization because it prevents competition between studies based on how well they pay subjects," he notes.

One criticism that might be made of this model is that if a site offers relatively low amounts of money for participation then the only people who will find those offers attractive are poor people, Dickert says.

"My counter to that is that we think research is a good thing and people are providing a valuable service," he says.

As long as the compensation is fair, then no single group should be preferentially induced to participate, he adds.

Reimbursement model

This model has research sites paying participants only enough to cover their expenses. It's based on the viewpoint that research participation should be revenue-neutral for participants, and it does not provide financial compensation for participants' effort or discomfort.[1]

The chief drawback would be that the model might make it even more difficult to enroll people in clinical trials.

Dickert favors the wage-payment model because he believes it is the most ethical approach to paying research subjects.

Some more recent research has drawn on his wage-payment model and found it appropriate even for younger children who are recruited to participate in studies involving their specific diseases.[2,3]

IRBs might keep these different types of models in mind. But considering a study's incentive pay should be a separate issue from reviewing the protocol, Dickert says.

"I think IRB members should evaluate a study first and later evaluate the payment that's offered," he says. "If a study is unapprovable, it doesn't matter how much subjects are paid."

Also, investigators, sponsors, and participants would benefit from more explicit and better guidelines regarding payments to participants, Dickert says. ■

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FDA amended rule on non-IND foreign trials criticized

Some say it weakens ethical protections

The FDA's amended rule for acceptance of foreign clinical studies not conducted under an investigational new drug (IND) application has drawn fire from health advocates who say it weakens ethical protections.

The amended rule, which was published in its final version earlier this year (21 CFR Part 312) replaces the requirement that such studies be conducted in accordance with ethical principles stated in the Declaration of Helsinki with a requirement that they be conducted in accordance with good clinical practice (GCP), including approval by an independent ethics committee.

The amended rule takes effect Oct. 27.

While the stated purpose of the amendment is to "help ensure the protection of human subjects and the quality and integrity of data obtained from these studies," it has been criticized by some involved in international health research.

"I think the primary implication of this is that the United States has acted with arrogance toward the rest of the world, and told them that the standards that apply to you are not the ones that are of interest to us," says **Peter Lurie**, MD, MPH, deputy director of Public Citizen's Health Research Group in Washington, DC.

Lurie and **Robert Reinhard**, a community advisory board member for the San Francisco Department of Public Health, say the change from the Declaration of Helsinki to GCP raises several ethical issues:

- **Use of placebo.** There has long been debate about whether it is ethical to provide placebos to subjects in the control arm of a clinical trial in a

developing country when effective treatment is available in the developed world. The Declaration of Helsinki specifically calls for placebos to be used only the in absence of existing proven therapy.

• **Post-trial obligations to research subjects.** The declaration states that at the conclusion of the study, all participants should be assured access to the best proven treatment identified by the study.

• **Obligations to the communities where research is conducted.** The declarations states that medical research is justified only when the population in which it is being carried out stands to benefit.

Reinhard and Lurie say that these issues are not addressed in the GCP.

"The GCP is a generally reasonable document," Lurie says. "But it is not, primarily, an ethics document. We don't mind if the GCP is in there in addition to some ethics standard like the Declaration of Helsinki."

He notes that the declaration itself was amended at the urging of the United States to give greater leeway for use of placebo.

Attempts to seek comment from the FDA were unsuccessful. However the published final rule does address complaints such as Lurie's and Reinhard's that were submitted while the rule was under consideration.

The rule states that the U.S. government does not fully support the most recent revision of the declaration "because it contains certain statements that may be inconsistent with U.S. law and policy [e.g., concerning use of placebos in clinical trials]." The rule also addresses the obligations in the declaration to provide post-trial treatment to participants: "[The requirement] invokes issues of health care policy that are not directly related to FDA's mission of ensuring that medical products are safe and effective."

Role for IRBs

Reinhard says he has filed objections with the FDA to the final rule and has asked for a hearing, but has not heard back from the agency.

In the absence of any change to the rule, he and Lurie say it's up to IRBs to raise these ethical issues when reviewing trials to be conducted in the developing world.

"It's not a requirement, it's not an obligation," Reinhard says. "Nonetheless, IRBs have the opportunity to use either persuasion or policy matters or other features to achieve or accomplish things the FDA is unwilling to do."

Lurie notes that various IRBs might have different positions on issues such as placebo and post-trial treatment.

"The general problem is that IRBs tend to defer to the local investigators," he says. "If somebody comes in and says this is the only way to do this, people on the IRB are in general not going to feel that they're well placed to resist that." ■

CNE/CME Objectives and Instructions

The CNE/CME objectives for *IRB Advisor* are to help physicians and nurses be able to:

- **establish** clinical trial programs using accepted ethical principles for human subject protection;
- **apply** the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- **comply** with the necessary educational requirements regarding informed consent and human subject research.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.

COMING IN FUTURE MONTHS

■ Increase IRB office income with systematic fee collection

■ Develop better QI program tools

■ Improve turn-around time by following these tips

■ Learning from pediatric research participants

CNE/CME *questions*

9. Which of the following are the domains listed by the Association for the Accreditation of Human Research Protection Programs for accreditation processes?
   A. Leadership, the IRB, the grants, and contracts
   B. Investigators, IRB members, research administrators, and participants
   C. The organization, the research review unit, investigators, sponsored research, and participant outreach
   D. None of the above

10. Informed consent documents should include what information about withdrawing from studies?
   A. A statement that the subject has a right to withdraw at any time without loss of benefits.
   B. An explanation of any potential consequences of withdrawing early from the study
   C. An explanation of what procedures will be required if a subject withdraws, along with the rationale for those procedures.
   D. All of the above

11. According to a researcher, Neal Dickert, MD, which of the following models suggested for paying research participants might be the most fair and practical?
   A. Market model: This would pay people according to the risk they take and the benefits they receive, and it would be competitive, so people who are among a highly sought-after research group might receive several offers.
   B. Wage-payment model: This is equitable since people are receiving payments based on unskilled wages for their time, discomfort, and effort in participating in research.
   C. Reimbursement model: This model is the most fair because no one is paid for participating, but they do receive reimbursement for the expenses they incur during research participation.
   D. None of the above

12. The FDA's amended rule for acceptance of foreign clinical studies not conducted under an IND application requires that studies be conducted in accordance with which of the following requirements?
   A. The Common Rule
   B. Good Clinical Practice
   C. The Belmont Report
   D. The Declaration of Helsinki

Answers: 9. c, 10. d, 11. b, 12. b.