IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Reporting rules for adverse events, unanticipated problems differ slightly

IRBs and investigators often confuse the two

IRBs often struggle with decisions regarding the reporting of adverse events and unanticipated problems, and the recent increases in IRBs' workloads do not help the situation, experts say.

One of the biggest regulatory problems facing IRBs is dealing with the volume of information they receive and efficiently and effectively determining data items that require reporting vs. items that don't, notes **Carol Weil**, JD, compliance oversight coordinator and public health analyst with the Office of Human Research Protections (OHRP) in Rockville, MD.

"Different agencies and sponsors have different requirements, so it's difficult for IRBs to advise researchers of what needs to be reported to whom," she says.

For instance, the term "adverse event" does not appear in the Department of Health and Human Services (HHS) regulations that pertain to IRBs, Weil explains. "Under HHS rules, the requirement is for any unanticipated problems, and this includes adverse events and nonadverse events."

Nonetheless, IRBs and investigators continue to think primarily in terms of adverse events, Weil adds.

That term is found solely in the device and drug regulations, and it pertains to investigational test articles, says **Jeffrey A. Cooper**, MD, MMM, deputy director of the Association for the Accreditation of Human Research Protection Programs Inc. (AAHRPP) of Washington, DC. "It is not in the IRB and informed consent regulations, so if there's no test article, such as in a social-science study, then you can have an unanticipated problem, but no adverse event," he adds.

However, there is an overlap between the two, and this helps to confuse IRBs about reporting requirements.

"This area is so difficult because there are so many different perspectives," says **Ada Sue Selwitz**, MA, director of the Office of Research Integrity and an adjunct associate professor of behavioral sciences at the University of Kentucky in Lexington.

If IRBs only had to deal with HHS regulations pertaining to unanticipated problems, then it would be far simpler to set up effective systems and policies, she says.

"But in addition to unanticipated problems, there are industry sponsors governed by the Food and Drug Administration [FDA], and their regulations for adverse event reporting are dramatically different from the requirements for IRBs," Selwitz adds.

Add to this mix the fact that sponsors also are regulated by the FDA, and they may have their own interpretations of what the FDA requires them to report, and they in turn order investigators to handle adverse events a certain way, she notes.

Because of the confusion that adverse events and unanticipated problems reporting may cause IRBs, it's probably a good idea for IRBs to clarify their policies and procedures regarding the reporting of these items. Here are some suggestions for improving an IRB's adverse event/unanticipated problem reporting:

• **Clearly define adverse events and unanticipated problems.** "It's important that organizations make their investigators understand this concept of unanticipated problems and how this involves risk to subjects and others," Cooper says. **(See box, p. 27.)** "Unanticipated problems are major things that happen that are unexpected and present some change to the risk-benefit ratio of the research."

The University of Kentucky has written a draft policy that outlines what adverse events and unanticipated problems entail and how the investigator needs to report these events, Selwitz says.

For example, such a policy might say that it applies to any problem or adverse event that affects the rights, welfare, and safety of subjects and which could involve physical, social, and psychological risk or involve an inappropriate breach of confidentiality or invasion of privacy.

A policy also might differentiate between unanticipated problems, unexpected adverse experiences, and unanticipated adverse device effect, defining each and including examples.

"What's a risk or a problem?" Weil says. "You can read into the language the notion that if someone breaks a fingernail, then that's not a risk and not a problem."

Still, if there's a fairly innocuous problem that happens to everyone involved in the trial, then it might be irrelevant to human subjects protection and to the research, but it's still important to know, she adds.

Another aspect to consider is that despite an institution's best intentions to define and differentiate between adverse events and unanticipated problems, it's likely investigators will continue to use the term "adverse event" to refer to all of the above, Selwitz notes.

"We're dealing with a constituency of

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What Is a Serious Adverse Event?

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is SERIOUS and should be reported when the patient outcome is:

Death
Report if the patient's death is suspected as being a direct outcome of the adverse event.

Life-Threatening
Report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death.
Examples: Pacemaker failure, gastrointestinal hemorrhage, bone marrow suppression, infusion pump failure that permits uncontrolled free flow resulting in excessive drug dosing.

Hospitalization (initial or prolonged)
Report if admission to the hospital or prolongation of a hospital stay results because of the adverse event.
Examples: Anaphylaxis, pseudomembranous colitis, or bleeding causing or prolonging hospitalization.

Disability
Report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities, or quality of life.
Examples: Cerebrovascular accident due to drug-induced hypercoagulability, toxicity, peripheral neuropathy.

Congenital Anomaly
Report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child.
Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide.

Requires Intervention to Prevent Permanent Impairment or Damage
Report if you suspect that the use of a medical product resulted in a condition that required medical or surgical intervention to preclude permanent impairment or damage to a patient.
Examples: Acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.

Source: Food and Drug Administration, Safety Information and Adverse Event Reporting Program, Rockville, MD.

investigators who think in terms of adverse events, so we have to balance these different perspectives and requirements," she says.

• **Provide examples of unanticipated problems.** One example of an unanticipated problem, which occurred during the course of one research study, is that a researcher's computer had been stolen from her office, Weil says.

The computer contained identifiable data, which could pose a risk of harm to human subjects, she adds.

"That was the kind of thing that you wouldn't see as a problem [directly] with the research, but it was reported as an unanticipated problem," Weil says.

Another example of an unanticipated problem is when an adverse event that is expected in a small number of research participants suddenly appears in a greater number of subjects. While this event was anticipated on a small scale, it became an unanticipated problem when it began to occur on a broader scale, she explains.

IRBs also would need to report an unanticipated problem in the rare case of an investigator being arrested for an unrelated crime. There was one example of this scenario, and the police wanted to go through the files of the researcher, which would have breached confidentiality of research subjects, Weil says.

"An unanticipated problem can arise from

almost any sort of information that the IRB might receive," Cooper notes. "Unanticipated problems could be unplanned changes, deviations, exceptions, or violations."

While most deviations, exceptions, and violations are minor and trivial, having no impact on risk-benefit ratio, there could be some that indicate there is a problem with the study's design, which may need to be modified because it involves unanticipated problems for subjects and others, he says.

For example, in the AbioCor Implantable Replacement Heart clinical trials, one patient was unable to return to his home after experiencing a stroke and breathing difficulties because his home did not have the infrastructure necessary for the necessary medical equipment.

Once this unanticipated problem arose, it would be important for the IRB to modify the informed consent so that future subjects would not be confronted with that problem, Cooper notes. "These things happen all the time, and they are things that people just didn't think about," he says. "The most important thing is that people recommend these as issues that are reported to the IRB."

• **Devise a good strategy and guidelines for reporting of unanticipated problems.** IRBs and institutions might offer investigators a series of instances in which unanticipated problems are reported and offer them a flowchart or guidelines for where, when, and how to report these events. **(See flowchart, p. 29.)**

"We're developing an unanticipated problems/adverse events reporting policy for our investigators that specifies what problems and events they need to report to the IRB, and when and how," Selwitz says. "The other challenge for IRBs is that it's critically important to know what the IRB's responsibility is for reporting these issues to either the FDA or OHRP."

The first step to developing a reporting strategy and guidance is to assess all regulations and policies that impact researchers and IRBs, she suggests.

Then harmonize and streamline the institution's policy based on the nature of the institution's research programs, Selwitz says.

Developing the policy will take time and work. The University of Kentucky had a committee of eight people who worked on the new policies for more than a year, she reports. "We took at least five or six months assessing the different requirements," Selwitz adds.

• **Be familiar with OHRP's guidance on this subject.** "It's important to be familiar with the regulations that deal with unanticipated problems and also to be familiar with the guidance OHRP has published on unanticipated problems," Cooper says. "It can be found on the OHRP's findings and guidance document on-line."

HHS has rules requiring that institutions have policies in place for ensuring that adverse events and unanticipated problems are promptly reported," Weil says. "That means there ought to be a written policy somewhere so investigators know the time frame for reporting and so that the IRB knows which institutional officials they need to report to and how that information gets up to OHRP."

• **Offer guidance on when it is necessary to require a modified consent form.** "We ask IRBs to make a determination of whether or not it's important to amend the consent form, either because it's a risk that's not mentioned at all, or because it's identified as one that's expected to have a lesser occurrence than what happened," Weil says.

For instance, suppose 80% of subjects have headaches, and headache is only listed as a rare risk, then the consent form would need to be modified to show that a headache is a common problem, she explains.

On-line flowchart

Jeremy Wood, PhD, communications consultant and founder of IRBtool.com, has created an on-line SAE flowchart called SAEtool (www.saetool.com). The free program is designed to help users determine whether and how FDA regulations may apply. Each screen offers the user a series of questions or prompts, such as "My question is related to: Drug, Biologic, Medical Device." The user selects the appropriate response and is sent to the next appropriate screen. For example, if you were to select Drug, the screen to follow would ask you to select from among the following the scenario that applies to your situation:

• an Investigational New Drug covered by an IND (Investigational New Drug application);

• postmarketing reporting of adverse drug experiences;

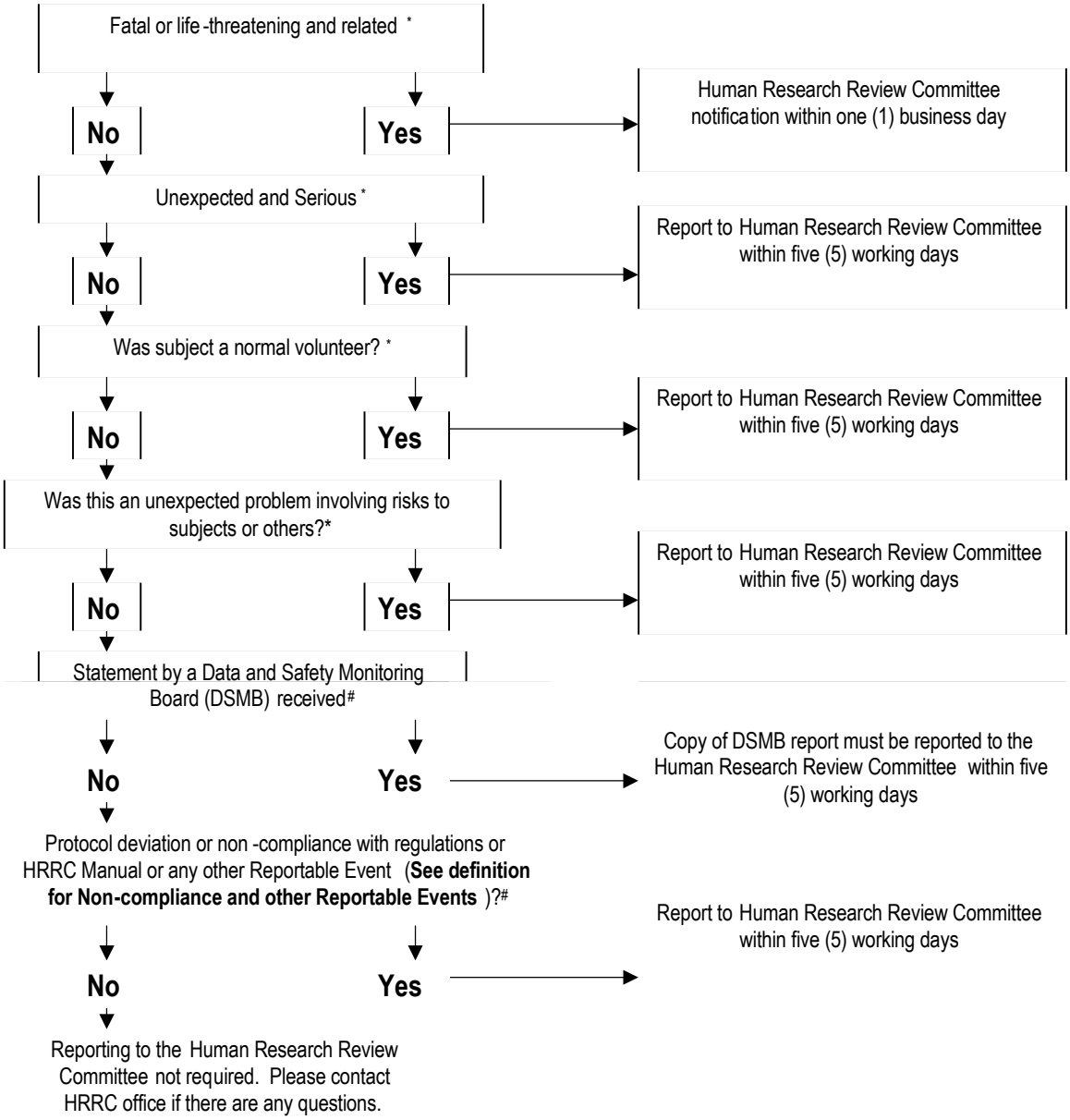
• a prescription drug marketed for human use without an approved new drug application;

• none of the above.

Once the user has selected all of the elements that apply to his or her situation, the tool will advise the user whether an adverse event has occurred and/or needs to be reported to federal entities.

(Continued on page 30)

Flowchart for Investigator Reporting Adverse Events or Unexpected Problems



***** Internal adverse events (events that occur onsite or at a site where a UNM/VA Investigator is the coordinator for a multicenter study) must be reported on the Human Research Review Committee (HRRC) Internal Adverse Event Reporting Form. This form must be entirely completed and signed by a study investigator or it will not be reviewed by the HRRC. External adverse events should be submitted attached to an External IND Safety Report Log or a cover memo.

Rather than completing an adverse event form, Data Safety Monitoring Board reports, Noncompliance, and other Reportable Events may be submitted with a cover memo including HRRC #, principal investigator's name, study title, dates, and brief description of issues surrounding event being reported.

Source: University of New Mexico, Health Sciences Center, Human Research Review Committee, Albuquerque.

Though the tool may be useful to investigators, IRBs still must have their own policies in place regarding reporting adverse events and unexpected problems. "The FDA Investigational New Drug regulation (21CFR 312.66) requires the investigator to report promptly to the IRB 'all unanticipated problems involving risk to human subjects . . .'" says **John Isidor**, JD, CEO of Schulman Associates IRB in Cincinnati. "Accordingly, it is imperative for the investigator to understand and comply with the adverse event reporting policy of the reviewing IRB." ■

Embryo research creates heated ethics debates

At issue: Do embryos have rights?

A debate that has become more heated in the 21st century is whether all embryonic research should be subject to human subject research protection and IRB review.

Taken to an extreme, the standard might require the evaluation of whether there is a benefit to the embryo itself and whether the research can be conducted in the absence of such a benefit, says **Nancy L. Jones**, PhD, MA, associate professor of pathology at Wake Forest University School of Medicine in Winston-Salem, NC, and a fellow for the Center for Bioethics and Human Dignity, affiliated with Trinity International University in Deerfield, IL. She also was appointed to U.S. Secretary of Health and Human Services Secretary's Advisory Committee on Human Research Protection in December 2002.

"Is this entity before it's 14 days old something different?" Jones asks. "Is it a tissue culture?"

Historically, animal embryonic research has treated animal embryos as a tissue culture system rather than a whole animal system, she reports.

"So when you apply some of the same things to human embryos, the question is, "'Where should it fall?'" Jones asks. "The most important question is what is the morality of the human embryo, and that's where a lot of the debate is."

Prior to 1994 when the National Institutes of Health (NIH) had a panel look at embryo research, most embryonic research was limited to studies that directly assisted procreation, Jones says.

"In other words, we would improve in vitro fertilization [IVF], help people have children," Jones explains. "So there were restrictions on what you could do with human embryos."

Even now, the research ethics community distinguishes between using embryos for constructive purposes of fertility and procreation and using embryos for destructive purposes in which there is no benefit to the embryo, she adds.

"There was a thought that it was wrong to create an embryo for purposes other than procreation," Jones says. "So if you had some leftover embryos from fertility treatment or research, then it was one thing to use those leftovers, but it was considered taboo to create an embryo specifically for a purpose other than procreative research."

Cloning research pushed the envelope even further, although the research ethics community now has a consensus that human cloning is not right. However, ethicists are divided between those who believe it will always be wrong and those who believe it is wrong now because there are too many health uncertainties for cloned humans, she notes.

"To me, the essential question our culture has to work out is, 'What is the human embryo?'" Jones says.

There are three basic points of view about this ethical issue:

- One point of view holds that the human embryo has intrinsic value because it is 100% consistent with human life, Jones says. "Therefore, people would say that if we're going to apply human subjects research to embryos, we have to go back to this: You can't let one segment of the population bear the brunt of research that they're never going to have any benefit from," she says.
- The second view is that embryos are merely a collection of cells that are under a genetic code and therefore more analogous to a tissue culture, Jones explains. "That view would say that all research should be allowed because it's not human; it's genetics."

NIH's 1994 report on embryonic research issued an intermediate moral view that states embryos are not people and do not have the full moral status of a baby, but the embryo's moral rights increase the further developed it becomes, she says. "It's a form of life, but it doesn't have the full moral status that a baby would have," Jones adds. "But it would have increasingly more weight as it moves along the developmental line and becomes more and more like a baby."

- The third view is that our definitions of personhood, consciousness, reasoning, feelings, and sensations all depend on brain life and, at 14 days of life, the human embryo has a very

primitive brain, she explains.

Based on this view, embryonic research would have the condition of being allowed for destructive purposes before the 14th day of life and only if it is not implanted, Jones says.

"Then Congress reacted negatively, and that's where we got things in an appropriations bill that said researchers couldn't allow embryos to be created for research or destroyed," Jones says. This applied to research conducted with federal funds.

Private money, different standard

Research involving private funding is less regulated, she adds.

With private money, researchers can take an embryo, let it grow to blastocyst stage, and then take out the inner cell mass and establish a cell line, which is different from creating or destroying an embryo. Cell lines can use federal money for this reason, although one of the first things President George W. Bush did in office was rule that research could continue on existing cell lines, but researchers could not create new cell lines.

So this brings researchers and ethicists to the question of how embryonic research should be reviewed, Jones says. "If you're going to start soliciting people to donate eggs or leftover embryos, then that would have to go through an IRB review."

While women were not permitted to donate eggs or embryos unless they were undergoing IVF, this restriction changed when Jones Institute for Reproductive Medicine in Virginia Beach, VA, recruited people to give sperm and eggs for embryonic research, she reports.

"A local body reviewed the study," Jones says. "The institute did this specifically for creating an embryo for destructive research and to make embryonic stem cells."

In 2001, after investigators published their work in creating embryonic cells for the purpose of curing chronic illnesses, there was a public outcry that led to Bush's stem cell decision, and the institute was forced to stop this type of recruitment, Jones adds.

When the ethical issues of research stir up political and scientific issues, it shows that the scientific community needs further scrutiny of human subjects protections, she points out.

"Maybe some research needs to be classified as experimental and there is a need for a different classification, or maybe a new category," Jones says. "But I think it's too much to ask local IRBs to be competent on all of these novelties, so we need some kind of regional or national group of people who have the expertise to guide this area in an ethical manner." ■

Stem cell trials present novel issues for IRBs

Hopkins group to examine potential risks

The furor surrounding the derivation and collection of embryonic stem cells has eclipsed the many other ethical, legal, and social issues that should be examined before these therapies move from the laboratory to human clinical application, say researchers working at Johns Hopkins University in Baltimore.

"By focusing on the derivation of stem cells from embryos and fetuses, the discussion of the ethics of stem cell research has, in large part, become tied to the ongoing debate over the moral meaning and significance of early human life and the beginning of life," says **Ruth Faden**, PhD, MPH, professor of biomedical ethics and director of the university's Phoebe R. Berman Bioethics Institute.

"These polarizing issues aren't amenable to solution by political fiat or by discovering some fact of the world through scientific inquiry. And we are in a situation where the other pressing ethical issues raised by stem cell research are neglected or totally ignored because the attention that is focused on seemingly intractable disagreements," she notes.

With experts predicting the first human trials of stem cell within the next five years, institutions need to begin examining these other issues now in order to have the ethics advance with the science, Faden tells *IRB Advisor*.

At Hopkins, members of the bioethics faculty have formed a collaborative program with faculty from the university's Institute of Cell Engineering to attempt to anticipate the moral and policy challenges that stem cell science and cell engineering will pose and provide the opportunity for careful, interdisciplinary analysis of these challenges to assist both policy-makers and the public.

The Program in Cell Engineering, Ethics, and Public Policy (PCEEPP) was created in March 2002, and is a formal, ongoing collaboration.

"Prior to the program's creation, there was an existing relationship between the faculty of the two institutes, with individuals jointly involved in projects examining ethical issues in stem cell science

and research; however, through the program, this effort was formalized," Faden explains.

PCEEPP recently published a report, "Safety issues in cell-based intervention trials," in the November 2003 issue of the journal *Fertility and Sterility*.[1]

According to their findings, clinical trials of stem cell therapies will present a number of novel issues in terms of risks to human subjects and questions of justice and access to new treatments.

Safety concerns

First, there are serious safety concerns that must be addressed before stem cell therapies can be tested in human subjects, Faden says.

For instance, the program members agree with the National Academy of Sciences that the presence of mouse feeder cells in the culture upon which current stem cell lines are maintained raises the specter of cross-species disease transmission should those cells be reintroduced into a human.

Although work currently is under way to develop new mouse-free feeder lines, all of the stem cell lines approved for federally funded research under the Bush administration's policy have been in contact with mouse feeder cells.

"The risk [of disease transmission] is a theoretical risk, but it isn't a necessary risk," Faden says. "New lines will be mouse-free, and that's the fact that led us to say it would be unethical to use the extant cell lines in humans."

Another safety issue is the need for some kind of suicide switch that could control the functions of the stem cells once transplanted into subjects, she continues.

"One of the big hurdles that remains to be overcome with stem cells is the possibility that, after transplantation, they go somewhere other than where they were intended to go, or they start producing the wrong cell types," she says. "In both of these scenarios, we need some way to deactivate the cells so that they don't harm the individuals who received the transplant."

There also will be complex issues involving justice and appropriate selection of research subjects, she adds. By their very nature, stem cell-based therapies will be suitable for use in some humans and not in others.

"This variability tracks — to some degree — ethnicity, so it appeared very important to us to flag the downstream justice concerns that may arise," Faden notes.

Stem cell transplants will be fairly similar to some types of solid organ transplants in that the subjects will face the possibility of immune rejection. As such, recipients of stem cell transplants will likely face the same scenario as persons who receive solid organ transplants in that they must be appropriately matched to their type of stem cell to avoid immune rejection.

This will result in disparities across ethnic and ancestral groups, Faden notes. "Due to genetic variability within the African-American ancestral groups, African-Americans disproportionately have difficulty obtaining matching in solid organ transplantation, and the same would likely be true of stem cell transplants," she explains. "Unlike solid organs, however, we have a choice in which stem cells are available for transplantation. Indeed, we may even be able to engineer the genetic code of the stem cell."

Determinations about which stem cell lines are studied and, therefore, eventually evolve into treatment options should be a concern. "Given the difference, our group addressed the question of how we should select which stem cell lines become available for transplantation, and what strategy would be most just in the American context," Faden says.

Given the complex challenges involved, it may be necessary for additions or alterations to the existing oversight process for human subjects trials, the program members noted.

They believe that serious consideration should be given to the establishment of patient advisory boards, consent monitors, patient advocates, and other procedures to concentrate attention and energy on the interests of subjects and their families as the first human trials go forward.

It's possible that a national advisory committee, similar to the Recombinant DNA Advisory Committee, which currently oversees federally funded human gene intervention research, would be needed to provide additional guidance, Faden notes.

"The pre-clinical and the first human trials of stem cell-based therapies will likely be quite difficult," she says. "Over the years, there have been many proposals for strategies to improve protections for human subjects in high-stakes, high-risk research. The first human stem cell trials certainly fit this description."

Reference

1. Dawson L, Bateman-House AS, Mueller Agnew D, et al. Safety issues in cell-based intervention trials. *Fertil Steril* 2003; 80:1,077-1,085. ■

SPOTLIGHT ON COMPLIANCE

OIG reaffirms its views on cost-sharing waivers

Commercial benefit influences process

By **J. Mark Waxman**, JD
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In the year 2000, Health Care Financing Administration (now known as the Centers for Medicare & Medicaid Services) issued its National Coverage Determination (NCD) extending Medicare coverage to "routine costs of qualifying trials," as well as those items and services made necessary to diagnose or treat complications arising from clinical trial participation.[1] The impetus behind the NCD was to put trial participants on the same footing as those who were not participants, as well as to encourage or at least not penalize trial participants, in the event complications arose as a result of trial participation, even if the costs incurred for the trial itself could not be reimbursed.

Given the encouragement the NCD gives Medicare beneficiaries to participate in clinical trials, the issue then arose as to whether those who might participate in such trials could be further induced to do so through a waiver (without consideration of financial hardships) of cost-sharing obligations as well. That, however, might well be crossing the line with respect to prohibited inducements applicable to the Medicare program generally.

In February, the Office of the Inspector General (OIG) addressed this question in an Advisory Opinion.[2] It concluded that, at least in the case of a government-sponsored trial, it did not.

The Medicare and Medicaid programs prohibit payment or receipt of remuneration to beneficiaries whom the donor "knows or should know" is likely to influence the use of a provider or supplier of covered services.[3] Remuneration is broadly defined as and generally includes anything of financial value, and in particular the waiver of all or a part of any beneficiary cost-sharing obligation (absent specific case by case financially needy or uncollectable cases).[4]

The anti-kickback statute[5] also may have impact. It prohibits remuneration paid, offered, received, or solicited to induce referrals. The prohibition under this provision is similarly board, and would cover any "arrangement" where "one purpose" of the remuneration involved is to induce the referral. Clearly, it is quite possible that a waiver of a payment, otherwise due, would become such a referral.

The clinical trial at issue was a Bypass Angioplasty Revascularization Investigation Diabetes Trial (BARI2D). The trial was initiated, funded, and managed by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. Its goals were twofold: 1) to compare the effectiveness of two-drug therapy approaches; and 2) to compare the effectiveness of drug therapy combined with early surgery to drug therapy without surgery.

The trial was to be conducted over a seven-year period, involving some 40 clinical centers and 2,800 patients. To participate in the trial, a patient was required to have both stable diabetes and coronary artery disease.

The arrangement in question stemmed from the need for trial participants to self-monitor their blood glucose levels. Supplies to do this, monitors, blood testing strips, and lancets, were to be supplied by a specific manufacturer. Under the arrangement, a nationwide supplier of blood glucose testing products would purchase the necessary supplies from the manufacturer and provide them to the trial participants.

The supplier then would bill Medicare, Medicaid, and private insurance programs. Uninsured patients would receive the supplies free of charge. Medicare patients would receive a waiver of cost-sharing obligations. The articulated goal of this approach was to encourage enrollment and enhance participation.

Of importance to the OIG, the study was not 1) a commercial study; 2) a product-specific study; or 3) a product-oriented study. Instead, it characterized the study as "scientific" in looking at public health and clinical issues in the study area. It also noted that the types of drugs and supplies to be used, as well as the treatment protocol, were developed by investigators in the centers and NHLBI scientists, whose work was in turn reviewed by an independent protocol committee. A Data Safety Monitoring Board also was appointed to provide additional independent advice.

The submission to the OIG certified that the

arrangement would not be dependent upon or operate in any way in concert with any other arrangement between the supplier, the manufacturer, and/or others involved in the trial.

The NCD was designed to allow trial participation on "the same basis" as a beneficiary might otherwise have access to Medicare benefits. This, of course, would mean that program requirements, such as cost-sharing, are applicable. Accordingly, the blanket waiver proposed for BARI2D, would likely create a material inducement in some cases and certainly could influence the selection of a provider or supplier. As a result, the prohibitions of the Social Security Act could certainly be implicated. Nevertheless, the OIG concluded that sanctions would not be imposed.

Initially, the OIG recognized the risks that inducements pose in the clinical trial context. Inducements might lead participants to use items or services for which there are effective and more appropriate treatments readily available and also could affect referral patterns leading to fraud and abuse risks.

In evaluating the proposed cost-sharing waiver for this trial, however, a number of factors led OIG to conclude these risks were low enough to be counterbalanced by the positive goals of BARI2D. Those factors were:

1. The role of a governmental agency in creating and managing the trial. The fact that the agency was in a position to control clinical questions and the treatment protocol to be followed mitigates exposure to the improper influences the statutory prohibitions are designed to prevent.

2. The clinical centers involved were selected in accordance with governmentally determined specifications.

3. The trial was not created to study or benefit any specific commercial product.

4. Resolution of the issues at the heart of the study would likely benefit all affected patients, including Medicare beneficiaries.

These factors allowed OIG to distinguish this trial from those "initiated, organized, funded, managed, or otherwise sponsored" by pharmaceutical companies or "private interests" without substantive governmental involvement.

Not surprisingly, the OIG sanctioned a governmental study that appeared to have relatively little substantive decision making by other parties. Whether it is possible that in some other contexts, where a nongovernmental sponsor is involved, a waiver program would be approved, remains questionable. Indeed, the specific lengths to which OIG's opinion distinguishes BARI2D from one that might have similar independent scientific decision making, but might be of a particular product or even a class of products, would not appear to make the prospects of an approval of a similar cost-sharing waiver, or even receipt of some other type of unpaid-for benefit very likely.

References

1. See www.cms.hhs.gov/coverage/8d2.asp.
2. OIG Advisory Opinion Request No. 04-01 (http://oig.hhs.gov/fraud/docs/advisoryopinions/2004/ao0401G.pdf).
3. Section 1128A(a)(5) of the Social Security Act.
4. Section 1158A(i)(6) of the Social Security Act.
5. See section 1128(B)(b). ■

Reader Question

Under HIPAA, subjects do have rights to their results

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Question: What rights to their research-related results do patients have?

Answer: Historically, research data were regarded to be the property of the researcher and not available to research subjects. Most research data are not of value to study subjects in diagnosing or treating medical conditions. There are two reasons for this: 1) the data are not verified to the extent required for making medical decisions for diagnosis or treatment; and 2) the hypothesis being tested is not sufficiently developed to allow a practical application of the research results.

There is, however, an ethical imperative to inform research subjects of any personal health information that would be of value to them. For example, the study might require a chest X-ray. Even though it is not an objective of the study, if the X-ray reveals possible lung cancer, the researcher is obliged to inform the subject of the discovery so that a confirmed diagnosis can be made and any appropriate medical care can be started in a timely manner. On the other hand, subjects may decide

they do not want to know about a positive finding of a condition for which there is no effective treatment, such as Huntington's disease.

Public Health Service (PHS) policy requires subjects of PHS-funded or conducted research and their sex partners to be informed of positive test results for HIV.[1]

The advent of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule in 2003 gave to patients the power to determine who has a right to use or disclose their protected health information (PHI). Although the rule primarily addresses treatment, payment, and other routine health care operations, its purview extends to the research use and disclosure of data containing personal identifiers by covered entities.

HIPAA applies only to "covered entities," those who are involved in health care treatment, payment, or related operations. Noncovered entities are not required by law to observe the safeguards provided by the HIPAA Privacy Rule, but many see compliance with its provisions to provide insulation against any question of adequate maintenance of privacy and confidentiality.

The HIPAA Privacy Rule requires disclosure of his or her PHI to that individual on demand.[2] This provision includes research data when the research is combined with medical treatment. The individual's right of access to the research data maintained by a covered entity may be suspended provided the individual agrees to such suspension at the time authorization for the conduct of the research was obtained.[3]

The PHI that is part of the study must be made available to the research subject after the conclusion of the study and study-related activities, such as analysis of the data. The PHI that is revealed includes any data that contain personal identifiers of the requester. However, the PHI of other study participants would not be revealed. Nor does this provision appear to require providing to the requester any data analysis or study conclusions that were carried out after PHI was removed from the study data.

In addition, the suspension of access involves only the PHI that is in the study records. The requester would continue to have the right of access to PHI that is maintained in nonresearch medical records. In many cases, this would be a copy of the same data that the researcher obtained from the medical records.

In addition to the practical outline presented above, there may be state and local requirements that affect the rights of study subjects to research data that contain their personal identity.

References

1. OHRP Guidance at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc88jun.htm and http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc90may.htm.
2. Privacy rule at: 45 CFR 164.524.
3. 45 CFR 164.524(a)(2)(iii). ■

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- **explain** the potential for conflict of financial interests involving human subject research;
- **discuss** reporting adverse events during research. ■

CE/CME *questions*

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9. Under Department of Health and Human Services regulations, which areas of research requirements pertain to the term "adverse events"?
A. All areas, including IRB reporting requirements.
B. Any area that also pertains to unanticipated problems because the two terms are used as synonyms.
C. Solely in the device and drug regulations, pertaining to investigational test articles.
D. Solely in the IRB regulations, pertaining to medical research trials only.

10. Three points of view concerning the definition of "What is the human embryo?" include which of the following?
A. The human embryo has intrinsic value because it is 100% consistent with human life.
B. Embryos are merely a collection of cells that are under a genetic code and therefore more analogous to a tissue culture.
C. Our definitions of personhood, consciousness, reasoning, feelings, and sensations all depend on brain life, and, at 14 days of life, the human embryo has a very primitive brain.
D. All of the above

11. In evaluating the proposed cost-sharing waiver for the Bypass Angioplasty Revascularization Investigation diabetes trial, which of the following factors led OIG to conclude that a cost-sharing waiver was appropriate:
A. The role of a governmental agency in creating and managing the trial.
B. The clinical centers involved were selected in accordance with governmentally determined specifications.
C. The trial was not created to study or benefit any specific commercial product.
D. All of the above

12. The HIPAA Privacy Rule requires disclosure of PHI to a subject on demand.
A. True
B. False

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