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An essential resource for managers of clinical trials

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NJ stem cell research law sparks renewed ethics and legal debates

Investigators need to understand, navigate complexities

In January, New Jersey became only the second state in the union to pass legislation formally permitting research using embryonic stem cells.

Similar to a 2002 California law, the New Jersey measure explicitly prohibits any attempt at human reproductive cloning, but specifically permits research involving "human embryonic stem cells, human embryonic germ cells, and human adult stem cells from any source, including somatic cell nuclear transplantation."

Embryonic stem (ES) cells are primitive cells, present in human embryos at the earliest stages of development, that have the potential to develop into any type of cell found in the body. Scientists believe that, if they can learn to direct how embryonic stem cells develop, they then could grow lines of healthy cells to replace diseased cells in people with different illnesses.

However, use of ES cells in research is controversial because it involves the destruction of a human embryo, and the major source of the cells has been embryos left over from assisted reproductive procedures and discarded by fertility clinics.

In August 2001, President Bush limited the use of federal funds for stem cell research to only those studies using a set of approximately 50 preapproved cell lines, stem cells already derived from embryos prior to that date.

The language of the new state laws is much more permissive — allowing researchers to independently obtain embryos and derive new stem cell lines.

However, this means institutions and researchers in these states must carefully navigate the intersecting federal and state laws in order to undertake such studies.

Federal funding still cannot be used, meaning that institutions conducting federally funded research in other areas still may shy away.

"States, while they can control certain kinds of practices, they don't really fund research, they don't have any money, and they are not really a player in setting standards the same way that the National

Institutes of Health [NIH] and other federal agencies can set standards," says **Paul R. Billings**, MD, PhD, vice president and national director of genetics and genomics for the Laboratory Corporation of America in Research Triangle Park, NC.

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It's also not completely clear how to interpret the federal restrictions, Billings adds. Whether investigators at institutions receiving federal funding also can conduct stem cell research using private funds, or whether a federally funded institution should refrain from all such research as a condition of continuing federal funding, is not clear.

"If you have a university that receives both private and federal funding, they are worried that they will lose their federal funding if they engage in research that could flaunt the federal standard," he says. "Some have set up separate, nonprofit entities to administer such studies outside the normal research track and receive private funds that way."

Institutions also may contract with private companies to conduct research on a contractual basis, so that the primary agency doing the research is not the university, and they are only a subcontractor, Billings says.

Growth in the private sector

The impact of the new laws still will be largely in the private research sector, Billings notes, and should encourage more research because companies can be confident that the research will be permitted and supported.

"In California, companies like Genron can now feel free to operate without the fear of having their business licenses revoked," he explains.

Various private companies, and well-funded infertility researchers probably will be the groups to benefit from and make the most use of the new laws, but that may still involve obtaining the approval of an institutional review board, Billings notes.

"One of the key issues in this type of research is where you obtain the materials from, and the consent process that it involves," he says. "That most likely will occur in some sort of study protocol and fall under the review of a local IRB [institutional review board]."

If researchers are going to derive stem cells from embryos left over from an in vitro fertilization (IVF) cycle, most centers will require the consent of people who created the embryos, and this may require some sort of review before the embryos can be collected.

"If the investigator is hooked up with any kind of university, or if the investigator thinks he or she might at some later time want to get some federal funding, or publish the data, most of those kinds of investigations are done with IRB

approval," Billings notes. "There would be some review of how the material that is being worked on was gathered, and under what manner was it gathered, and was there consent and did the consent meet the Common Rule and other standards for disclosure of risks and benefits. They'll be looking at where the cells come from, are they coming from public banks and resources that are well described, are they asking people for new contributions; if so, how are they consented, how are the commercial issues dealt with, all of those things."

Examining ethical and public policy issues

Aside from the regulatory issues, some experts feel that stem cell research presents unique challenges for clinical investigators as these cellular therapies move from the lab into clinical trials.

The Program in Cell Engineering, Ethics, and Public Policy at the Phoebe R. Berman Bioethics Institute at Johns Hopkins University in Baltimore has convened an interdisciplinary working group of experts in science, law, and philosophy to discuss the novel ethical and policy challenges in stem cell research, says **Ruth Faden**, PhD, MPH, the program's co-director.

Although clinical applications for ES cell therapies are likely still years away, it's important that institutions, the public and researchers begin to examine the unique issues this type of research presents, she says.

First, tension regarding the use of human embryos may complicate the development of safe and effective cell lines.

Many researchers feel, for example, that the current federally approved cell lines should not be used in clinical trials because they were initially grown on mouse cells and have the potential to harbor mouse-specific viruses, Faden says.

Given that safer alternatives would be easily available, it would be unethical to expose human subjects to these cell lines.

"Conducting a federally funded clinical trial of human embryonic stem cells under current federal policy would require using cell lines that none of us feel should be used in people, since it is now feasible to create safer lines," Faden says. "All clinical trials, and by extension the experiments leading to them, should be conducted with newer cell lines not eligible for federal funding. The likelihood of getting to a clinical trial using private funds, however, is very slim."

Second, because human stem cells were not developed in the laboratory until 1998, few safety questions relating to human application have been addressed in animal research. And, third, pre-clinical and clinical testing of biologic agents — particularly those as complex as stem cells — presents formidable challenges in terms of developing the needed standardized assays and of recruiting appropriate populations for early phase trials.

For instance, researchers believe that therapeutic use of embryonic stem cells will require that the cells match the recipients in ways that are similar to matching patients' blood types for transfusions or for transplants of organs, bone marrow, and tissue.

With a small number of cell lines available for study, it's likely that early trials could include only select members of the population, raising issues about whether such trials would be withstand scientific rigor and how issues of justice and access to therapies by minority populations might be addressed.

In a report published in the journal *Fertility and Sterility*, Faden and colleagues call for a national commission to oversee the development of ES cell research as it moves into the clinical arena.[1]

Education for IRBs and investigators

Guidance and education for institutions contemplating ES cell research also should be a national priority, agrees Billings.

"I think that clearly local IRBs need information resources that allow them to understand nationally where the field is going," he says. "While you want IRBs to reflect regional standards and regional sensitivities, or even local sensitivities, there ought to be a large-scale informational or even expert resource that they can go to for expert opinions about various issues that might confront them. For instance, it may very well be that an IRB reviews a stem cell protocol and doesn't realize how commonly [adult] stem cells are used in therapeutics already."

Currently, no federal agency has responsibility for such oversight, though this could change if pressure from the states forces the research forward, Billings notes.

Investigators considering participation in a stem cell-based therapeutic trial should educate themselves about the federal and state regulations involved and be aware of the complex political and social implications this research presents, he adds.

"Clinical investigators need to understand the

applicable regulatory law and that is something they frequently don't understand," Billings says. "And be aware that if they are working with embryonic cells or the products of IVF, there are controversial issues. Some people believe that these cells are the moral equivalent of human beings," he adds. Whether an investigator agrees with that opinion or not, it is important to recognize that some people do and it will play a role in the decisions IRBs make about oversight and whether patients decide to participate.

"I am not suggesting that this be given any more weight than any other belief held by a particular group of people," Billings says. "But it is important to acknowledge that people have such feelings and to consider that in whatever review processes and review of document processes that might occur. That is simply recognizing the plurality of view that exists in the United States about this issue."

Reference

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

Pharmacogenetics trials offer new challenges

Recruiting subjects is top concern

The brave new world of genetics and pharmacogenetics research provides some exciting possibilities as well as some major challenges to researchers.

For example, pharmacogenetics holds the possibility of identifying individuals who may obtain the greatest potential benefit from a particular drug and identifying individuals who may be at greatest risks for side effects from a particular drug, explains **Barbara Handelin**, PhD, chief executive officer of Kenna Technologies Inc. of West Chester, PA.

The Pharmacogenetics Working Group was formed to address the many common challenges associated with pharmacogenetics research, she notes. "The working group has representatives from 20-plus pharmaceutical companies who are engaged in various levels and degrees of studies," Handelin says.

One of the major challenges facing investigators and clinical trial administrators who are engaged in genetics or pharmacogenetics research is recruiting subjects because people often are concerned about their privacy with regard to genetic information.

When a trial is designed to provide the enrollee with the genetic information or when there is a way for the information to be linked back to the individual, it is not possible to guarantee that the information never could be put at risk of disclosure, genetics research experts say.

And any time such information is disclosed, there's the potential that it will be used to discriminate against an individual, which is why those working in this industry have been in favor of legislation that would protect subjects from discrimination. One such bill, called the Genetic Information Nondiscrimination Act of 2003 was passed in the U.S. Senate and still is pending in the House of Representatives.

The bill would prohibit employers and health insurers from discriminating against people based on genetic information, says **Laura Lyman Rodriguez**, PhD, special advisor to the director of the National Human Genome Institute in Bethesda, MD.

"There have not been many cases of actual discrimination based on genetic information, but there is potential for it, and there is a great fear in the public in terms of this possibility," she says. "We're hoping the [bill] can be proactive in keeping people from becoming afraid either for health reasons or for employment.

While the Health Insurance Portability and Accountability Act (HIPAA) provides for the privacy of health information, including information obtained during clinical trials, it doesn't protect people against discrimination in the event that the information is accidentally released.

"Presumably [genetic information] should be anonymous and shouldn't get out," Rodriguez says. "But there are no protections in place with regard to nondiscrimination."

A nondiscrimination law would ease potential research subjects' minds and maybe make them more willing to participate, particularly in trials where the genetic information will be used in assessing health outcomes, she adds.

"We want to encourage participation in genetic research since more and more genetic aspects are included into protocols," Rodriguez says. "And if people are afraid that this information could get out and be used against them in some fashion,

then they might not join a study, and we don't want that to happen."

The public's fear of disclosure of private medical information is well founded, says **Mark A. Rothstein**, JD, director of the Bioethics Institute at the University of Louisville (KY) School of Medicine.

"All medical records should be subject to stringent safeguards, which we currently do not have, and our attempts to do so have been totally wrongheaded," he says. "The reason there is not anything relevant in place is because third parties can make a condition upon signing of a release an authorization of disclosure of all medical records in an individual's file, so there's no protection."

While some states have laws that protect against the dissemination of genetic information, those laws do not prohibit an employer from gaining access to medical information, including genetic information, Rothstein explains.

"So the problem isn't that numerous companies are discriminating; the problem is that people are dissuaded from taking genetic tests because they think their employers are going to have access to the information," he says. "Laws prohibiting discrimination don't have an impact on access."

On the other hand, researchers sometimes are so afraid of having too few people enroll in their genetics studies that they will make the research anonymous and limit its power, Rothstein notes.

"It's a very serious problem," he says. "I'm constantly talking to researchers about the best way to do it and how to get the proper level of informed consent."

Access to information

Clinical trial administrators and researchers also need to decide the best way to give participants any outcomes or information resulting from genetic research, Handelin says. **(See story on improving informed consent with genetic research subjects, right.)**

"Is the principal investigator appropriately trained and experienced in explaining the testing and results of the genetic test, or do they have nurses or someone else who will give this information to families and patients?" she asks. "If this is a researcher who got into genetics because his favorite disease has a genetic component, then he may not be the right person to deliver this information."

Another issue that sometimes comes up during recruitment for a genetic protocol is the possibility of coercion by people other than the investigator and clinical trials team.

For instance, when investigators are conducting genotype specific research, they need to recruit individuals with specific known genotypes, Rothstein says.

Often, these individuals are known because of their family members' participation in other genetic research regarding a specific disease, and sometimes one family member may attempt to coerce another into participation, he notes.

"You have an issue then of what role a referring physician should play and what inducements should be given to referring physicians or subjects for participating in the research," Rothstein says. "Also, what commercial interests are retained by researchers, and what rights, morally or ethically, should they have in the financial products." ■

Ways to improve genetic trials informed consent

Be sensitive to disclosure risks

While an argument could be made that collecting genetic information from individuals is no different from collecting any other type of health information, the fact remains that the very word "genetic" may raise additional concerns among potential research participants.

For this reason, a few genetic ethics and research experts have offered these suggestions for how clinical trial administrators and researchers may best handle the informed consent process during genetic or pharmacogenetics clinical trials:

• **Disclose financial interests.** "Researchers need to make full disclosure of financial interests," says **Mark A. Rothstein**, JD, director of the Bioethics Institute at the University of Louisville (KY) School of Medicine.

The importance of this policy was highlighted in 2000 when families of children suffering from Canavan disease, a rare neurological disorder, sued researchers over control of the Canavan gene, he explains.

Families of children who had Canavan disease had encouraged a geneticist to research the disease. The families provided tissue samples that were essential to the success of the research, which eventually discovered the gene responsible for the

disease. The Miami Children's Hospital, where the research was conducted, then licensed the genetic test and barred the Canavan Foundation from offering free genetic screenings. The families from whom these tissue samples were obtained were never offered informed consent or disclosure about the financial implications of the research, according to news reports of the lawsuit.

The hospital eventually settled the lawsuit and the terms were not made public, Rothstein says.

As a result of this case, disease foundations now are filing their own patents, and they've become more savvy in terms of the contracts they sign with researchers, he adds.

But the important take-home message for clinical trial administrators and researchers is that they must disclose all financial interests to potential enrollees, Rothstein says.

• **Be clear about potential risks and benefits.** Most potential risks only are relevant if the research involves individually identifiable data, he notes.

"Potential risks are only generally relevant if the results find their way into the clinical file of the individual," Rothstein says.

It's important to make certain that the likely and pertinent risks are thoughtfully discussed with research participants, says **Laura Lyman Rodriguez**, PhD, special advisor to the director of the National Human Genome Institute in Bethesda, MD.

While less probable risks could be included in the discussion, the focus should be on the more important aspects of the research, she adds.

"There are areas where particular attention might be paid, and one is the potential impact on family members," Rodriguez says.

For example, if the trial provides for participants to receive their own genetics information, then potential risks may include the psychosocial impact of that information on the participants, as well as on their families if they choose to share the information.

"A participant should be told when enrolling whether individual results will be returned; and if there is an option to find out what the individual results are, then they have the option also to not receive them," Rodriguez says. "Some people may not want to learn the information because of how it might effect them personally."

• **Have a direct dialogue with the IRB (institutional review board).** Investigators need to speak with IRBs directly to explain what they're doing and to inform IRB members about the nature of the genetic research and the informed consent process, suggests **Barbara Handelin**, PhD, chief executive officer of Kenna Technologies Inc. in West Chester, PA.

Training and guidance integral

• **Encourage institutions to develop guidance.** Institutions and IRBs need to have a conceptual framework for genetics research that involves human subjects, Handelin says.

She suggests that some of the issues that need to be considered within such a framework or guidelines are as follows:

— What are the privacy concerns and measures that your institution cares about?

— If genetics are part of the protocol, does the institution have some special requirements for researchers? For example, would an institution agree to have any protocol, especially an industry-sponsored one, involve DNA samples from subjects that are associated with personal identifiers, such as names, social security numbers, and clinical history, Handelin says. "Or would the institution be in the camp of saying, 'You can do it, but you have to make the sample anonymous?'"

— Does the institution have a gatekeeper or repository keeper who can be the privacy firewall for the institution and for any subjects participating in genetics research?

— What are the logistical mechanisms for permitting patients to opt out of a genetics study?

— If participants opt out of a genetics study, how does the institution want to be sure that the sponsor did everything it said it was going to do, such as destroying samples, stripping samples of all identifiers, etc.?

• **Add depth to the informed consent process.** Generally, the informed consent process is similar to what one would use for any type of human subjects research, Rothstein notes.

"You need to identify the most important matters that would be relevant to a reasonable, potential research subject," he says. "Set out these issues, disclose them, and make sure it's not a rote process."

Also be sure that all questions are asked and answered and that people have time to think about whether they'd like to participate, Rothstein adds.

However, since genetics research is evolving so rapidly, there are many instances when samples collected for one particular type of genetics research may come in handy for another type down the road. This possibility raises the question of how informed consent may be obtained for unknown future studies.

"Nobody should ever sign off on a protocol that asks for blanket consent up front," Handelin says. "On the other hand, a sponsor or IRB might say, 'Here's the specific question that we want to ask right now for this study.'"

Then the clinical trial administrator might want to ask patients whether they could keep the sample for future studies that have not yet been determined, Handelin adds.

It would be up to IRBs to decide whether they want investigators to have permission to ask that last question or whether they want investigators to return with a specific informed consent whenever additional research is required, Handelin says.

"DNA is a constant and because it is such a rich source of information about people and their medical predilections and how that relates to their current or future disease process; it is a resource that most researchers want to hang on to once they collect it," Handelin says.

• **Provide subjects only with genetic information that meets medical standards.** One issue that becomes pertinent to risks involved in genetic research is how personal genetic information is disclosed, when the protocol is set up so such a disclosure is possible.

For example, when a medical patient is tested for genetic information, that test would meet the standards of the Clinical Laboratory Improvement Act (CLIA), Handelin explains.

However, these same high standards are not always required for anonymous clinical research involving genetics because the objective is to obtain statistical information involving a population, not health care information involving a particular individual.

Handelin, who once ran a genetics diagnostic laboratory, does not believe that investigators should give genetics research participants any of their personal genetics results unless those tests had been conducted under rigorous CLIA conditions.

A research laboratory may not be able to provide the same rigor that a clinical laboratory has to do when it is giving people information with which they will make a medical decision, says Handelin.

"One way to deal with this is if the test information is profoundly important and it can be duplicated in a CLIA-registered lab, then you can provide it back to the participant," she adds. "But if it can't be duplicated, then, no, don't do it."

The risks for an individual who receives inaccurate genetics information is far greater than the risks for a group of people, Handelin adds. ■

Lawsuits can be a result of poor communication

Improved consent process can offer protection

The recent lawsuit against Abiomed Inc. of Danvers, MA, and others involved in clinical trials involving the AbioCor Implantable Replacement Heart shows that sometimes the best preparation and informed consent process still cannot prevent litigation.

It also shows that research subjects and their families sometimes fail to understand issues that clinical trial administrators and others think have been clearly communicated.

Irene Quinn, wife of James Quinn, who died about 10 months after receiving an AbioCor heart in November 2001, sued Abiomed, as well as Tenet Healthcare Corp. of Santa Barbara, CA; Drexel University and Hahnemann University Hospital, both of Philadelphia; and David Cassarett, MD.

Cassarett was employed for patient advocacy services during the clinical trial, says **Haavi Morreim**, PhD, professor in the College of Medicine at the University of Tennessee-Memphis, and chair of the Independent Patient Advocacy Council (IPAC).

IPAC was created by Abiomed to provide patient advocacy services and advise the corporation on the ethical aspects of the trials. IPAC is funded through an irrevocable trust and is self-governing and independent of Abiomed.

The lawsuit, filed by plaintiff's attorney Alan C. Milstein of Pennsauken, NJ, made a number of claims that highlight how differently a research subject and researchers may look at the same clinical trial and informed consent process.

For example, the lawsuit claimed the following: "The defendants, through their agents, represented to the Quinns that they would work to set up a trust fund for Mrs. Quinn, which would be available to her following the experiment."

This is the type of issue that demonstrates how poorly a subject and a subject's family might understand the clinical trial process.

Abiomed's 13-page informed consent for the AbioCor clinical trials makes no mention of any such trust fund. However, the subject and his wife may have heard about another AbioCor clinical trial subject who did benefit from a trust fund established by a bank and local community in order to help the couple defray traveling costs

during the man's surgery and recuperation.

"I can't say what was in the mind of the plaintiff, but obviously Mr. Milstein did not understand," Morreim says. "He was alleging [Quinn] would receive a trust fund at the end of the trial, and no IRB [institutional review board] is going to approve a surrogate decision maker coming into substantial sums of money after the patient is no longer alive."

The lawsuit was settled out of court, first by all defendants except Abiomed and Cassarett, and then by Abiomed after the corporation's insurance company ordered the attorneys to settle. Cassarett paid no part of the settlement, which totaled $125,000, and resulted in all claims being dismissed with prejudice, he says.

One of the major problems with any type of litigation against clinical trials sponsors, investigators, and health care organizations is that the plaintiff's attorney controls the public's information about the case, Morreim says.

"That makes it difficult for defendants, who are subject to confidentiality requirements," he says. "Even when the plaintiff has waived patient confidentiality by filing a lawsuit, medical ethics expects us to honor privacy and confidentiality."

Therefore, Abiomed and other companies in similar situations may have evidence to rebut the charges, but these never come out unless the case goes to trial.

"This case was settled because the insurer demanded it, and so the evidence that the defendants had to vindicate their name and reputations will never be public," Morreim says.

Communicate more clearly

This underscores the importance of improving the communication and informed consent process with subjects and taking steps that may reduce the risk of exposure to litigation. Here are a few of the steps clinical trial administrators can take to make certain subjects are fully informed about their potential risks, benefits, and other issues:

• **Give patients time to absorb information.** "In terms of conversations, it would seem that periodic pausing helps," Morreim says. "Pause periodically and ask the enrollee, 'Tell me what you are thinking; what have you heard?'"

Listen for gaps between what the patient advocate or clinical trial administrator has described and what the enrollee has heard, he advises.

"It can be a good idea to jot down questions to remember them, and it's especially important to do so because we bring questions to the principal investigators or to whoever is the suitable person to answer them," Morreim says.

If the person discussing the trial with the subject sees that the subject is tired or under stress, then take a break and come back to the conversation later, he says.

"Allow the person to rest between conversations," Morreim says. "There's no rule that the informed consent has to be done in one sit-down session."

For the AbioCor heart trials, there are numerous conversations held at each site for all prospective enrollees, so it's never done in one face-to-face conversation, he notes.

• **Emphasize what isn't known about the treatment/device/medication.** "Emphasizing uncertainties can be important," Morreim says.

For instance, in the trial of a new drug or device, there are various outcomes that could happen and not all of them are expected, he notes.

One way to broach uncertainty with an enrollee is to say, "Unexpected things can happen sometimes; sometimes they are minor; sometimes they are serious, and sometimes they are very serious," Morreim suggests.

• **Talk about the enrollee's values and goals regarding participation.** "We feel it's very important to talk about a patient's values and goals for participating in the research," he says. "Because [AbioCor] is a device that involves potentially prolonging or not prolonging life, they need to think about their goals for end-of-life care and what sort of quality of life is OK, and what is not very good quality."

It's important to let enrollees know that they may want to think about or talk about these issues, but the topic shouldn't be forced, Morreim says.

"We invite people to talk with each other and to talk with the clinical team and, if they wish, with the patient advocate," he explains.

The idea is to encourage participants to discuss this to the extent that they're willing to do so.

"Then if things do go badly, at some later point when the family members or whoever has to make a decision, the principal investigator and others can have a clear basis for knowing what the patient would want them to do," Morreim says. "This is important for high-profile, end-of-life research like AbioCor."

One strategy for approaching this type of discussion is to say to the patient and family, "Now I'm going to ask a question; and if you're uncomfortable and if you'd rather not discuss it at this time, then that's OK," he says.

"You also can say, 'Some people feel that life is precious and worth extending no matter what the quality of life; other people think that if life doesn't have at least a certain minimum quality, like being able to communicate, then it may not be worth going forward with aggressive interventions,'" Morreim says. "Whatever that person's view is, it's OK."

The idea simply is to elicit their thoughts on these issues and to help them think about their own values, he adds.

• **Discuss the role of informed consent.** Patient advocates and clinical trial administrators who discuss the informed consent process with participants need to make sure it's clear that they are not there to recommend what the participant should do, Morreim says.

"We do emphasize, 'I'm not here to tell you what to do; instead I'm here as a sounding board to help you think through and reflect on your own values and reflect on what's important to you as you decide whether or not to enter this trial,'" he explains.

"It's important to reinforce the information that the principal investigator provides and help them think of questions they might not otherwise have thought of," Morreim says. "Discuss what happened previously in the trial in general terms, protecting the privacy of other patients."

Although clinical trials administrators and investigators are not required to update the informed consent as major developments arise, this probably is a good strategy, anyway, Morreim says.

"In most trials you can't do this because the trial is blinded," he notes. "But we think it's a good idea to keep patients and their families reasonably well updated within the constraints of privacy of other patients." ■

Do you have a plan for research-related injuries?

Most don't have a subject compensation plan

No investigator or coordinator wants to believe it could happen. But in clinical trials, injuries or adverse events are always a possibility.

The question for many is, What will happen to study subjects who are injured in the course of their research participation? Beyond any emergency medical care, will they be compensated for the cost of any needed medical follow-up? What about lost time at work or a lingering disability?

Although many researchers believe that ethically research subjects should not have to absorb the costs of research-related injures, there often is little help available for subjects injured during a trial.

"Federal regulations do not require institutions or sponsors to have policies in place to compensate subjects for research-related injuries," says **Larry D. Scott**, MD, assistant vice president of the human subjects program at the University of Texas Health Science Center (UTHSC) at Houston. "The regulations only require that they disclose to subjects whether or not any such compensation is available."

Consequently, most institutions do not have an established policy for compensating injured subjects, he says.

At UTHSC, the institutional review board often requires device manufacturers and pharmaceutical companies who sponsor trials there to agree to pay for the cost of the medical care needed by any subject injured during the course of the study.

But for all other studies, the informed consent documents usually indicate that although the costs of immediate emergency medical care will be covered, there is no provision for compensation for other costs due to research-related injury beyond what is paid for by the participant's own health plan, he says, noting that some payers will not cover costs related to an injury sustained as part of a research study.

"There are valid arguments for and against asking health plans to compensate injured subjects," Scott notes. Although some feel it should not be the responsibility of an individual's insurer to cover costs related to research, others argue that health plans have a responsibility to further progress in medical science and technology, and this means supporting research participation by not excluding claims for injuries related to the participation of their members.

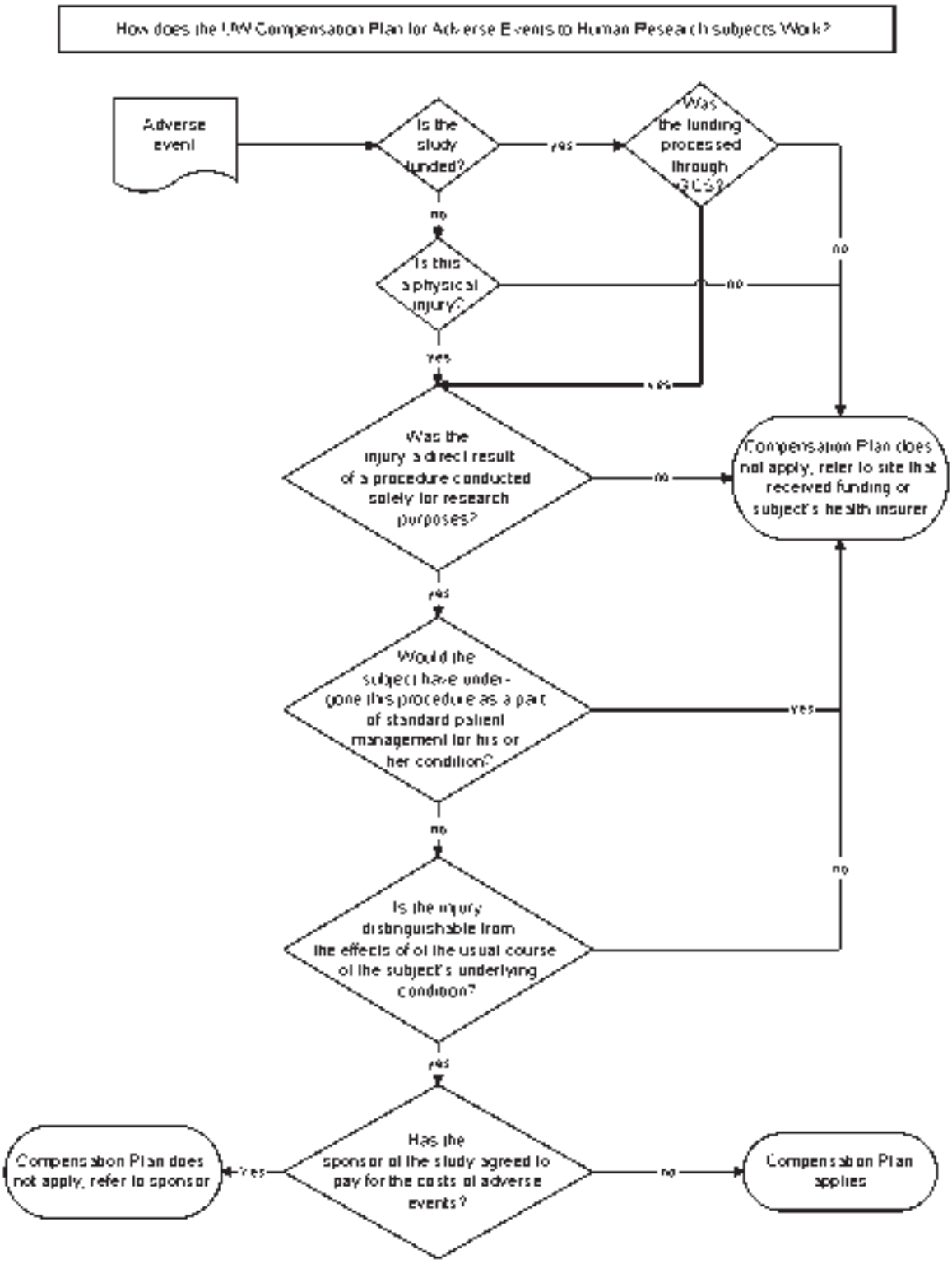
Medicare, in fact, does cover costs associated with research-related injuries for its beneficiaries as long as the research study involved some potential for benefit to the participant, Scott adds.

Because research-related injuries are very rare, most institutions are not giving this issue a high priority, Scott notes.

But with the media coverage given to the deaths of research subjects Jesse Gelsinger at the University of Pennsylvania and Ellen Roche at Johns Hopkins

(Continued on page 11)

Compensation Plan Flowchart



Source: University of Washington, Human Subjects Division, Seattle.

University, the public is beginning to get the impression that participation in medical research is a very dangerous and risky proposition.

This may seriously affect research participation in the future, Scott reports.

"I definitely think this is a question that IRBs [institutional review boards] need to be asking more often and investigators need to be asking more often," he says. "If someone is injured during the course of this trial, what compensation is available to that person?"

There are actually a number of options that go unexplored at many institutions, Scott notes.

First, as at UTHSC, the IRBs or investigators can negotiate a compensation plan with industry sponsors.

Second, they can explore whether some third-party payers or the research institution itself would be willing to compensate subjects in the event of an injury.

As he noted before, Medicare does cover some research-related injuries incurred by its beneficiaries. And Veterans Affairs (VA) covers medical costs related to the injuries incurred by subjects at VA-sponsored trials at their medical centers.

Institutional plans

A few research centers have implemented their own policies about compensation for research-related injuries.

The University of Washington in Seattle, for example, has a self-insured plan to compensate subjects injured during the course of an IRB-approved research study as long as certain conditions are met **(see chart, p. 10)**:

- The injury is a physical injury — the plan does not cover impairment of mental processes or emotional distress.
- The injury is clearly not the result of procedures or processes the person would normally encounter as part of medical treatment for his or her condition.
- The injury is not the result of noncompliance with the research protocol.
- The study sponsor does not have a plan for compensating research-related injuries.

Since its implementation in 1972, the program has not had to bear extensive costs of research-related injuries and has been a cost-effective program for the institution, Scott notes.

Although they are hopeful that other institutions will follow their example, without a set nationwide standard and absent a regulatory requirement, it's not very likely, notes **Helen McGough**, director of the human subjects division of the University of Washington.

"I do not believe there is a standard in the [research] community regarding compensation for research-related injuries," she says. "It is common practice to expect that sponsors will pay the costs of treating research-related injuries in commercially sponsored research, but there is no guarantee since there is no regulatory requirement. And again, because there is no regulatory requirement, institutions themselves vary in their willingness to absorb the costs."

Few institutions go as far at the University of Washington, says Scott. He is aware of only one other center with a similar policy — Wake Forest University in Winston-Salem, NC.

Even then, the compensation plans only cover the direct medical costs associated with physical injuries.

There is often no provision for economic losses incurred due to loss of work or to long-term follow-up care, Scott notes.

In the future, as research trials of new medical technologies become more complex, yet offer much more potential for benefit to the society at large, the federal government should explore large-scale measures to support research participation, he explains. "Gene transfer studies are a good example. They carry significant risks for participants, but the knowledge that could be gained could have enormous potential for the public good."

In much the same way as Congress enacted the National Vaccine Injury Compensation Plan (NVICP) to protect vaccine manufacturers from lawsuits and ensure adequate production of vaccines to benefit the public health, the government could consider setting up a fund to compensate research subjects.

"Particularly for studies deemed to have significant potential for improving medical knowledge or discovering new treatments, this could be a solution," Scott says.

Industry sponsors should also shoulder some of the responsibility for supporting research, by establishing common standards relating to compensation for injuries, says McGough.

"One of my hopes is that pharmaceutical companies, device manufacturers and biotech companies will develop industry standards and unequivocally accept their responsibility to pay for the costs of treating research-related injuries," she says. "Our institution spends many, many hours negotiating with individual sponsors — hours that could better

be spent on other protection issues if there were industry standards."

A second option, McGough notes, is to ask federal sponsors of research to look into the costs of providing coverage as part of the grant and contracting process, she adds. "The first steps have already been taken through the Veterans Administration and Medicare. A third avenue is to ask the private health insurance companies, perhaps through an industry association, to develop clear guidelines for covering the costs of research-related injuries in clinical trials." ■

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. ■

CE/CME *questions*

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. ■

1. Which state has not passed legislation permitting research involving embryonic stem cells?
A. California
B Utah
C. New Jersey
D. None of the above

2. Investigators working in genetic or pharmacogenetics research often fear that they will have difficulty recruiting subjects because of the potential risks from disclosure of genetic information. As a result, some researchers have made this mistake with their protocols because:
A. They make the research anonymous and limit its power.
B. They assure subjects that there is no possible way that the genetic information could be disclosed to anyone other than the subject.
C. They fail to give subjects proper informed consent.
D. All of the above

3. Which of the following is a step that clinical trial administrators can take to improve communication with subjects and, possibly, reduce the risks of litigation?
A. Give patients time to absorb information during informed consent.
B. Emphasize what isn't known about the treatment, device, or medication.
C. Talk about the enrollees' values and goals regarding participation.
D. All of the above

4. Federal regulations require institutions to take what action regarding injuries to research subjects?
A. Have a limited compensation plan in place.
B. Negotiate compensation with industry sponsors when possible.
C. Clearly disclose what if any compensation for injuries sustained during research participation is available.
D. None of the above

Answers: 1-B; 2-A; 3-D; 4-C.