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## INSIDE



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# Smallpox plan puts hospitals between tough choices for its staff and public

*Risks must be balanced with public health concerns*

At the University of Connecticut Health Center in Farmington, infectious diseases physician **John D. Shanley**, MD, faced a difficult decision last month. Would he be one of his hospital's smallpox response team volunteers and receive the vaccine?

As a child, Shanley received the inoculation and experienced no ill effects. He has studied vaccinia, the virus used in smallpox vaccine, and observed cases of vaccine complications. These place him among those favored by public health officials to be on the front lines of preparations to respond to a bioterrorist attack.

But a member of his household has eczema, and Shanley routinely treats AIDS patients in a hospital clinic. These people would be placed at risk for transmission of the vaccinia virus and at high risk of experiencing potentially fatal complications if he chooses to participate.

"I am in kind of a funny spot. If you read the CDC [Centers for Disease Control and Prevention] guidelines, I shouldn't get it, unless I move out of my house [for about two weeks, during which the virus is contagious], which is probably what I am going to do," he tells *Medical Ethics Advisor*. "I also work with vaccinia in research and have elected not to take the vaccine. Using proper laboratory technique, I have a very small chance of getting it [vaccinia]. If I take the vaccine, I have a 100% chance of getting it. But as long as this whole thing is going on right now, I have another reason to do it, so I'll probably go ahead and get it."

Hospitals and health care workers across the country face similar dilemmas as they consider the federal government's proposal for protecting the public from an attack with weaponized smallpox virus.

According to the plan, announced Dec. 13, an estimated 450,000 public health personnel, police officers, firefighters, and emergency health care workers will receive pre-event vaccination. These vaccinations, unlike those mandated for members of the military, will be voluntary. The civilian volunteers would be protected from the virus and

able to care for victims of a smallpox outbreak — if one should occur — while the rest of the population receives the vaccine.

Following the announcement, state health departments began contacting hospitals and asking them to form response teams at each facility. Shanley's facility is slated to be the first in Connecticut to form a team. After the volunteers are vaccinated, they will fan out to hospitals across the state to educate their health care workers and administer the vaccine.

"The plan is that we will identify critical people who will volunteer for this and who would be essential for the hospital to run in the event there was an index case," he explains. "That is the basic plan and it would include emergency room physicians, nurses, infectious disease doctors, radiologists, respiratory therapists, and people who take care of the physical plant, etc."

## 'Not just a personal decision'

Recruiting volunteers won't be the hard part, Shanley speculates. But hospitals are already struggling to ensure they will be able to maintain adequate staffing, ensure that no patients or other health care workers are jeopardized, and that the volunteer vaccines have adequate protections.

"With this vaccine, it is not just a question of personal choice — of a person being informed of the risks and benefits and making a decision," explains **Gregory J. Moran**, MD, associate professor of medicine in the department of emergency medicine and division of infectious diseases at Olive View-UCLA Medical Center in Sylmar, CA. "The person getting the vaccine is potentially putting other people at risk as well. It is a live vaccine, and it is possible to spread the virus to other contacts. It is not just a personal decision or personal liberty issue."

## Vaccine has high adverse-event rate

The smallpox vaccine is a live-virus vaccine, which contains the vaccinia virus. People inoculated with vaccinia develop immunity to infection with variola, the virus that causes smallpox.

However, vaccinated people can experience complications. Some people develop a condition known as progressive vaccinia, in which the virus spreads from the inoculation site and causes a serious infection. A small number of people can develop encephalitis and die from receiving the vaccine.

And vaccinated people can transmit vaccinia from their inoculation site to other people until the site has been covered by a scab, which occurs approximately two weeks after administration.

People with compromised immune systems, or who have certain skin conditions are at high risk for contracting vaccinia and experiencing severe complications. **(See list, p. 16.)**

According to the Centers for Disease Control and Prevention (CDC), for every 1 million vaccinations,

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there will be one to two deaths; 14-15 life-threatening reactions (which may include gangrene, encephalitis, and severe skin infection), and 50-900 other minor side effects, such as rashes, fevers, and viral eruptions from the inoculation site.

"The vaccine is not really an acceptable vaccine by 21st century standards, except in the event that there really is an exposure," Shanley says. "Whenever you talk about vaccines, it is a balance between perceived and actual risk of the disease vs. the adverse effects of the vaccine. And with the adverse effects of this vaccine, there better be pretty good reason to give it."

## Some hospitals opt out

After studying the federal plan, a few hospitals decided that the risk of potential harm to healthy health care workers and the potential for transmission of vaccinia to vulnerable patients was too great balanced with the uncertainty of a smallpox attack.

Grady Memorial Hospital in Atlanta and Virginia Commonwealth University in Richmond will not participate in the federal program and ask their health care workers to be vaccinated.

"Grady has balanced the known dangers of the smallpox vaccine, which can, in some instances, cause serious side effects, against the unlikely risk of exposure to the smallpox virus," says **Curtis Lewis**, MD, the Grady Health System's chief of staff and senior vice president. "As a result, Grady will not vaccinate its health care workers for smallpox at this time, but would move rapidly to vaccinate health care workers if a case of smallpox is reported or a clearly imminent danger of smallpox transmission is shown to exist."

In coming to the decision, Lewis says hospital officials relied on opinions from its infectious diseases experts and other authorities, including a former member of the CDC's smallpox eradication program.

In addition, the state health department indicated that it had no solid information that Georgia was at risk for a smallpox attack, he adds. Based on the available information, they determined that not participating was their best option, he says.

The hospitals' position is an understandable one, notes Shanley. Given that the actual risk of a smallpox attack seems very remote and the risks of complications from the vaccine are significant, some hospitals may feel that they have a higher obligation to protect the patients already there.

Health care workers at his medical center have also expressed concern about the risk of transmitting vaccinia to vulnerable contacts, he says.

"Even though the ACIP [Advisory Committee on Immunization Practices] guidelines say that you don't have to furlough workers as long as they keep the site covered and clean, there is still a risk of transmission," he notes. "The risk is small, but it is not zero."

His hospital will probably reassign vaccinated volunteers to low-risk work and he will probably stop seeing AIDS patients in the clinic until his inoculation site is healed, Shanley says. "Ethically, I just cannot take the chance of acting as a vector for them."

## Ensuring voluntary participation

If hospitals decide to participate in the federal program, some protections for the volunteer health care workers need to be in place first, adds Moran.

"The CDC has made it pretty clear that this is going to be voluntary, so I don't think that anyone is going to be forced into it," he notes. "But I think there probably are some implementation issues that the hospitals need to address. They need to do their implementation in such a way that people don't feel coerced into doing it."

At Olive View-UCLA, the facility will determine categories of health care workers and others who should be vaccinated, he explains.

"We will select a certain number of people needed from emergency medicine, from infection control and infectious disease, also ward nurses and others that might have to take care of that first group of people on the ward," he says. "We will come up with just some general allocations of numbers and then leave it up to individual departments and groups to decide within themselves who is interested in and volunteers to be vaccinated."

It is unlikely that there will be too few volunteers to step forward, he says.

"Based on just a kind of informal polling locally, I think the majority of people are willing to take it, and there are a sizeable minority of people who aren't," he says. "I think we can work around it."

## Liability protections for vaccinated workers

Another big area of concern is whether vaccinated health care workers can be held legally liable for inadvertently transmitting vaccinia to

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patients, says Moran.

Section 304 of the Homeland Security Act specifically covers the vaccine manufacturers and personnel who administer the vaccine — stipulating that the federal government will be the sole entity offering compensation for adverse events. But it is not clear that this section will cover the vaccinated health care workers.

"For example, say I am an emergency physician and am vaccinated and, while I have this lesion on my arm, even though I have it properly covered and keep it clean, a patient with HIV comes in and somehow is infected and has a complication," Moran says. "They may potentially sue me because I should have known better than to take care of an immunocompromised patient if I had the smallpox vaccine — even though ACIP does not recommend any restrictions on patient care, there is always the potential for that to happen."

It isn't fair to ask the health care workers themselves to bear the burden of liability, he says. "Since we are asking health care workers to get vaccinated, not so much for the benefit of them as for the benefit of society, I think it is fair that we ask society to bear the burden of liability."

In addition, the issue of workers' compensation for complications suffered by vaccinated health care workers has not been addressed and should be, before inoculations begin, Moran says.

### *Dealing with those not 'chosen'*

In addition to ensuring protections for the volunteers, hospitals also should have a plan for addressing the concerns of the health care workers who are not selected to serve on the designated response teams.

It its proposed implementation plan, the CDC has indicated that state and local health departments would administer the vaccine to the initial health care volunteers at special clinics set up for the purpose. Only specific volunteers designated by the hospital will get the vaccine.

Health care workers or other personnel in departments not included as part of the emergency

## List: These personnel shouldn't get vaccine

Some people are at greater risk for serious side effects from the smallpox vaccine. Individuals who have any of the following conditions, or live with someone who does, should **NOT** get the smallpox vaccine unless they have been exposed to the smallpox virus:

- **Eczema or atopic dermatitis.** (This is true even if the condition is not currently active, mild, or experienced as a child.)
- **Skin conditions such as burns, chickenpox, shingles, impetigo, herpes, severe acne, or psoriasis.** (People with any of these conditions should not get the vaccine until they have completely healed.)
- **Weakened immune system.** (Cancer treatment, an organ transplant, HIV, or medications to treat autoimmune disorders and other illnesses can weaken the immune system.)
- **Pregnancy or plans to become pregnant within one month of vaccination.**

In addition, individuals should **not** get the smallpox vaccine if they:

- are allergic to the vaccine or any of its ingredients;
- are younger than 12 months of age. However, the Advisory Committee on Immunization Practices advises against nonemergency use of smallpox vaccine in children younger than 18 years of age.
- have a moderate or severe short-term illness (these people should wait until they are completely recovered to get the vaccine);
- are currently breast-feeding.

***Again, people who have been directly exposed to the smallpox virus should get the vaccine, regardless of their health status.***

If offered the smallpox vaccine, individuals should tell their immunization provider if they have any of the above conditions, or even if they suspect they might.

For more information, visit www.cdc.gov/smallpox, or call the CDC public response hotline at (888) 246-2675 (English), (888) 246-2857 (Español), or (866) 874-2646 (TTY).

*Source:* Centers for Disease Control and Prevention, Atlanta.

## Here are estimates for hospital care teams

For management of a single presumptive smallpox patient, assume:

- **ICU:** eight adult ICU nurses, eight pediatric ICU nurses, four adult intensivists or pulmonologists or fellows, four pediatric intensivists or pulmonologists or fellows.
- **ED:** 15 doctors and nurses.
- One infectious disease (ID) consult, one dermatology consult.
- Four respiratory therapists, four radiology techs, two engineers.
- **Total:** 41 workers — assuming 12-hour shifts, initially allowing for backup and vacation absence. Since there are efficiencies in managing more than one patient, 100 staff should allow for care of three or four patients with a presumptive diagnosis of smallpox.
- **Nationwide hospital teams:** approximately 400,000 to 510,000 health care workers.

**Possible Composition of Hospital Care Teams**:

- **ED staff:** MDs, RNs
- **ICU:** selected MDs, RNs
- **General medical unit*:** selected RNs, MDs: hospitalists, internists, pediatricians, obstetricians, family practice, when essential providers of primary medical care
- **House staff:** selected medical, pediatric, OB and family practice, when essential
- **Subspecialists**: regional team of local consultants with smallpox experience, dermatologists, ophthalmologists, etc.
- **Infection control staff**
- **Respiratory therapists**
- **Radiology technicians**
- **Security personnel**
- **Housekeeping personnel**

* Defined by negative-pressure rooms, appropriate for smallpox wing.

*Source:* Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices, Atlanta.

team categories may feel that they are being denied the protection the vaccine offers, Moran says.

"We are just going to have to recognize that there are a limited number of doses available in the first round, and it is likely that there will be more vaccine offered at a later stage to those who want to be vaccinated," he says. "People will just have to understand that the experts designated in their facility are just going to have to make some decisions about what the priorities are."

Hospitals also should consider that many of the drugs related to smallpox preparation and treatment are investigational new drugs (INDs) and are yet to be approved by the Food and Drug Administration (FDA), says Shanley.

The existing smallpox vaccine supply consists of the Dryvax vaccine, which is FDA-approved, he explains. That vaccine is grown from calf lymph. However, the newer versions of smallpox vaccine will be grown using new tissue-culturing technology.

Vaccine manufactured in this manner has yet to be approved.

And the vaccinia immunoglobulin product — the medication given if a person experiences a severe reaction to the vaccine — also is not yet FDA-approved.

"That changes how you do your vaccines," Shanley warns. "This might fall under the human use committee at our university. If it is a voluntary program and a pre-event situation, then we must give the participant informed consent, do all the paperwork, and the tracking is completely different."

The question for most institutions, he asks, is: Which institutional review board would have jurisdiction?

"That pretty much hit us out of the clear blue and we don't have an answer yet," he says. "But before we do anything that has to be clearly defined — who will review this and is this considered under the purview of the IRB?"

Right now, most facilities are asking the same questions and trying to have answers in place by the time the government begins releasing the vaccine to health departments, he adds. "We are all still scurrying around trying to figure out how to do this." ■

# Bioterrorism brings wave of dilemmas for hospitals

*Informed decisions face an unknown threat*

The recent massive preparations for a potential bioterrorist smallpox attack may radically change the way the nation's health system is expected to respond to public health threats, at the same time ushering in a new wave of

dilemmas for hospital ethics committees and administrators, say some policy experts.

Though the actual risk of a smallpox release is unknown, last month, hospitals from Boston to Butte were soliciting volunteer health care to serve as the nation's massive first line of defense.

"It is definitely uncharted territory," notes **Robert I. Field**, JD, PhD, director of the graduate program in health policy at the University of the Sciences in Philadelphia. "There are questions about how likely a smallpox attack could be. It's not the easiest weapon for a bioterrorist to use. Even if the people preparing it were themselves immunized, it could spread to those around them. It is less likely than some other threats. On the other hand, it seems more likely given the experience with the anthrax letters."

In the past, health care decision makers were often better able to balance the known risks of a health threat with the impact on the functioning of the health system. When it comes to bioterrorism in general, and smallpox in particular, no one knows the true likelihood of such an event. No one city or region seems more vulnerable than another.

Such factors significantly affect people's ability to make truly informed choices, says **Stephen Pauker**, MD, MACP, associate physician-in-chief and vice chair of clinical affairs at Tufts-New England Medical Center in Boston.

"Ordinarily, people would make decisions [about being vaccinated] based on how they, as individuals, view themselves as likely to be exposed, or the likelihood of a smallpox epidemic, whether they will walk around being anxious about the possibility and would feel better if they were vaccinated," he explains. "Then, they would look at the risks of being vaccinated and whether the risk of developing a side effect is worth not having the anxiety of knowing you are walking around vulnerable to smallpox."

The problem, he notes, is that no one really has reliable information about either of those scenarios, he says. Given the history of the smallpox vaccine, the risk of complications would seem small.

But the vaccine has not been widely administered in many years and the incidence of skin conditions and other disorders that would make receiving the inoculation more risky has gone up. And no one can really predict how likely a smallpox attack is, he notes.

The lack of hard information about level of risks means most people will make their decisions about receiving the vaccine based on emotional factors, not scientific ones, he predicts.

The same holds true at the institutional level, he adds. Health care facilities have little reliable information about their potential for seeing smallpox cases compared to those in other areas. So they must balance their perception of the risk with how they feel the vaccine program will affect their ability to care for the patients they know they will have.

"We have to balance the ethics of the individual vs. the ethics of society," he says. "The epidemic will only spread if there are enough unvaccinated people. So, by my taking the risk of being vaccinated, I am making a contribution to society."

But what about the impact of inoculating a percentage of a hospital's staff with a live-virus vaccine that poses risks to existing patients? Many hospitals are planning to reassign vaccinated health care workers for a certain period of time, and have contingency plans in case adverse reactions necessitate lost time from work. Given the strained staffing ratios and financial situations at many institutions, this is no small matter.

Some hospitals have chosen to not offer the vaccine to health care workers at this time.

"I think that is certainly a supported position," says Field. "Each hospital has to figure that out. It is a difficult question. You are weighing two different kinds of risks: one is a medical risk and one is more of a political risk. How do you compare one against the other?"

On top of the hospital situation, he notes, the massive vaccination campaigns are drawing public health resources away from combating naturally occurring diseases.

Local health departments already are predicting they will have to curtail existing programs unless they receive additional dollars to conduct the smallpox vaccine campaign.

According to a report in *The New York Times*, Jan. 4, health officials across the country indicate they

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have already spent most of the $940 million that Congress allocated last year for the Department and Health and Human Services bioterrorism preparedness programs, spending the money on programs to combat anthrax threats.

Programs such as cancer and tuberculosis screening and dental examinations for children will have to be cut back to pay for the smallpox vaccination programs.

"That is a bigger issue with biopreparedness. Are we compromising existing health needs?" he asks. "The fact is, we still face much, much larger threats from TB, AIDS, and the flu. It raises some questions about how we will place our bets." ■

# Experts say Clonaid isn't likely to have cloned baby

*Media attention may spur action to limit science*

Scientists knowledgeable about the process of cloning animals say they doubt the Canadian-based group Clonaid actually has produced a cloned human baby, as the sect announced Dec. 27. But, some experts say, the publicity generated by the claim may push lawmakers to restrict scientific research into both reproductive and therapeutic cloning.

"From what we can see now, it looks like a hoax," says **Gerard Magill**, PhD, director of the Center for Health Care Ethics at St. Louis University. "They are not a scientifically reputable body and have yet to come forward with any data. Given the difficulty of the technology, it is extraordinarily unlikely they could accomplish such a goal."

But their claim does raise the specter of the birth of a human clone as realistic possibility, he adds.

"It does raise the issue of human cloning as something that is on the scientific landscape," Magill says. "If not them, then someone could. We know there are scientists with the expertise — fertility experts who are working on this."

The immediate fallout may likely be a ban on reproductive cloning in the United States, he predicts.

"I think there is the same unanimity of opposition to reproductive cloning in the nation today as there was 20 years ago," he says. "It wasn't a policy issue then because it was hardly possible. But not until 1997 did it become possible. Now, with it being on the landscape and there being such hype in the media about the claim, that is the kind of thing that spurs lawmakers."

### *Scientists condemn alleged attempts*

While many cloning experts expressed doubts about the validity of the claim, others renewed their objections to any attempts to clone humans while efforts to produce cloned animals still prove very unstable.

"All of the reports from cloning experiments describe a high incidence of late abortion or the birth of dead animals," said **Randall Prather**, MD, PhD, distinguished professor of reproductive biotechnology at the University of Missouri-Columbia, on Jan. 6. "When live cloned offspring have been produced, many have been subject to abnormalities that were apparent only after birth. These abnormalities include premature death at different ages, respiratory failure, absence of an immune response, and inadequate kidney function."

Such problems are believed to be the a consequence of inappropriate gene expression resulting from incomplete "reprogramming" of the adult cell used in cloning, he continued. "There is absolutely no reason to expect the situation to be different in humans."

Prather's statement was jointly signed by two other cloning experts, Gerald Schatten, MD, professor and vice chair of obstetrics, gynecology and reproductive sciences, and cell biology-physiology at the University of Pittsburgh School of Medicine; and Ian Wilmut, MD, an embryologist at the Roslin Institute in Edinburgh, Scotland. Wilmut was part of the team of scientists who cloned the sheep, Dolly, the world's first cloned animal.

"Furthermore, human brain development is far more complex than in animals," Prather continued. "The neuropsychiatric consequences for cloned children might be devastating. Until there is compelling and scientifically validated evidence that the situation is different in human embryos, it is grossly irresponsible to attempt to clone children."

All three scientists called on lawmakers in different countries to enact "responsible" human reproductive cloning legislation.

### *What constitutes responsible restriction?*

However, the secretive Clonaid announcement is only continuing to cloud the public

debate on the ethical challenges raised by reproductive and therapeutic cloning, says **Celia Fisher,** PhD, director of the Center for Ethics Education at Fordham University in Bronx, NY, and bioethicist-in-residence at Yale University in New Haven, CT.

"Major ethical considerations for reproductive cloning involve: a) the immediate and potentially long-term health risks for the child since there procedure has not been perfected in animals; b) the risks to human species, in that widespread cloning would reduce the genetic variability of humans that allow us to have populations that include members with diverse genetic makeup — some of whom will be capable of adapting or surviving new environmental, health, or social events that may arise; and c) since our society has already endorsed other artificial methods of reproduction, there is no essential need in society for cloning as a form of reproduction, per se," Fisher says.

But the ethical issues for therapeutic cloning are different, she explains.

In therapeutic cloning a fertilized egg is not implanted in a womb, but whether the embryo itself is a human life still is an issue for ethical debate.

The reason for therapeutic cloning is not to produce a new living being, but to produce genetic material to be used to help the survival of others.

"The judgment of whether the fertilized embryo is a human life will further effect the ethicality of therapeutic cloning: if the embryo is a life, then one is using that life simply as a means to further another's ends," she says. "If it is not a life, then we are using genetic material to save the life of others."

The attention given to the Clonaid claim continues to blur the distinction between the separate issues.

"I think the burden of proof is on Clonaid to provide opportunity for independent and objective tests of whether they have produced a cloned child," Fisher states. "Otherwise, their claims should be considered bogus."

### Science has interest in validating claim

The scientific community will not want to waste energy and attention on a hoax, if that is what the Clonaid announcement proves to be, but is interested in ensuring that any tests of the claim proceed in an objective and valid way, predicts Magill.

**SOURCES**

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- **Gerard Magill**, PhD, Center for Health Care Ethics, St. Louis University, 3545 Lafayette Ave., St. Louis, MO 63108-1099.

"The scientific community is very anxious to offer its services to do the necessary DNA testing in a reliable way," he says. "That would involve a complicated series of tests on the DNA, it might involve mitochondrial DNA, and testing would have to be performed at different labs to ensure there was no overlap. The DNA of the parents and baby would have to be kept completely separate. In other words, I think the scientific community is ready to put all of its muscle into doing very objective scientific analysis."

However, there first has to be some evidence that baby Eve exists, and that her parents are willing to undergo the necessary testing.

"I think the scientific community is going to pay a lot of attention to this because they realize that there is more than a potential hoax here," Magill says. "There are multiple groups trying to do this, and they all want to know if it is possible. However, at the same time, they will want to be extraordinarily careful not to have their name complicit with a hoax." ■

# Duke: Industry-sponsored studies may be trouble

*Few agreements met standards*

Academic medical centers frequently engage in industry-sponsored research that does not adhere to basic standards needed to protect the independence and objectivity of the investigators and the interests of patients who consent to be subjects, a study by researchers at Duke University in Durham, NC, has found.

A survey of research agreements entered into by academic medical centers and sponsors between November 2001 and January 2002 indicated that few agreements meet the standards established by

the International Committee of Medical Journal Editors (ICMJE).

The Duke researchers surveyed 108 member institutions of the Association of American Medical Colleges (AAMC) to determine the extent with which their contracts with clinical trial sponsors met the three main provisions of the ICMJE guidelines:

- whether authors of reports of multicenter trials had access to all trial data;
- whether the authors or an independent committee controlled editorial and publication;
- whether investigators were fully involved in the design and conduct of the trials.

The researchers found that the agreements rarely included such provisions. Only 1% required that authors of multicenter studies have independent access to all data from the trial, though institutions at coordinating centers for multicenter trials stipulated this level of access at a higher rate (50% of contracts).

The industry sponsors also typically control decisions regarding the publication of data from clinical studies. Provisions addressing the editorial content of the multicenter manuscripts appeared in 40% of contracts, while independent committees that would guarantee publication were specified in less than 1%. The agreements also did not ensure dissemination of findings from research on stored biological materials collected during clinical trials — these materials are collected by the industry sponsors for use in future research.

"These contracts are important because the truth of the matter is research is governed by the contracts between the sponsors and institutions, not by the study protocols approved by the IRB [institutional review board]," says **Kevin Schulman**, MD, lead author of the study and professor of medicine at Duke University Medical Center.

The research agreements are the only documents that legally bind the industry sponsor in terms of their conduct related to the research, Schulman explains. "Items like trial governance and publication of results are contained in the study protocol, but rarely in the research agreement, and the sponsor is not legally bound to follow the study protocol. Separately, the research agreement is named as the superseding document in the event of a disagreement between researchers and sponsors in most cases."

For example, a pharmaceutical company many initiate a multicenter trial of a new drug and sign research agreements with a number of different sites. These individual sites recruit participants into the trial and submit data to a central source. Study protocols are approved by each site's IRB, says Schulman. But those protocols do not guarantee that data from all sites will be published, researchers writing up the study results for publication will have access to all data or that the sponsoring company will not simply just decide to pull funding if the initial results of the trial do not prove favorable.

"The agreements generally allow access to site-level data, but that is scientifically invalid in a multicenter trial," Schulman explains. "If I have 50 patients at Duke in a 10,000-person trial, what does it mean if I try to analyze the data on those 50 people? It doesn't mean anything."

## Guaranteed publication necessary

The most troubling aspect of the survey's findings was the lack of assurance that all study results would be reported, Schulman says.

A basic tenet of clinical research is humans participate to yield information that will help advance medical science and benefit society. A key facet is that results of the research will be made public — good or bad.

"If you cannot guarantee that results of a research trial will be published, then how can you ethically tell a person that what they are participating in is research?" Schulman asks. "If a company comes in and sponsors a study, the IRB signs off on the protocol, you recruit patients at that site and tell them they are participating in a research trial, but later the study doesn't go the way the company hoped it to, and the results are never published? What are you recruiting people to at the site level?"

Conducting experiments involving humans, telling them it is a research study, with no guarantee the results will ever be shared with others is not research, he emphasizes.

"If clinicians told participants up front that they were being asked to participate in a marketing study for a private company and that they would be exposed to a potentially toxic medication for the purpose of the manufacturer finding out whether the medication was effective and they could make money at their discretion, we would probably get a lot less participation," Schulman notes.

Not only do many research agreements not guarantee the objectivity of the research, but some investigators have been severely pressured to discard or not reveal study results that were

not favorable to the sponsoring company, says **David G. Nathan,** MD, president emeritus of the Dana-Farber Cancer Institute in Boston.

In the same issue of the *New England Medical Journal* that features the Duke report, Nathan co-wrote a report on the case of Nancy Oliveri, a Canadian clinical researcher at the Hospital for Sick Children in Toronto.

Oliveri was the lead researcher on a study of the iron chelator, deferiprone. The study was sponsored by Apotex, a Canadian generic drug manufacturer.

As part of the research contract, Oliveri and colleagues signed a confidentiality agreement that was consistent with the policy of the hospital at the time.

However, Oliveri then became concerned about the drug's potential liver toxicity. She conducted a second study comparing hepatic iron levels in patients taking a similar drug and the test drug. Upon finding that certain patients did not do as well on deferiprone, she decided to submit the findings for publication and present the new data at a scientific meeting.

Apotex subsequently sued Oliveri for violation of the initial confidentiality agreement and the hospital administration referred her for research misconduct to the province's medical licensing board. The board later found no basis for the misconduct allegations, and she was not disciplined.

Though the case is an egregious example of what can happen, it does illustrate the importance of protecting the independence and integrity of clinical researchers, Nathan says.

"This is a huge problem for the American Association of Medical Colleges," he tells *Medical Ethics Advisor*. "The deans of the schools must get in agreement."

It is not only the academic medical centers that must pay attention, however, adds Schulman.

Many multicenter studies are conducted with sites that are not teaching hospitals. Frequently, patients may be recruited at smaller hospitals and even in individual physician's offices.

"There really needs to be one set of research ethics, regardless of where and how the participants were recruited," he says.

## Potential solutions

To ensure the integrity of industry-sponsored research, Schulman believes a standard research agreement should be used whenever a medical center or other site contracts with a company to participate in a research trial.

The contract would require publication of the study results, the establishment of an independent board to monitor the progress of the study and would require that the person or group writing the report have access to all site data.

"Everyone doesn't want or need access to all of the data," he explains. "But if it is a 200-site survey all of the investigators need to know that there is a process in place whereby someone they respect, with access to statisticians and someone who can deal with the numbers, is going to head up the effort to write the report. They need to know that the overall results are going to be published before they recruit their patients into a trial."

## Would committee resolve problem?

An independent coordinating committee also would protect the study from undue influence from the company's corporate objectives, he adds.

"In terms of trial governance issues, what if you've exposed all of these people to this medication — particularly in a Phase Four setting — and the sponsor realizes the results aren't going their way and wants to pull the plug. If you had an independent committee, at least you'd have one check on that," he says. "If you decide a trial isn't working because you can't recruit enough people, that is one thing. We make mistakes sometimes in study design and we can't get the subjects we need. But you would want someone who doesn't have that outside interest to represent the patients."

## COMING IN FUTURE MONTHS

- Research subject access to study results
- Prenatal screening for CF
- Assisted reproduction and second-generation infertility
- Maine Rx: Allowing states to use access to public programs as market leverage

## SOURCES

- **David G. Nathan**, Dana-Farber Cancer Institute, Office of the President, DFCI D1644, 44 Binney St., Boston, MA 02115.
- **Kevin Schulman**, Duke University Medical Center, Duke University Hospital, Erwin Road, Durham, NC 27710.

Nathan agrees with Schulman's proposals, but also feels that there should also be some standing authority in place to hear and resolve conflicts between industry sponsors and the institutions or researchers they contract with.

"We suggest in our article that a standing committee of the National Academy of Sciences-Institute of Medicine might be established to consider such conflicts and make recommendations to resolve them," he says.

For example, if a corporate sponsor and study author differ in their interpretation of results, an independent body should be available to resolve the dispute.

"It is most important to interpret the results independently," he says. "If the investigator and company do not agree on the interpretation, there must be away to adjudicate the problem."

It is also important that clinicians recruiting patients into industry-sponsored trials make themselves aware of the need for these protections and that they ensure the integrity of the project, says Schulman.

The center's institutional review board should also bear some responsibility, he adds.

"IRBs are signing off on this 'research' that is not research," he says. "There is still the question if you consent the person to participate in research, and that is not what in fact the project is, what have you done? Some courts have held that a consent agreement is a form of contract. If the contract says you are participating in research, when the institutions or investigators involved have no assurance that's the case, then you have a hard time fulfilling your end of the contract." ■



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5. Health care workers who are vaccinated against smallpox run the risk of transmitting ___ to vulnerable contacts during a brief period after vaccination?
A. Cowpox
B. Smallpox
C. Variola
D. Vaccinia

6. Section 305 of the Homeland Security Act:
A. Protects vaccine manufacturers and people administering the vaccine from liability in the event of an adverse reaction.
B. Protects vaccine manufacturers, persons administering the vaccine and the vaccinated health care workers from any liability concerns.
C. Provides compensation to public health workers administering the vaccine.
D. It provides compensation to health care workers who experience side effects from the vaccine.

7. Cloning experts believe the announcement that a woman has given birth to a cloned human is:
A. Likely a hoax.
B. Unable to be verified without more information.
C. A potential threat to the future of reproductive cloning research.
D. All of the above

8. IRB oversight of industry-sponsored research protocols:
A. Is currently sufficient to protect the academic freedoms of researchers.
B. Is not currently sufficient to protect the integrity of the trial.
C. Needs to be enhanced by implementation of standard research contract language.
D. None of the above

**Answers: 5-D; 6-A; 7-D; 8-C.**