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Trends in clinical research require updated policies on tissue banking

Experts offer guidance and examples

Researchers and clinical trials managers may have noticed that the best practices standards in tissue banking have been evolving in recent years due to scientific advances, greater public scrutiny on human subject protection, and new privacy rules under the Health Insurance Portability and Accountability Act (HIPAA).

For example, investigators in years past may not have asked subjects to provide informed consent for something unknown, such as a future use of a tissue that is not specified at the time their consent was sought. But now science has produced so many striking examples of how tissue samples stored for one purpose later produce valuable information for an entirely different purpose that it seems wise to anticipate unforeseen future uses of a subject's tissue and data, experts note.

"It used to be often held in IRB circles that if the subject didn't know what the research proposed was, he or she couldn't give informed consent," says **Elizabeth Hohmann**, MD, chair and director of the Partners Human Research Committees at Massachusetts General Hospital and Brigham and Women's Hospital in Boston.

"Over the past five to eight years, I believe we have moved away from that with the widespread creation of tissue banks and DNA collection," she reports.

The key is for researchers and clinical trials managers who desire to keep open future options for a particular database of information and tissue samples to find ways to help subjects understand what they are doing and why, Hohmann says.

"We need to help people understand who is overseeing this collection and that they are being used in scientifically and ethically appropriate ways," she adds.

At the same time, there's a greater scientific need for consent to cover future uses, the privacy regulations under HIPAA make this more difficult to accomplish.

There are research challenges, particularly with regard to large multicenter databases and the application of the common rule and

HIPAA regulations, notes **Marianna Bledsoe**, MA, program director for resources development at the National Cancer Institute in Rockville, MD.

"There's a wide range of interpretations by IRBs and institutions, and these are creating some considerable challenges," she says.

For example, a study's informed consent document is different from the study's privacy authorization statement.

HIPAA uses the term authorization to refer to permission for the use of that person's medical information for the purposes of research. The requirement for an authorization may be waived if certain conditions are met. IRBs are responsible for determining when and how the waiver is sought and used, explains **Roger Aamodt**, PhD, chief of the Resources Development Branch of the National Cancer Institute.

Under HIPAA, greater scrutiny is being given to privacy and confidentiality protections that are built into the research than in the past, he notes.

"The changes in the law have certainly changed how people have to do business, and the biggest example of that is that, under HIPAA, the information that's being protected is any identified information, and the regulations have specific terms for what is identifiable in a covered entity, which includes anyone who bills for medical services," Aamodt says.

Cooperative research projects that involve hospitals, medical centers, doctors' offices, and others may be subject to privacy regulations.

"So data that's released appropriately from one center can find its way into another one and become protected health information even when it wasn't protected originally," Aamodt says. "That means potentially that for multi-institutional studies, research groups at the very least have to have multiple authorizations or deal with multiple privacy boards or IRBs to get approval to do the study."

Also, the HIPAA authorization form for research is required to be specific to a research project, comments **Julie Kaneshiro**, MA, policy team leader of the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services (HHS).

"In other words, an authorization is only valid if it is authorizing a use for a specific research project, and it can't be for a class or unspecified future research projects," she says.

"This is somewhat different than HHS regulations regarding informed consent, where we have said that informed consent can be broader in the event of tissue banks and repositories," Kaneshiro says.

So while HHS rules would allow a database connected to tissue samples to be used in an identifiable form for future studies of the specimens,

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the privacy rule does not without specific authorization for each of these future uses, she explains.

For an informed consent document to be used appropriately, it would require some sort of language indicating that an investigator doesn't know what specific research project he or she might want to conduct down the road because the knowledge and data are not yet available at the time of a first study, Kaneshiro says.

"Assuming you're using identifiable information about individuals, it would be human subject research and need IRB review and informed consent under the IRB or waiver of informed consent," she adds.

Another difference between the HHS informed consent regulations and the privacy rule is that human subjects research under HHS is limited to people who are living, whereas the privacy rule also extends to the deceased, Kaneshiro notes.

This means that even decade-old tissue samples of a cohort of patients who all have died from a particular disease would need to meet all documentation requirements under HIPAA. An exception to this is in the case of research that precedes the privacy rule's implementation date of April 14, 2003. HIPAA permits a grandfathered informed consent, an IRB waiver of such informed consent, or authorization to disclose the information for research, according to recent guidance issued by OHRP. The document can be found at http://privacyruleandresearch.nih.gov/.

The key is that the informed consent must have been on file prior to HIPAA's implementation, Bledsoe says.

No blanket authorization

The gray area is in anticipating future needs.

"HIPAA doesn't allow blanket authorization," Aamodt says. "It's still possible to get consent for future research that you don't specify at the time you're giving consent, and HIPAA allows you to create a database of identified data with general authorization just to create the database," he adds. "The problem comes if you want to use that material; because the way the law is written, you have to have authorization for each specific use."

This means clinical staff will need to go back to the IRB or privacy board and obtain a waiver of authorization, or they will need to go back to each individual patient and obtain authorization for each specific use, Aamodt explains.

"So you can imagine a situation in which someone has created a tissue micro-array, a paraffin block into which they've inserted cores of samples from various tissue samples," he notes. "You may have several hundred patients represented on one slide, and if you had to get authorization from each patient for each study, and you cut 200-400 slides from each block, then you're in a situation in which you would have to make a tremendous amount of effort to contact all patients to get information or to convince an IRB that it doesn't need authorization."

While most clinical trials managers and investigators are handling this by de-identifying the information, this isn't always in the best interest of science.

"The key thing that people are struggling with is how to do this and how to do this well," Hohmann says. "It's important for investigators to think up front about what their research goals are."

For instance, in some cases, the goals might not include widely sharing samples for other uses, whereas in other cases this goal of sharing might be a priority, she notes.

"If you do anticipate that you'll need a larger tissue bank and will make tissues more widely available for others, then you need to focus on that," Hohmann adds.

Tissue banking issues

Massachusetts General, for example, has begun to develop guidance for investigators and research staff about tissue banking and has been investigating the possibility of starting a centralized tissue bank, she notes.

Just as there are commercial companies that have created tissue banks and contracted with hospitals and other research institutions, it's also possible for the research institution to create its own bank. The idea is that the institution's physicians and research staff would need to give patients clear education and choices at the time of a surgery in which a tissue might be available for banking, Hohmann says.

The physical process of setting up a tissue bank is the easy part; it's the education, informed consent, and storage of data/confidentiality issues that pose the biggest challenges, she adds.

The two main ways to store tissue samples and data are to store these after a pathological diagnosis in a way that doesn't retain a link to the individual from whom it was obtained or to maintain that link with the sample, Hohmann explains.

"It's much more valuable of course if you retain a link to the individual, so you then can find out whether they had chemotherapy A and how well they did and that might correlate with some

research finding," she says. "So the richness of the information and its value scientifically is so much greater if you retain the link to the individual."

The flip side is that when samples are stored with identifiable information then they pose greater risk of an inadvertent release of information and, thus, psychological and financial harms, Hohmann adds.

Another challenge is informing patients about these possible uses of their tissue samples, and the process would need to be more involved than the casual mention of such a possibility.

"A surgeon can say, 'You're having a breast biopsy; and after we're done, we might use the leftover tissue, and here's who you can contact if you want to talk about that,'" Hohmann explains.

Part of the informed consent process also might include reviewing with the patient a consent document, showing the patient a video about tissue banking, and asking the patient to decide whether they are interested in participating in this program, she says.

Lastly, clinical trials managers and investigators will need to have agreement letters between themselves and the recipients of any data and tissue samples that are shared with other researchers, Hohmann remarks.

These agreements should clarify the uses for what's shared and specify that tissues are not to be subsequently transferred or sold and also that the recipient will not try to identify the person from whom the sample came, Hohmann says.

OHRP officials are planning to update guidance on tissue repositories and databanks and may release this additional guidance some time within the next year, Kaneshiro says.

"We're not proposing any policy changes to existing guidance," she adds. "But because of all the questions arising about this — and not just because of HIPAA — there seems to be quite a bit of interest and confusion about how the regulations pertain to tissue banks and databases." ■

Blood substitute study raises consent questions

Community education makes the difference

In emergency medicine and critical care, clinical trials are difficult to conduct. The unpredictable and time-sensitive nature of these specialties means that controlled, randomized, clinical trials are difficult, sometimes impossible to design.

For example, in most situations, prior informed consent for new emergency procedures cannot be obtained because the patient's condition is life-threatening and must be treated immediately, or the patient is unconscious and unable to consent.

To encourage carefully monitored research into new life-saving interventions, federal regulations provide an exception to the rule requiring patients be given informed consent before they are enrolled in clinical trial.

To be eligible for the exemption, investigators must demonstrate that:

- patients who would be included in the trial face a life-threatening situation;
- currently available treatments are unproven or unsatisfactory;
- consent from the patient would not be feasible because of the patient's condition, and because treatment must be initiated before an appropriate representative can be reached;
- research cannot reasonably be conducted otherwise;
- risks and benefits of the experiment are considered reasonable in light of the patient's condition and what is known about other therapies;
- participation in the research holds the potential for direct benefit of the subject.

If these conditions are met, federal regulations also require investigators to develop methods to publicly communicate information about the study in the community where it will be conducted, to publish the results of the study once it is complete, to use an independent data safety monitoring board, and have the protocol approved by the U.S. Food and Drug Administration.

PolyHeme, for example

One such protocol is now under way at 20 medical centers nationwide. Paramedics working for these centers will be administering an experimental blood substitute to patients in the field who meet certain criteria.

PolyHeme, a substitute blood product manufactured by Evanston, IL-based Northfield Laboratories, is made from chemically modified hemoglobin derived from human blood and is designed to be an alternative to transfused blood in the treatment of acute blood loss.

According to information published by the manufacturer, PolyHeme is universally compatible and

does not require blood typing prior to its use. And, unlike stored donated blood, which can only be stored for 28-42 days, the experimental product has an estimated shelf life of 12 months under refrigerated conditions.

If proven effective, PolyHeme could dramatically improve outcomes for trauma patients. Donated blood cannot be carried on ambulances because of problems with storage and the need to match a patient's blood type. People who suffer severe blood loss in the field are normally given transfused saline to maintain blood volume and pressure during their transport to a medical facility. An oxygen-carrying blood substitute however, could better maintain blood-oxygen levels and help reduce the incidence of hemorrhagic shock.

PolyHeme has been previously tested in surgical patients and used during in-hospital resuscitations, with no reported adverse events.

But investigators believe it is essential to test the product in emergency patients to determine how they will respond.

The problem, however, is that patients who suffer severe blood loss in the field are unable to give informed consent prior to participation in a study. Often, the patients are unconscious. But even if they are not, paramedics cannot take time out from performing lifesaving procedures to explain the potential risks and benefits.

The research is just one example of studies being conducted under the 1996 federal exemption from consent regulations for research into emergency, lifesaving procedures.

Critics fear abuse

Some patient advocates say the exception is unethical because it permits experimentation on human subjects without their prior consent.

The study "is another one along that slippery slope that's essentially demolishing your individual right not to become experimental subjects unless you give prior, voluntary, informed, comprehending consent," **Vera Sharav**, president of the New York-based Alliance for Human Research Protections, told the Associated Press on Feb. 20.

But many medical ethicists say there are important characteristics of emergency care that warrant exemptions to standard research practices.

"Emergency medicine and critical care are the two areas most in need of clinical research, but it is very difficult to conduct study protocols in this setting," says **Norman Fost**, MD, MPH, director of the Program in Medical Ethics at the University of Wisconsin-Madison Medical School.

Emergency and critical care specialists frequently don't have the time to design and conduct randomized clinical trials of new procedures or therapeutics. Yet they often want to employ innovative new therapies if they believe they offer their patients the best chances of survival and recovery. Clinicians frequently try new therapies on an ad hoc basis with little or no supervision.

For many years, prior to the increased emphasis on "evidence-based medicine," physicians frequently tried untested treatments on patients in a variety of settings — particularly in emergency medicine and critical care.

They shared information with one another in published articles and at meetings, but it often took years to determine that treatments believed to be effective were, in fact, ineffective or bad or dangerous for some patients, he says.

Clinical trials, approved by an institutional review board and supervised by data safety monitoring boards, may actually offer patients with emergency conditions more protections — even without their informed consent — than they would enjoy outside a research protocol.

"Informed consent is a process, not a means to an end," Fost says.

Its purpose, he contends, is to prevent people from being enrolled in research that they would not want to be involved in if they were aware of the risks and benefits.

However, prior informed consent is not always necessary to accomplish these goals, Fost adds.

The federal regulations require investigators to publicize the research in the community and seek public input, he says. And the informed consent exemption only applies to emergency research in areas where there is not an effective treatment available.

In many cases, community members where such research takes place indicate that they would welcome the opportunity to have access to the experimental treatment, he continues.

Investigators at Denver Health Medical Center, one of the hospitals participating in the multicenter trial, designed an extensive public education campaign in advance of seeking permission to test the PolyHeme product, says **Jeffrey Long**, clinical research specialist and the PolyHeme study coordinator at that site.

"A team of representatives from Denver Health, including the principal investigator, co-investigators, emergency room physicians, EMS personnel, and representatives from our public

relations department, and myself met with several local community groups and provided a 20-minute presentation, detailing the study design and federal regulations as well as previous experience with the product," he reports. "The presentation was followed by a question-and-answer period that lasted between 15 and 20 minutes."

At the meetings, the team provided an anonymous survey to be filled out and returned. In addition, they placed notices in several local publications and got local coverage of the proposed study on local TV stations and newspapers.

"We also created a web site and offered both a call-in number, as well as e-mail and mailing addresses for correspondence concerning questions and comments regarding the study," Long adds.

They developed print and radio advertising in both English and Spanish and scheduled the principal investigator, Ernest E. Moore, MD, to give a presentation before the city council that was then featured on public access television.

"The reaction during our community consultation was positive," Long recalls. "I was pleasantly surprised by the enthusiasm surrounding the trial that was witnessed during our community consultation efforts. Multiple attendees told us that, should the situation arise, they hoped the PolyHeme product would be available for them and their families."

In the event that community members did not want to participate in the study, they could let investigators know through one of the established avenues of communication and would be provided with a small bracelet to wear, indicating they refused participation.

"The regulations don't require this measure to be taken; however, we felt obligated to provide everyone with the opportunity to express their wishes to refuse participation," Long says.

Fears that the federal exemption from informed consent requirements in emergency research would lead to a rash of no-consent protocols have proved to be unfounded, adds Fost.

Since its implementation, only 15 such studies have been approved.

Fost attributes this to the stringent requirements and some confusion among research sponsors and would-be investigators about what the requirements for community consultation and public disclosure really are, he adds.

The federal regulations are not specific about the extent of public information required and, thus many sponsors are wary of attempting such research, Fost claims. The result, he contends, is that many beneficial studies never get performed, leaving emergency critical care patients with fewer options.

"If this element of the exception requirements could be clarified, I think it might help sponsors and investigators feel more comfortable designing and proposing these protocols," he states.

To ensure they met the federal requirements for appropriate community education and consultation, Denver investigators spent more than five months planning and developing a communications strategy for dissemination of study information to the public and building a response mechanism for local community members, Long says.

"During this period, we met with or petitioned medical professionals, some of which previously attempted and/or conducted this type of research; local paramedics; various members of the local community and the Colorado Multiple Institutional Review Board, to name just a few," Long says. "Each provided insight into how to reach community members and address potential concerns."

The paramedic division played a crucial role by working as a part of the team developing the protocol and a strategy that would be easily understood by the public, he adds.

For investigators and coordinators planning other emergency trials, Long recommends first going over the federal exception regulations with a fine-tooth comb.

"Most important, you need to understand and meticulously adhere to FDA regulations in order to assure the protection of the rights and welfare of research subjects," he says. "Second, formulate a detailed plan and include the IRB in each step of that plan. Develop a collaborative relationship with your IRB, accept their criticism as positive, and solicit their feedback during the application and the community consultation and public disclosure period." ■

Research on the dead: Standards are required

University committee examines protocols

A cardiovascular surgeon develops an experimental intravascular blood oxygenation device that has the potential to eliminate the need

for mechanical ventilation in severely injured patients.

However, testing the device in human patients would be unethical because of the great risk of harm, and the still-unknown chance for benefit.

The surgeon wants the opportunity to test the device in patients who have been declared brain-dead prior to the withdrawal of life support. With no remaining brain function, these patients are no longer living, and so face no risk of harm. But they have intact, functioning cardiac and circulatory systems, which would allow clinical researchers to gather the vital information.

If you think this sounds logical yet gruesome at the same time, you're not alone.

This scenario actually occurred in 2001 at the University of Pittsburgh.

Surprisingly, the proposed research protocol fell outside the purview of the university's institutional review board because the intended subjects were no longer living. Federal regulations stipulating human subjects protections do not apply.

"The IRB saw no need for approval, but the investigator still wanted some oversight and opinions on the appropriate way to proceed, and came to the ethics committee for consultation," says **Michael A. DeVita**, MD, FACP, assistant professor of anesthesiology and critical care medicine at the University of Pittsburgh Medical College and its ethics committee chair. "This was our test case."

After much study by the ethics committee, and discussion with the administration, the university decided to establish a separate panel, the Committee for Oversight of Research Involving the Dead (CORID), to evaluate and approve protocols using deceased subjects.

An emerging research arena

As medical technology improves and treatments become more complex — and involve more risk — clinicians are increasingly looking to study particularly difficult interventions in brain-dead patients. Lifesaving therapies could be perfected without endangering patients who need help now, and such protocols could prevent medical errors in future patients.

Using the dead for research purposes is actually not new.

For many years, medical residents have practiced difficult procedures, such as endotracheal intubation or central line insertion, on recently deceased patients.

Investigators have often collected tissue samples, such as liver biopsies, from brain-dead patients in order to study the effects of a particular condition.

And some investigators have conducted other research on the bodies of brain-dead cadavers. Because the practice is not regulated and not often discussed, little information is available, DeVita says.

However, as such studies grow in number and variety, and involve different levels of complexity, researchers are beginning to question whether more oversight is needed.

For example, many inherently feel that the families of brain-dead patients should give consent for such protocols — particularly if they are invasive or require a significant amount of time. But when should consent be required? Who should obtain consent and what information should be provided to family members?

Maintaining brain-dead cadavers on life support also raises other ethical concerns. For example, should dead patients be kept breathing, their blood circulating, so that we can perform research? And how long should a dead person be left on a ventilator so that his or her body can be used?

However, federal regulations only require the oversight of an institutional review board if a study involves living patients, DeVita explains. Most people feel that some oversight is necessary, however.

The question is, where to draw the line between the stringent protections required to protect living people, and the attitude that "if the patient is dead, do whatever you want," he says.

In deciding how to proceed, Pittsburgh officials first looked to the institutional review board to determine whether they could appropriately review these protocols, even though federal law does not require it.

There are several reasons that was not workable.

Like most IRBs, the one at Pittsburgh was already overloaded with protocols involving human subjects. And members were concerned that if they used different criteria for evaluating research on the dead, an audit by officials from the U.S. Office of Human Research Protections would land them in hot water.

"There is no established avenue for allowing IRBs to use different standards for different types of research," DeVita says. "There was concern that they would be cited and it would endanger other research."

In deciding whether a formal oversight process was needed, university officials and the ethics committee considered three things: 1) Are researchers in this area able to quantify the potential risks to subjects well? 2) Did the potential for abuse exist? 3) And if abuses occur, would they be easily discovered?

The answer to all three questions, they felt, was yes.

Originally, they felt the protocols could be reviewed by the medical school ethics committee, but concluded that this would not be sufficient. The ethics committee only had jurisdiction over studies involving patients at that institution, but would not have influence over investigators at other sites or deceased patients or tissue materials brought in from other places. A separate panel was needed.

The goals of CORID, they decided, would be to provide guidance to investigators, and protect the deceased people and their families.

Though potential subjects would be deceased, clinicians still have an ethical responsibility to honor — as best as possible — the person's preferences and values about whether or not they would want their body to be used in a research protocol. And there are general issues to consider about respect for human corpses.

"Some things are reasonable to do, and some things are just not reasonable to do," he says.

There also are confidentiality issues to consider, DeVita continues. Researchers could discover new information about the person.

Families may also have concerns — they have dispositional rights to their family member's body that should not be interfered with. So clinicians and investigators need to be sensitive to their feelings with regard to appropriate treatment of the cadaver.

As for investigators, most admit that they don't know the limits — what is reasonable research conduct? And they want to operate with a set of rules, DeVita says.

CORID's first goal was to develop a set of ethical standards of practice for investigators to follow.

"We started out with the ethical principles and then developed standards based on those principles," DeVita says.

To conduct research involving dead patients, investigators must demonstrate that:

- their study has scientific merit;
- they will be able to provide informed consent to family members;
- the protocol would involve an unusual or unexpected use of a cadaver, but that the intervention would be for only a limited time and conducted in an appropriate location;
- investigators have a plan to provide feedback on the research to the family members;
- the subjects' confidentiality will be protected;
- investigators will disclose conflicts of interest;
- investigators will document that their study will not interfere with possibility of organ donation;
- documentation will be made of the expect impact on hospital resources and the financial impact of the subject's family.

Since CORID's formation, it has received 29 submissions of protocols for review from 17 different departments, says **Mark Wicclair**, PhD, professor of philosophy and adjunct professor of community medicine at the University of Pittsburgh Center for Bioethics and Health Law.

"CORID review is not limited to brain-dead cadavers, it can review any study involving deceased patients and use of cadavers," he notes.

Of the submissions received to date, 20 have involved proposed use of cadavers and tissues obtained at autopsy, five have been case studies, three have involved use of brain-dead patients, and one involved use a cadaver without a functioning cardiovascular system in a clinical setting.

The majority of investigators were referred to CORID from the institutional review board, and

Guidance on research involving the dead

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involved investigators who were unaware of the separate committee, Wicclair says.

Twenty-six of the submissions were approved and three received conditional approval — the committee asked for protocol modifications or more review from investigators.

"We did not reject any outright on ethical grounds," Wicclair notes.

CORID now is focusing on other issues involving appropriate research processes and procedures, including how tissues should be collected and stored, whether family visitation during the study intervention should be permitted and what policies and procedures need to be in place; and what policies should be about the physical effects the study intervention might have on the body.

There has been confusion on the part of some investigators about providing appropriate informed consent to family members and maintaining confidentiality of the deceased person involved, Wicclair says.

And in studies involving brain-dead patients, questions about who should approach the family to seek informed consent for research have come up.

"Who should be responsible for getting informed consent?" Wicclair asks. "Is it the organ procurement organization representative or is it going to be the investigator talking to the family?"

CORID members felt that it ought to be the investigator so that the research protocol would not be confused with consent for organ donation.

The duration of the research protocol has also been a concern and the committee agreed that a set limit had to be in place.

"There are concerns about resource utilization, the impact on the family and the question about respect for the cadaver," he says. "We were agreed that it could not go on indefinitely, but we had to establish what was long enough and what was too long."

After considerable debate, the committee agreed on a time limit of 72 hours — interventions of a longer duration would not be allowed.

In examining the university's experience with CORID, it has become clear that research involving the dead was neither rare nor limited to only a few departments, Wicclair says.

Investigators have been able to satisfy ethical standards of research established by the committee, and the committee has served not to thwart the research protocols but to facilitate such research and promote appropriate ethical standards, he states. ■

A few simple rules ensure data sharing compliance

NIH official explains the ins and outs

The National Institutes of Health (NIH) wants all research supported with NIH funds to be shared with other investigators and made available to the public, but how can this philosophy be reconciled with privacy laws and concerns?

Sharing data is a policy of common good, notes **Belinda Seto**, PhD, deputy director of NIH's National Institute of Biomedical Imaging and Bioengineering.

However, confidentiality of data and individuals' privacy also are of utmost importance to the NIH, and these were important even before the privacy rules of the Health Information and Public Accountability Act (HIPAA) were implemented, she says.

While clinical trials managers and investigators often say that these two goals create a heavy burden on their time, especially when a data set is popular and there are multiple requests to share, it doesn't have to be unduly burdensome, Seto adds.

For instance, investigators can request in the original grant for money to cover the cost of sharing the data.

"Even if they didn't remember in the original application to ask for the funds, once the data set turned out to be popular and in demand, they can write to NIH and ask for a supplement to the original grant for the purpose of data sharing, and NIH will consider that," Seto says.

While the de-identifying of data takes time, it is necessary, she notes. "We believe the privacy of individuals who participated in clinical studies must be guarded and respected, and even in sharing data there are ways to protect the confidentiality of data." She offers these insights into how clinical trials managers and investigators might best meet both goals and all privacy regulations:

• **Keep data secure.** Data should be stored in secured, locked places, and an individual subject's identity can be protected through various mechanisms, Seto says. They include:

— statistically protecting identities;

— randomizing samples with coded names and numbers;

— eliminating opportunities for deductive identifying.

Basically this requires a common sense

approach of changing the way data is de-identified according to the size sample, Seto says.

"If you have a small sample of 25-50, or even 100 people, then obviously the safeguard for privacy would be different from guarding a sample size of thousands," Seto says. "For example, if you were doing an epidemiological study, you might not want to give a census tract for a study that is small in sample size."

NIH investigators analyzed data from the adolescent health study that is supported by the National Institute of Child Health and Child Development. The study involves congressionally mandated data collection of sensitive health information from more than 20,000 students. Data collected include sexual behavior, drug use, and other sensitive information that shouldn't be linked back to the individuals who participated in the study, Seto explains.

However, the NIH study found that if someone knew only five parameters on an individual, such as the person's zip code, census tract, age bracket, school attended, and one other characteristic, then they would be able to deduce which student gave which survey answers, she says.

"Most of our investigators are very knowledgeable about not giving names such as 'John Jones' and telephone numbers and addresses, but the idea is to raise the level of sensitivity about deductive identification," Seto says.

This is particularly important when data from one clinical trial is shared with other investigators because some of these parameters that may be desired for other analyses and research could be problematic with regard to privacy issues.

"When you share data, you have to be careful about what the recipient of the data needs," Seto says.

HIPAA provides examples of 18 identifiers that can be taken out of data. "HIPAA also allows you to look at feasibility study preparation to research," Seto says. "Under HIPAA, you can see some of the identifiers and don't have to de-identify all elements for a small data set in a feasibility study."

• **Limit the data you share with others.** For example, with regard to the school student survey, NIH allowed only a subset of data to remain in the public domain, Seto explains.

Data from only 6,500 individuals were released to public access. This subset was representative of participants so as not to skew data in a way that would encourage someone to draw incorrect conclusions, she adds.

"If someone wanted to see more than the 6,500, we would have data use agreements with them, which is a contract and has legally binding authority to make sure they don't disclose identities," Seto says.

Even with these agreements, researchers would be required to view the data only in a certain location, and they were not permitted to leave the facility with any information. If they wanted to use the data, it would have to be done with on site work, she notes.

Extreme examples of other types of data sets that might require such safeguards would be cases where the population being study is by nature quite small, such as with certain rare diseases and, perhaps, with a study of a group that is self-limiting, such as billionaires, Seto says.

"You'd be surprised how if you have multiple pieces of data, you can pretty much pinpoint who an individual is," she says.

In these rare disease cases, it would be wise to take out information about the city and treatment center, Seto adds.

• **Negotiate data release and ask for a data use agreement.** Other than taking off a person's name and other directly identifying information it's difficult to make a policy that would work in all cases with regard to data sharing, so Seto recommends that clinical trials managers and investigators provide a bear minimum amount of data to investigators.

The best way to do this is to ask the investigator who has requested the information what exactly he or she needs for the secondary analysis, and then give them no more than what they request, she advises.

"Of course, the investigator will start with the response of, 'The more I know, the better,'" Seto says. "But under HIPAA and even prior to HIPAA, NIH would not let you have any more identifiers than you needed."

So if an investigator asks for identifying data that could pose a privacy problem, then talk with the investigator to determine how an analysis might be done without that piece of information, she suggests.

For example, a clinical manager or investigator could say, "You wanted to look at the demographics of the disease, income levels, and education levels, and gender and race/ethnicity," Seto says. "But you do not have to pinpoint a specific community — you can say a rural community or an inner city."

She says that's why clinical trials managers

and investigators might consider requiring data use agreements for all shared data requests.

"I've always asked for data use agreements because it's just so much more protection for both sides — for both the giver and recipient of data," Seto says. "If you didn't have a data use agreement, then that second person can share with a third and fourth person downstream."

Most data use agreements are written plainly and will stipulate the conditions for sharing data. Some institutions may ask that the agreement either be written by a lawyer or reviewed by one, she notes.

While it's not necessarily a matter of wanting to control the data, it is important to avoid abuses, which could be damaging to the individuals who gave you the data, Seto says.

"I always stipulate that whatever future uses they have with others, they have to follow the same conditions," Seto says. ■

Smallpox vaccine draft guidance issued by FDA

The FDA this month issued draft guidance for companies developing drugs to treat the side effects of vaccination against smallpox with vaccinia virus.

Although it is not believed that smallpox vaccine complications requiring treatment would be widespread in the event of a terrorist attack, the agency said plans for drug development should be designed to make use of all data collected.

The draft guidance summarizes appropriate nonclinical studies recommended during early drug development. It includes sections on chemistry, manufacturing and controls, nonclinical toxicology, microbiology; and clinical pharmacology.

The guidance concludes with sections addressing the acquisition of human efficacy and safety data, issues surrounding the design of clinical trials and sections detailing data-collection requirements and recommendations.

Before Sept. 11, 2001, smallpox essentially was a memory for most people in the U.S. Routine vaccination for the incurable, highly transmittable, often deadly disease ended in the 1970s when it was eradicated. Smallpox has a case-fatality rate of 30% or more and has the ability to spread in any climate or during any season, the Center for Civilian BioDefense Studies at Johns Hopkins University in Baltimore said.

The old vaccine used on children born before the early 1970s was developed decades ago and provides good protection, but causes a vaccinia infection at the inoculation site. Also, people who are immunosuppressed or have eczema or other skin conditions could suffer complications. Healthy people, on rare occasions, also could develop infections.

The draft guidance is available on-line at www.fda.gov/cder/guidance/5518dft.pdf. Comments and suggestions should be submitted within 60 days to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. ▼

New technology, lack of consent leads to lawsuit

A recent Tampa, FL, lawsuit involving a patient who died after robotic surgery to remove a cancerous kidney has raised informed consent issues regarding new technology.

"The conventional surgery was basically jettisoned and this robotic surgery was not only suggested but really pushed," said a lawyer for the patient's family in a lawsuit filed against the hospital.

With new technology, it's critical to discuss the reason for using the technology, says **Steven Schwaitzberg**, MD, director of the Minimally Invasive Surgery Center at Tufts-New England Medical Center in Boston.

"When the choices affect the approach to the surgery, significantly, such as robotics, then those issues need to be discussed with the patient," he says.

First, the surgeons must have the reasons for use of the new technology firmly planted in their own minds, "because unless that occurs, it's hard to have a coherent discussion with the patient," Schwaitzberg explains.

With some technology, such as larparoscopes, the advantage is obvious, even if you just consider

cosmetic issues, he adds. "[T]he advantage of using a robot is less obvious for routine procedures such as cholecystectomy but may have a clear role in more complicated procedures," Schwaitzberg says.

The point to make with patients is that you want to provide a procedure that is of equal or greater benefit with new technology, but warn them of the possibility of unforeseen outcomes, advises **Mary H. McGrath**, MD, MPH, FACS, chair of the Committee on Emergency Surgical Technology and Education at the American College of Surgeons and professor of surgery, Division of Plastic Surgery, at the University of California San Francisco Medical Center. ■

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.

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. ■

9. What is one chief difference between Department of Health and Human Services policies on tissue banking and what's required under HIPAA?
A. HHS does not require an informed consent in the cases of tissue banking, but HIPAA does require an authorization.
B. HHS requires a time limit to how long tissue samples can be stored, but HIPAA does not.
C. HIPAA authorization for research has to be specific to a research project, while HHS regulations say that informed consent can be broader in the event of tissue banks and repositories.
D. None of the above

10. To be exempt from federal regulations regarding informed consent, investigators must demonstrate:
A. They face a life-threatening situation.
B. Currently available treatments are unproven or unsatisfactory.
C. Participation in the research holds the potential for direct benefit of the subject.
D. All of the above

11. According to our article on research involving the dead:
A. IRBs are not permitted to review protocols involving nonliving human subjects.
B. IRBs do not have to review protocols involving deceased subjects.
C. IRBs normally review protocols involving deceased persons as subjects.
D. CORID also oversees research involving the nearly dead.

12. Clinical trials managers and investigators might best meet privacy regulations by doing which of the following:
A. Keep data secure
B. Limit the data you share with others.
C. Negotiate data release and ask for a data use agreement.
D. All of the above

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