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ADMINISTRATOR
An essential resource for managers of clinical trials

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Given rules and regs, is emergency department research even possible?

Chaotic nature of ED, lack of administrative support create problems

As one might expect, emergency physicians prescribe a lot of pain medication. Surveys of emergency department (ED) patients indicate most patients present there in moderate to severe pain. But ED physicians have a difficult time knowing which medications will work best for their patients because research specifically targeted to emergency conditions is lacking.

"We have lots of drugs approved by the Food and Drug Administration for use in the emergency setting, but we've never studied them in the emergency department," says **Knox Todd**, MD, MPH, director of the Pain and Emergency Medicine Initiative in Atlanta, a project dedicated to researching the legal, ethical, and clinical challenges to improving pain management in emergency medicine. "That is one issue we always have with the FDA and approvals."

Industry sponsors don't have a high comfort level in working with emergency providers because the setting is vastly different from the traditional office-based setting of pediatrics, primary care, gynecology, and other specialties.

The nature of emergency care is that it is unscheduled — hordes of patients may present to an ED with very different medical needs, yet another day the same ED may see few patients. In addition, the patients who do show up will likely never return to the ED for follow-up care.

"A number of people in the pharmaceutical industry are coming to me, saying they know they should be conducting studies in emergency medicine, but they don't know how to go about it," Todd adds. "There is a large learning curve to doing it."

For example, an investigator may need to observe the participant for longer than a typical ED visit. But where will this observation take place? Space outside the ED will likely have to be allocated because most EDs don't have extra space available.

"Maybe follow-up visits could be arranged, but it will have to be thought of in a novel way; perhaps the participants can come back to the ED at a time when the department is underutilized and not as busy," Todd says.

Emergency departments are frequently very busy, however. And in addition to the lack of space for observation or follow-up evaluations, many will not be able to allocate support staff to perform the necessary coordination and record-keeping duties necessary for clinical trial administration.

"Trying to do research in a busy clinical environment means you are going to either have people who are dedicated and very motivated to do it, or you will have to bring in additional resources," Todd explains. "Maybe you could train a research nurse to coordinate the study at a couple of sites — possibly a mobile research nurse who could head out to take over the efforts of a clinical trial from other folks at the individual departments who have other things they should be doing."

He currently manages the emergency medicine portion of a large, federally funded, multicenter study examining the effects of air pollution on asthma, stroke, and heart disease. As part of the study, he is collecting data from 20-30 EDs in metropolitan Atlanta. Todd speculates that it might be easier to conduct clinical trials in emergency medicine if sponsors were able to link multiple emergency departments to maximize participation and data collection, while sharing the financial burden of administrative support.

"One of the things I am thinking about for the future is whether there is any interest in setting up a clinical trial network that is a population-based network which could benefit from the local kinds of strength in numbers you get from being able to add resources in a small geographic area," he says.

"I don't know whether the economies of scale in urban areas like metro Atlanta, with its density of emergency departments, would be useful. But we have certainly found in our epidemiologic studies of air pollution and heart attack and stroke that we need the density of experience. We are able, within this [National Institutes of Health] NIH and [Environmental Protection Agency] EPA-funded study, to capture 1.3 million ED visits a year in a database to model the impact of air pollution." It remains to be seen whether this model will also prove useful for industry sponsors looking to set up a multisite trial, Todd points out.

Studies are possible

Well-controlled, industry-sponsored trials are possible in EDs, but they require a different degree of advance planning, support and, many times, cooperation with other specialties to make them work, says **Dexter Morris**, MD, PhD, a clinical investigator studying stroke treatment and prevention in the research division of the University of North Carolina (UNC)-Chapel Hill's department of emergency medicine.

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Conducting research in an ED is challenging for a number of reasons, he says. As Todd mentioned, the chaotic nature of most EDs makes organized study difficult. In addition, many departments rely on a high percentage of travel nursing staff, who are not as familiar with the community and who are less motivated to work on research projects.

"You also have rotating attendings, not the same people there every day and, because of the pressure to reduce waiting times and get patients in and out, you don't have the leisure time to explain and conduct studies," he says.

Emergency medicine also is a newer specialty, and there is not as much of a focus on performing clinical research as there is in other specialties, such as cardiology, neurology and infectious diseases, Todd contends.

Nevertheless, some conditions, like stroke and other sudden-onset, life-threatening illnesses (trauma, acute myocardial infarction, snake and animal bites, etc.) can only be adequately studied in the emergency setting, he adds.

Morris has had success working in conjunction with the department of neurology on several stroke studies.

"For a while, we would alternate principal investigators between the ER and neurology for the trials," he notes. "As many of the stroke [treatment] centers have grown, they are beginning to design their own protocols, mainly involving combinations of intra-arterial and intravenous tPA based upon brain MRI readings. These are probably less standardized, though there are some national trials that are ongoing."

The department at UNC has helped facilitate research by hiring a graduate student in statistics to work part time helping with the design and analysis of clinical trials. And a special summer research program encourages medical students to come in and staff the emergency room and do a variety of pilot studies, he adds.

In the past, Morris has also been able to use the clinical trials department established at the hospital where his ED was located to find IRB and record-keeping support.

"The key thing is getting support to do the trials, either from a clinical trials office or being able to hire your own research coordinator in the department," he advises. "You have to have someone dedicated who will constantly be bird-dogging things and checking to make sure things are going well. Otherwise, the work will not get done and interest will wane."

Once a department or ED group is able to get a body of research going, the research can pay for itself. But getting established is the key. "The department needs to make the commitment that clinical research is important and hire a nurse and/or coordinator with interested physician supervision," Morris says.

"Then it will take off on its own. Sponsors will recognize this and support it, and, at the same time, be wary of sites that don't have this level of support," he adds. ■

Risk management making its way into clinical trials

Informed consent, patient safety key areas

Developing and adhering to a solid risk management strategy is an important foundation for preparing for the possibility of clinical trial problems, including those pertaining to patient safety, regulatory issues, and civil suits, experts say.

One of the key issues in the risk management process is informed consent. "It seems to me that the area that people still need to pay attention to is really to have a good informed consent process," says **Jeffrey Trunzo**, RPh, MBA, CIP, vice president of the Chesapeake Research Review Inc. in Columbia, MD.

While everyone focuses on the informed consent document itself, that's not the primary informed consent function, he notes.

"The process really is meant to have potential subjects understand that they are in research and to understand what's going to happen to them," Trunzo says.

The research field is beginning to understand that informed consent is a major factor in risk management, says **Allison Weber Shuren**, MSN, JD, health care attorney for Arent Fox in Washington, DC.

"People spend a lot of time writing a document, but they're just beginning to understand that informed consent is not just handing someone a document," she says. "Informed consent is a process of truly educating someone about the risks of a trial and letting them know whether it's therapeutic or whether there will be any financial gain for their participation."

From a research sponsor's perspective, patient safety must be adequately managed both on site

and through checks and balances, explains **Christopher Gallen**, MD, PhD, vice president and chief of operations for clinical research and development at Wyeth in Collegeville, PA.

"We have a responsibility within the company," he adds. "We want to check the data very carefully across all patients, as well as look for outliers and high-risk findings in patients."

It's important for sponsors to work with clinical trials staff and investigators to make certain all medical concerns are addressed and that investigators don't overlook problems, Gallen notes.

Gallen, Shuren, and Trunzo offer these suggestions for improving risk management of clinical trials:

1. Review your recruitment process. "Subject recruitment is an area where people can get themselves in trouble," Trunzo says. "Almost all clinical trials in the United States don't make their recruitment timeline."

One of the reasons clinical trials recruitment often is difficult is because the inclusion/exclusion criteria are not designed realistically, the experts say.

"One thing that really makes these unsuccessful is if you have a protocol that is designed for patients who don't exist in the real world," says Gallen. "Someone — often a less experienced person — will design a trial and will try to exclude everyone who would make any extra difficulty in the trial, so they can get a clean answer."

But by the time potential subjects are checked against the inclusion/exclusion criteria, there are very few subjects left, he adds. "For instance, someone starts out with a combination of criteria that individually can make some sense, but cumulatively excludes everyone," Gallen says.

A solution would be to develop a more realistic way to write inclusion/exclusion criteria, he suggests.

Some programs are aggressive in their recruiting efforts through paying high-dollar compensation to healthy volunteers for phase I clinical studies and paying recruitment bounties to investigators and study coordinators, and sometimes even to patients, Trunzo notes.

However, the truly bad programs are rare, he adds. "There are lots of good recruitment programs that create awareness about diseases, and there's nothing wrong with providing moderate amounts of monetary awards to compensate people for their time and transportation," Trunzo says. "But when people say they want to stay in a study until the end — even when they're having bad effects — because they want to collect the payments, then that's when it turns around into a problem."

One risk management solution would be to spread study visit reimbursement equally as the study progresses, instead of offering subjects a big bonus at the end of the study, he suggests.

"It may not be in their best interest to finish, so just reimburse them up to the time they participated," Trunzo says.

Another risk management strategy is to hire a trials coordinator who is paid to recruit subjects at a rate that fairly reflects the cost of the person's work, Shuren explains. "As long as that person is a third party who has no incentive for putting people into a trial arbitrarily, then it's a very good strategy to say that the physician knows his patient population and can say who might be a good candidate for a trial, but to have someone else do the triage for it. The third party could be a trial coordinator."

Financial incentives paid to clinical trials staff and investigators for recruiting subjects can be outrageous and sometimes coercive, she says.

Likewise, if the investigator is the person doing the recruitment, then the financial incentives should be no more than the cost of the investigator's time, Shuren adds.

Wyeth wants to attract the first-rate investigators to clinical trials so they are paid fairly for their work, Gallen says. "We don't want to create incentives that lead people to engage in bad behaviors," he adds. "As a consequence, we're pretty careful to try to be fair and pay a rate that a first-rate person would receive to do the work, but not so much that it becomes a financial coercion to induce people to engage in bad behavior."

"If a person is paid a salary and spends 10 hours per week recruiting patients, then there's a dollar value to that time," Shuren explains. "Stick to fair market value of the services provided."

2. Run a well-organized trial with timely documentation. Reporting adverse events in a timely manner to the appropriate regulatory agencies is another area that has caused risk management problems for some clinical trials, Shuren notes.

"We're seeing more focus on this mainly because of big [tort] cases that have come up in the last few years," he says. "Some of these have been adverse events that have not been reported in a timely manner or accurately. If they had been reported correctly then patients might not have been harmed, according to the allegations."

Most of the regulatory problems arise from paperwork problems, Gallen notes.

"The attention to detail when putting a patient into a trial was not as good as we'd like," Gallen explains. "The first sign of defense is to have monitoring follow-through and to highlight problems to be addressed."

When Wyeth reviews audit findings at clinical sites, company auditors often find that a large majority of the problems relate to paperwork for which there are electronic copies in the files, Gallen says.

Items such as IRB approval forms and informed consent documents may be missing information, but these problems could be avoided through an internal, electronic auditing system, he explains. "We can look through the documents and audit them ourselves inhouse to figure out what the problems are and get back to the monitors to correct the problems," Gallen says. "With this policy, we can do — inexpensively — 70% of the audit at 100% of our sites, at our own leisure."

3. Avoid the appearance of a conflict of interest. "One hang-up the industry is struggling with right now is whether or not subjects have the right to know if there's a conflict of interest on the side of the investigator," Shuren says. "You can have conflicts that interfere with the informed consent in trials."

It's critical to consider the conflict of having an investigator serve both as a physician to a patient and as a clinical trials researcher for a study in which the patient is enrolled, she notes.

The question that needs to be posed when investigators wear both hats is whether the use of the investigator's own patient population in a study is so coercive that patients may feel they have no choice but to enroll, Shuren says.

"Some of these contracts are quite lucrative for physicians," she explains.

Besides dealing with the risk of lawsuits, clinical trials staff and investigators who have the appearance of a conflict of interest could run afoul of state and federal kickback and referral laws.

"Contracts to run investigations should be viewed no differently than any other contract with a pharmaceutical or device company," Shuren notes. "In terms of the kickback laws, it should be in a safe harbor if it can be."

The federal government has identified a number of arrangements that technically would violate the kickback rule, but if the arrangements meet the criteria of a safe harbor then the government will not prosecute them, she explains.

For instance, it's all right for a clinical trials sponsor to pay a physician investigator for his or her time and resources spent recruiting, but if these incentives are much higher than what the physician's work would warrant, then they may give the appearance of being a way for the sponsor to funnel money to the investigator as a kickback or "thank-you" for other services the investigator has provided, Shuren says.

Sponsors may pay investigators for their clinical trials work and costs, but they can't use that payment to give the investigator a benefit for other reasons. ■

Risk management begins with informed consent

Here's how to avoid common pitfalls

Risk management issues that result in lawsuits often involve misunderstandings among subjects and clinical trials staff and investigators. By improving the informed consent process, these risks could be reduced, and here's how, according to experts:

• **Make certain the informed consent process does what is needed.** Informed consent cannot be handled in a generic way. For instance, informed consent for phase I clinical trials should be drafted differently than informed consent for trials that look at efficacy, says **Allison Weber Shuren**, MSN, JD, health care attorney for Arent Fox in Washington, DC.

Also, when there are problems with subjects that result in civil suits, a common complaint is that the subjects thought that the trial drug, device, or intervention offered to them was one that had a proven outcome rather than that there were some risks and potential benefits that are yet unproven, says **Jeffrey Trunzo**, RPh, MBA, CIP, vice president of the Chesapeake Research Review Inc. of Columbia, MD.

"Our IRB review process is one where we look at the form for overall comprehensibility and having terminology that most people can understand," he says. "And the form should have a font type with enough white space so that a person can read through a very long document. It's not uncommon for the document to be eight to 10 pages long."

One best practice is to allow potential subjects time to read the document and then to discuss it

with their families before returning to have all of their questions answered, Trunzo suggests.

"We think there should be pressure-free time," he says. "They need to know it's part altruism — they are contributing to a body of knowledge — and that there's a chance they may not get better."

Clinical staff should spend a lot of time talking with subjects about their expectations, Shuren notes. It's acceptable to delegate some of the informed consent process to clinical trials staff, including nurses and coordinators, but at some point the investigator or physician will need to be a part of the process, she says.

"Even if the coordinator provides the initial explanation of the trial and informed consent document and gives the subject some time to think about it, potential subjects still should be offered the opportunity to meet with the investigator to ask any questions,'" Shuren explains. "That's part of being an investigator, part of their duty."

Also, a good risk management strategy is to make certain the informed consent process continues throughout the trial, Trunzo says.

"If it comes to light that there are unexpected serious events, it's important to have a program so those risks that weren't known when the study began are communicated back to people in the study, so they'll know what those risks are and can decide whether to continue," he says.

"The whole goal of clinical trials, if designed right, is that they hope to discover problems during the clinical trial process, rather than have a drug approved and then yanked off the market," Trunzo explains.

"I think all data in humans should be shared with subjects," he says.

Some sponsors are so conscientious that they'll require investigators to share all safety data, including animal data that might be inconclusive, Trunzo adds.

• **Be vigilant with placebo-controlled trials.** From a statistical standpoint of proving a hypothesis, a study that proves that a product or intervention is effective against placebo is the gold standard for research, he points out.

"That's where you get the most clear results with a study population of a reasonable size," Trunzo says. The flip side of the argument is that if clinicians feel that there is an adequate treatment for the condition on the market and the company is creating another treatment, then they shouldn't perform placebo-controlled trials."

Instead they should compare the new product with an old product, he suggests.

Also, placebo-controlled trials may pose risk management problems when subjects do not fully understand that they may or may not receive the drug or intervention under study, Trunzo notes.

Another strategy is to create a trap door in which a patient will be taken out of the study and given an existing treatment if their condition worsens during the trial, he reports.

"There needs to be monitoring, and there's no need for human suffering," Trunzo says. ■

Data monitoring can affect risk management

It also may help manage risk

The age of information and the way 21st century computers can make it easy to collect and sort through data are important advantages in managing risk during the clinical trial process.

New technology also can help highlight and separate good data from poor data, even as a clinical trial is under way, says **Christopher Gallen**, MD, PhD, vice president and chief of operations for clinical research and development at Wyeth in Collegeville, PA.

Through taking advantage of existing technology, a clinical trial sponsor is able to check incoming data during a clinical trial and monitor the trial for outliers and high-risk findings, he explains. "Then we can contact the clinical trial staff to make certain that problems that look like a medical concern are addressed," Gallen says.

Monitoring a trial's data also is a good way to make certain that a trial is not being poorly conducted and therefore collecting bad data that would show the trial to be a failure when it really is a success, he notes.

Gallen highlights some other strategies developed at Wyeth that are designed to help improve the clinical trials process and manage risk:

• **Design a better inclusion-exclusion criteria.** The idea is to develop inclusion-exclusion criteria based on what physicians say they see in their patient populations, Gallen says.

"We're trying to work with clinicians who see a lot of patients with a given disease and have them look at the exclusion/inclusion of trials and compare these to people who come into their office," he explains. "We have the clinicians give us a report

that tells us of the 100 people they saw in a two-week period for a given disorder."

The reports will outline how many of these patients would be excluded by a set of potential criteria and whether the patients indicated any interest in participating in such a trial, Gallen adds.

This way, if it appears that a large percentage of potential subjects would be eliminated by one criteria, then that criteria could be modified or eliminated before the trial begins to enroll subjects, he notes.

"This is the way we can give our drug the maximum chance of having a successful trial," Gallen says.

• **Create a strategy to reduce risk of trial failure.** "The worst trial outcome is when you can't tell from the data whether a drug succeeded or failed," Gallen says.

Now with new data management technology, it's possible to reduce the risk of this outcome by conducting a statistical quality review of the data, he says.

This is how it works: A study is designed to look at patient outcomes from a couple of different measures, including a physician's subjective rating of whether the patient has improved or gotten worse and an objective tool that uses various criteria to measure the same thing, Gallen explains.

If both the physician and the rating tool show the same results, then it would appear that the trial is working. But if one measure found one result and the other found a different result, then this would be a problem, he says.

"If you plot out physicians' ratings and the tool's ratings, then you should see some constant relationship between the two, with some variation," Gallen says. "But if you do such a scatter plot, you also will see that in some studies at some centers there are patients that the clinician thinks are getting much better, but the rating scale is not showing it."

This shows that someone is making a mistake and it's either the physician or the person administering the rating tool, he notes.

"Most of the time, you wouldn't find out about this problem until the trial is over, but we're looking at a way to automatically detect those kinds of discrepancies early in the trial," Gallen says.

Once the problem is discovered, the investigator and clinical staff can be trained to improve the rating process and new centers beginning the trial can be given improved instructions on using the rating systems, he explains.

• **Produce better dosing ranges for a new trial.** Another strategy to improve clinical trials could be to use a process called adaptive randomization, Gallen says.

If researchers plan a dosing range trial, then the subjects enrolled in such a study could be spared participation in a study arm that produces no useful data.

For example, suppose that early on in a study a statistical analysis shows that one of three or four arms in a dosing range investigation is making subjects worse than a placebo, Gallen says. And if the analysis shows that this dose is of no use to these subjects and there is no way that it will improve enough to be considered helpful no matter how many additional people are placed on this dose, then it would be a good idea to drop this arm well before the study concludes.

"Adaptive randomization is a computerized, blinded way to look at incoming results on a trial," he says. "If a study arm has no chance of success, then you should close the arm and enroll the subjects in other arms."

This is a more efficient use of subjects' and investigators' time.

"So the idea of adaptive randomization is that it's a way of testing each arm to the point where you know that it doesn't work or you know that it does work, and it gives the arm the maximum rigorousness of a test," Gallen says. ■

Informed consent process at center of another suit

Ongoing consent seems to be lacking

In March, members of the Havasupai Indian Tribe of northwestern Arizona filed two federal lawsuits seeking a total of $75 million in damages against Arizona State University (ASU), the Arizona Board of Regents, and three university researchers. The lawsuit claims that blood samples taken from tribe members as part of a diabetes study were destroyed, lost, or used in studies of schizophrenia, inbreeding, and population migration without the donors' consent.

The tribe alleges that nearly 400 blood samples were collected from more than 180 donors between the years 1990 and 1994 as part of a larger study of the incidence of diabetes among its members.

According to the lawsuit, the tribe was told the study consisted of three parts: diabetes education, collecting blood samples from members for research, and genetic testing to identify which genes in the Havasupai caused diabetes.

However, researchers later used their access to Havasupai medical records, in addition to the blood samples, to initiate studies of schizophrenia and inbreeding, and transferred some of the samples to researchers at other institutions, some of whom used the samples in research into theories of population migration, the tribe's attorney, **Robert Rosette**, JD, of the Sacramento, CA, law firm Monteau & Peebles, LLC, told *Clinical Trials Administrator*.

The lawsuit alleges fraud; violation of federal, state, and local research regulations; improper transfer of blood samples; and infliction of emotional distress, he states.

Not the first

The Havasupai suit is the latest in a line of recent legal actions on behalf of participants in research studies who believe investigators misled or exploited them to further their professional aims.

• **In 2001,** the families of five cancer patients who died while participating in experimental bone marrow transplant research over a 12-year period at the Fred Hutchinson Cancer Research Center in Seattle sued the center, claiming researchers engaged in fraud, violated federal regulations governing the protection of research subjects, and violated medical and research ethics by failing to sufficiently disclose the risks of an experimental treatment designed to minimize the occurrence of graft-versus-host disease. In April, a jury cleared the center and the researchers of misconduct allegations, finding in favor of only one of the plaintiffs.

The jury ruled that the center negligently caused that participant's death by mishandling bone marrow donated by his brother.

• **In 2000,** a group of 380 women sued Tampa (FL) General Hospital for performing medical experiments, including multiple amniocenteisis procedures, on them while they were pregnant, allegedly without their consent.

A key allegation of the plaintiffs was that the consent forms used by researchers contained language not appropriate to the education level of the participants. The claim was for violation of the subjects' right to be treated with dignity and to be free of unwanted treatment. The case was settled out of court.

These cases and others like them are putting increasing pressure on clinical researchers and institutional review boards to improve informed consent processes. But it's important not to allow accusations and media coverage alone to shape research policy, says **E. Haavi Morreim**, PhD, professor in the department of human values and ethics in the College of Medicine at the University of Tennessee Health Science Center in Memphis.

Is too much expected?

Morreim has studied several court cases involving allegations of research misconduct and notes that legal arguments may distort both the actions of investigators and the legal and ethical obligations of both researchers and institutional review boards.

"I have noticed some statements made in the legal allegations that would seem to place unrealistic expectations on institutional review boards," she says.

"For instance, I have seen statements that indicate the IRB is supposed to 'ensure proper reporting' and 'make certain' that the trial conforms to ethical standards. How can an IRB ensure that a PI [principal investigator] does the PI's job of reporting? The only way that an IRB can *ensure* reporting is to look not only at what they receive, but also look over the shoulder of each investigator every day to see what they are doing and match what they are doing with what is being reported. That is beyond any reasonable expectation of an IRB's function," Morreim points out.

Other statements seem to indicate a perceived legal obligation to monitor the day-to-day progress of each ongoing study at their institution — an impossible task.

"I have read statements about the IRB's failure in appropriately monitoring the informed consent process and the conduct of the experiment," she continues. "I wonder, 'What are we expecting here?' I think we need clarification of what IRBs are supposed to do in the way of monitoring."

It's important that investigators and institutional review boards get clarification of their responsibilities from the federal Office of Human Research Protections or the Department of Health and Human Services in this area, rather than the various allegations, legal decisions, and articles covering the disputes, she contends.

A jury may determine that a plaintiff's

allegations are unfounded, or institutions may decide to settle legal cases for financial reasons.

Neither of these scenarios, however, provides an answer for other investigators hoping for guidance about appropriate research conduct, Morreim notes.

"So many of these suits get settled out of court, then you get these 'standards' for what investigators are supposed to do are left lingering out there as though they have validity," she says.

And information published about a case is not always accurate, she has found. "I always caution people to go to the primary sources, whenever possible," Morreim states. "If you want to know about a lawsuit, read what the parties file in court, not what is written about the case later."

Even then, the information may not be as clear.

With regard to the Havasupai case, she says judgments about the quality of informed consent can only be made by someone able to independently look at the informed consent documents and examine the context in which consent was obtained.

"I wouldn't know unless I saw the consent forms themselves and what statements they made about further uses of the material," she states. "And did investigators allow participants to take forms home and study them, or did they ask potential subjects to sign them right away? What language did they use? Was it understandable?"

Populations at risk?

One important function the lawsuits have had, however, is to shine a spotlight on the special challenges of research involving specific groups of people.

It is important for investigators and clinical trial administrators to realize that it's vital they not only adhere to the letter of the law, but the spirit of proper informed consent, says **Dale Hammerschmidt**, MD, an associate professor of medicine at the University of Minnesota School of Medicine and director of Education in Research Ethics and Compliance at the school.

Particularly with respect to the plaintiffs in the Havasupai, concerns about informed consent take on a new light when research subjects are members of a vulnerable population.

Discussions about protection of human subjects, and the federal regulations governing human research protections, have focused on the potential benefits and harms to the individual, and have been more cautions in their consideration of whole populations as units, he says.

However, when investigators conduct research that either reveals information about an entire group of people or holds them up to increased scrutiny or ridicule, informed consent documents that only deal with potential risks to each individual member as a person may be insufficient.

Culturally problematic?

It can still be argued that use of the samples for research that the Havasupai would find culturally problematic, for example, and which still identified them as a group, constituted an inappropriate breach of their right to informed consent, he adds.

"Was there, in fact, an understanding that the samples would *not* be used for something else?" he wonders. "Was information sought or generated that could itself be problematic? For example, did they discover health risks or problems for which there would normally be an intervention?"

Even if the individual members could not be identified in the data or in publications, the group might be identified in a way that created breach of confidentiality or other informational risks, Hammerschmidt says.

The Arizona State researchers gained the approval and cooperation of the tribal government by presenting their research project strictly as a proposal to study diabetes among tribal members, Rosette claims. Tribal leaders never would have consented to the research projects ultimately undertaken.

"Tribal governments are very communal in nature, and they have a lot of power in the community," he explains. "Their approval goes a long way in members' determining what outside projects they will participate in and which ones they won't."

Individual participants did sign consent forms, some of which contained general statements about possible future uses information from the blood samples, but none of which specified what type of research, he continues. And participants were definitely left with the overriding belief that their samples and information would only be used to study diabetes.

The projects involving studies of schizophrenia and inbreeding were offensive and degrading, but members were particularly upset by a project that used the genetic information to argue that the ancestors of the Havasupai crossed the Bering

Strait thousands of years ago. "Those arguments contradict their religious beliefs and are completely disrespectful of their religion and culture," he says.

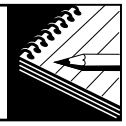
In addition, investigators now cannot determine whether the blood samples were appropriately anonymized after collection because no appropriate mechanism was followed for tracking them. Some of the samples apparently were lost completely, he claims.

The extended use of the information came to light in different ways. Some members of the tribe read publications that published the research results and recognized it was their tribe the articles were discussing. University personnel at ASU discovered what had happened and asked the university to initiate an internal investigation, Rosette says.

The university shared the results of the investigation with the tribe, which then decided to pursue legal action.

"I want to emphasize that we feel the university has been very helpful during this process," Rosette says. "Arizona State has a long history of working with the tribe; it sponsors a program on Indian law; and has a history of being very open and welcoming to Indian students, and in other interactions with the tribe. We don't think this unfortunate situation reflects on the environment at the university at all." ■

GUEST COLUMN



Experimental devices and clinical trials

Informed consent at heart of lawsuit

By **J. Mark Waxman**, JD
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A report in the March 25 *Philadelphia Inquirer* regarding the use of experimental treatment on an infant in connection with a heart repair highlights a series of issues related to both the use of devices not approved by the Food and Drug Administration (FDA) and, in turn, their use on minors, including infants.

According to the story, parents of a 3-year-old born with Down syndrome and a serious heart defect were offered a stent procedure, following two surgeries to correct an underdeveloped left heart pumping chamber, in lieu of a third surgery to reroute the blood flow. This stent procedure, less invasive than the generally accepted third surgery, was allegedly used on 20 children, but its study and use was apparently not considered part of a clinical trial.

The article claims that some doctors were actually testing whether the third surgery could be omitted. It asserts, however, that "records were being compiled for a study," but no IRB approval was either sought or obtained.[1]

The parents asserted a variety of shortcomings. First, they said that although the manufacturer's patient consent form clearly stated that the device was not FDA approved and could have a variety of potential complications, the consent form was not provided to them prior to the use of the stent. Instead, they assert the consent form was sent approximately one year later, and they were asked to backdate it. Second, they were never told that the stent procedure was experimental. Finally, they alleged the stent might clog that would result in the third major surgery in any event.

These facts raise myriad concerns about the processes and checks and balances that were in place at the hospitals involved in these practices. In particular: Why was this procedure not the subject of IRB review and oversight?[2]

A general definition of a medical device is "any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized." Clearly stents to reroute blood flow would be medical devices.[3]

Unless such a medical device is low risk or

COMING IN FUTURE MONTHS

- Improve staff/investigator education program
- Guidance to follow in managing electronic records
- Ethical use of placebos in clinical trials
- Gene therapy protocols using infectious vectors

substantially equivalent [510(k) devices], it must undergo clinical testing and a pre-market approval process. An investigational device is a medical device that is the subject of a clinical study focusing on the effectiveness and safety of a device, and must meet the requirements established by the FDA for an Investigational Device Exemption (IDE).

From the IRB perspective, devices are categorized as either significant risk (SR) or nonsignificant risk (NSR). For SR devices, both an FDA approval resulting in an IDE and IRB study approval is required. For an NSR device, an IDE application is not required (although abbreviated requirements must still be met).[4]

Sponsors make the initial SR/NSR determination. If a sponsor concludes the device is an NSR device, it provides the basis for that decision to the IRB, including information related to the FDA's assessment of the risks of use if that assessment has been made. The IRB will review all the information available to it to make its own assessment. The SR/NSR assessment will be made taking into consideration the full context of the trial or study in which the device will be used. For example, a surgery necessary to implant a device would form a part of the SR/NSR determination.

If the IRB determines that the study is SR, then it would notify the sponsor and investigator of its decision. They study would then not be approved until an IDE was obtained.

Policy statement on devices

Any hospital engaged in or allowing the use of new devices, those for which there is not an FDA approval in effect, should have in place a policy guiding their use. An appropriate policy would be along the following lines:

A. Any proposed use of an investigational device (ID) must be reviewed by the hospital for scientific [and financial] merit, as well as compliance with all applicable laws; and

B. Any proposed use of an ID shall be reviewed for determination as to coverage prior to their introduction.

References

1. In a subsequent article, it was claimed that the informed consent form had been lost, but was found.

2. The issues raised because infants were involved will be discussed in a later article. *See* also [Kennedy Krieger].

3. See generally 21 CFR Parts 312, 812.

4. 21 CFR § 812.2. ■

Government launches gene therapy web site

The FDA and the NIH have launched a web-accessible database on human gene transfer, called the Genetic Modification Clinical Research Information System (GeMCRIS).

A statement released by the agencies said the system is meant to provide information to the public and to improve the government's ability to monitor adverse events in gene transfer research, also known as gene therapy. Database users can learn the locations of trials taking place, which diseases or health conditions are being studied, and what investigational approaches are being taken.

Furthermore, investigators and trial sponsors conducting human gene transfer trials also will be able to report adverse events using a secure electronic interface on the GeMCRIS system.

For more information, go to www.gemcris.od.nih.gov. ▼

New legislation proposed to increase grant access

Biotechnology firms that have been unable to win Small Business Incentive Research grants due to a technicality in the law might be in the game again if legislation recently introduced in the House makes it to the president's desk.

Rep. Samuel Graves (R-MO.) recently introduced legislation designed to amend Internal Revenue Code language that limits Small Business Incentive Research (SBIR) grants to firms that are 51% owned by individuals who are citizens or permanent residents of the U.S.

At issue here is the definition of "individuals."

Steve Lawton, vice president and general counsel at the Washington-based Biotechnology Industry Organization, says the problem cropped up about two years ago when the term "individuals" was interpreted to exclude venture capital funds, which often heavily fund emerging biotechnology firms.

"That means a lot of our companies were not eligible for the SBIR program because 51% is not owned by individuals," he adds, adding that the Graves legislation resolves that issue.

Lawton notes the language partially was intended to stop a firm that was perhaps a subsidiary of a foreign-based company from accessing SBIR money.

The legislation would allow companies majority owned by venture capitalists to have a chance at SBIR grants. Specifically, Graves' legislation seeks "to permit business concerns that are owned by venture capital operating companies or pension plans to participate in the SBIR program." ■

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. ■

17. According to our article, which of the following is a challenge to conducting research in the ED?
    A. Chaotic, unscheduled nature of patient visits
    B. Lack of stable staffing levels
    C. Lack of administrative support
    D. All of the above

18. Well-controlled, industry-sponsored trials are not possible in EDs because of the chaotic nature of EDs and lack of administrative support.
    A. True
    B. False

19. An investigator may run into trouble with federal anti-kickback laws if the following occurs:
    A. The investigator serves both as a physician to patients and an investigator to the same people when they serve in a clinical trial.
    B. The investigator, who also is a physician, receives incentive pay to enroll subjects in a clinical trial, and the incentive pay is much higher than what the physician's work would warrant.
    C. The investigator offers subjects cash fees for participating in a study.
    D. All of the above.

20. According to our article, a lawsuit filed against Arizona State University by the Havasupai Indian tribe claims that:
    A. Researchers collected blood samples from tribal members without informed consent.
    B. Researchers used blood samples collected during a diabetes study in other research projects without the donor's consent.
    C. Researchers refused to allow other researchers to use information obtained from the samples with the tribe's consent.
    D. None of the above

Answers: 17-D; 18-B; 19-B; 20-B