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An essential resource for managers of clinical trials

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Says who? Laws are murky when it comes to surrogate consent

University of California sets model consent policy

Researchers in California have a bit less to worry about when it comes to consent. As of Jan. 1, 2003, there is a specific law to cover who can provide surrogate consent for participation in medical research. The law, AB2328, places some restrictions on the types of sites and the kinds of participants for which surrogate consent is acceptable.

Hot on the heels of the law's enactment, the University of California adopted a new policy on surrogate consent that may become a model for all institutions conducting human research. **(For excerpts from the policy, see p. 28.)**

California isn't alone. Illinois, too, has a law regarding using surrogates to consent to research. Unlike the California law, however, in Illinois, friends or guardians of a prospective subject's estate can provide consent.

The law there also limits the cases in which those who can't consent for themselves can be part of a medical research program. Specifically, legal surrogates can consent on behalf of a subject only if these conditions are met:

• The subject can benefit by participating in the research based on scientific information available and getting consent doesn't do anything to infringe on the proposed subject's rights.

• A protocol has been approved for emergency use, and the subject may benefit from the research.

• The subject has a terminal condition for which all other treatments and therapies have been unsuccessful, and an experimental program may or may not help them.

• The protocol is a last resort to save the life of the subject, and there is no advance directive. Any such directive takes precedence over the surrogate's decision.

At Winthrop University Hospital in Mineola, NY, **Helen Panageas**, IRB director, has been working on its policy for surrogate consent for the last year or so.

"We started by asking other institutions here in New York," she

says, "but we found that almost everyone was lacking a developed policy."

Panageas says she spent a lot of time surfing the web and asking questions based on what she read. One problem she ran into was a state case:

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T.D., et al vs the New York State Office of Mental Health [91 N.Y.2d 860, 690 N.E.2d 1259, 668 N.Y.S.2d 153 (1997)].

In February 1995, the New York Supreme Court found that the office of mental health's research regulations were "invalid and unenforceable" and that the commissioner in charge of the office did not have the authority to promulgate regulations concerning research using human subjects.

"In our state, that means that the state wouldn't say what groups could provide surrogate consent for those who couldn't consent for themselves," she says. At the time, most research institutions were using health care proxies or the DNR (do not resuscitate) advance directive hierarchy of spouse, adult child, parent, or adult sibling.

The case showed there was a problem, and although the state's department of health put together an advisory group to look at the issue of surrogate consent, Panageas says the state has never implemented it.

Taking a wild guess

So, unlike in California and Illinois, institutions in New York are forced to guess what might be good enough, she says.

"I talked to one institution that said they aren't doing any research using populations that can't give their own consent, but I find that really hard to believe. Most, though, just cobble together a policy."

Through her months of research, Panageas found that in many cases, that cobbling involved developing policies that required close IRB scrutiny of any studies that would use these populations.

"They try to determine if the study could be done using another group of subjects," she says. "If so, then the investigators have to use that other group."

If a study must use those who can't provide their own consent, then the IRB will allow the study to move forward, providing there is minimal risk, or greater than minimal risk but with potential direct benefit.

Next, the IRBs would determine whether the principal investigators should get the consent or whether that should fall to someone outside the study, says Panageas.

"The reason for that is they may have a really vested interest in the research and may be less stringent about getting consent," she says. "Not in a malicious way, but subconsciously."

In the end, Panageas formulated a policy that

was based in part on the State University of New York (SUNY) Stony Brook policy. It can be viewed on-line in the university's IRB policy handbook at www.sunyopt.edu/research/docs/IRB.pdf.

It enumerates the individuals who can provide surrogate consent as those who have legal authority to make decisions specifically about participating in research; family members in order of priority; and those named in health care proxies, although those are only for research protocols recognized by the medical community as offering the best treatment choice.

The policy gives the example of the latter as those with rare or aggressive cancers. In those cases, respected medical entities such as the National Cancer Institute recommend being part of research protocols as the best option.

If a patient has the ability to consent but may lose it, as with a dementia patient, the IRB at SUNY Stony Brook recommends that a formal surrogate be discussed with the subject early in the process.

The policy notes that the surrogates have to be told explicitly that they should make their decisions based not on their own beliefs, but reflecting what the subjects would think if they could make their own decisions. If that's not possible, then the surrogates must consider only the best interests of the patients.

Even if the subject can't consent initially, the policy states that the patient should be reassessed regularly throughout the study. If the capacity to consent is regained, then the patient should be given the information about the study as in an initial consent and be given the opportunity to quit the protocol.

Problems come from the top

One of the reasons the issue of surrogate consent is something of a hot topic is that there is little guidance from federal regulators. All the federal regulations state is that there must be a decision made by a legally authorized representative, "but what that is has to be defined at the state level. If it's not, or if what the state decides is too prohibitive, then what do you do?" asks Panageas.

"What investigators have to remember is that they need to get consent from someone who can give it," says **J. Mark Waxman**, JD, general counsel at Care Group Healthcare System in Boston.

"But what federal law doesn't specify is how you determine whether a specific adult is capable of being informed enough to give consent."

With vulnerable populations — children, pregnant women, prisoners, etc. — there are special provisions. "But when you have diminished capacity due to a disorder like Alzheimer's, drug abuse, or some degenerative disease, they may have diminished capacity that is still good enough to make a decision," he adds.

Determining capability to give consent

The responsibility must fall on the investigator and the IRB to make that determination.

Waxman gives two examples from his system's own experience. "Suppose you want to do a trial on a new drug for Alzheimer's or dementia patients. The question comes up when the study is being presented to the IRB about how you determine whether people can give consent or not. There may be some standards that the IRB can impose that say a subject has good enough understanding," he says.

"There are tests that you can give. And you may find people who can determine if they wish to be operated on or not, but they can't balance their checkbook any more. The IRB can determine what level of score potential subjects must achieve on these tests to participate, and at what level surrogate consent must be sought," Waxman explains.

Some samples of these tests that determine decision-making capacity are available at http://irb.ucsd.edu/decisional.shtml.

Another example, he says, involves a study that only can be performed on people having heart attacks.

"If you say to a heart attack patient, 'Be in my study,' would that person be able to make a rational decision? My gut instinct when this came up was no. But this kind of study can only be done on this class of people. In addition, people give consent to all sorts of procedures when they are in that condition.

"They say yes to procedures, medications, and even surgery. How is being in a study any different? If someone is informed enough to consent to having an operation, maybe that's good enough," he adds.

Waxman says some areas of the federal government are making progress in coming up with hard-and-fast guidelines. The Veterans Health Administration came out with a new handbook on human subjects research in July that devotes

an entire section to surrogate consent.

The new policy states that surrogate consent can come from a health care agent appointed by the patient in a durable power of attorney for health care; court-appointed guardians; or next of kin in this order: spouse, adult child, parent, adult sibling, grandparent, or adult sibling. Those are the only surrogate entities that can provide consent for research purposes in the VA. "I think it's a pretty good list," Waxman adds.

Laws must not be pre-empted

The policy also outlines when surrogate consent can be accepted, and — just to muddy the waters — it notes that other federal, state, or local laws can't be pre-empted by the policy.

There will always be murk in this topic, though, says Waxman. For example, if you are doing research with children, do you need consent from one parent or two? The federal regulations say one, but some states may require two. And in this day and age, what defines parent? If a grandparent has been raising her grandson as her own for a dozen years and is the only parent that child knows or has contact with, can the grandparent make decisions on whether the child should be in a research study? he points out.

Waxman says the best thing an IRB can do is bone up on the state and federal regulations. Reading something like the *Belmont Report* (available on-line at http://ohsr.od.nih.gov/mpa/belmont.php3) might help.

(Continued on page 30)

Policy on Surrogate Consent for Research — Excerpts

IN A NONEMERGENCY ROOM ENVIRONMENT:

Surrogate consent may be obtained from any of the following potential surrogates who has reasonable knowledge of the subject, in the following descending order of priority:

1. The person's agent designated by an advance health care directive.
2. The conservator or guardian of the person having the authority to make health care decisions for the person.
3. The spouse of the person.
4. The domestic partner of the person as defined in Section 297 of the Family Code
5. An adult son or daughter of the person.
6. A custodial parent of the person.
7. Any adult brother or sister of the person.
8. Any adult grandchild of the person.
9. An available adult relative with the closest degree of kinship to the person.

IN NONEMERGENCY ROOM SETTINGS:

No surrogate consent may be utilized if there is a disagreement whether to consent among the members of the highest available priority class of surrogates, (e.g., where two members of persons in the highest of categories 5 through 7 disagree and there is no person in categories 1 through 4 available.

The investigator is responsible for ensuring that the surrogate:

- has reasonable knowledge of the subject;
- is familiar with the subject's degree of impairment;
- is willing to serve as the substitute decision maker;
- understands the risks, potential benefits, procedures, and available alternatives to research participation;
- makes decisions based on the subject's known preferences, and where the subject's preferences are unknown, makes decisions based upon the surrogate's judgment of what the subject's preferences would be.

IN BOTH A NONEMERGENCY ROOM AND AN EMERGENCY ROOM SETTING:

- The surrogate shall complete the "Self-Certification of Surrogate Decision Makers for Participation in Research" form as an attachment to the informed consent document for the research study. **(See sample form, p. 29.)**
- Surrogates are prohibited from receiving any financial compensation for providing consent. This does not prohibit the surrogate from being reimbursed for expenses the surrogate may incur related to the surrogate's participation in the research.
- Potential surrogates must be advised that if a higher-ranking surrogate is identified at any time, the investigator will defer to the higher-ranking surrogate's decision regarding the subject's participation in the research.
- For nonemergency room environment research only, if the potential surrogate identifies a person of a higher degree of surrogacy, the investigator is responsible to contact such individuals to determine if they want to serve as surrogate.

Sample Surrogate Self-Certification Form

Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research

Section 1:
I am willing to serve as a surrogate decision maker for _____
(Potential Subject)

to participate in _____
(Title of research project and IRB #)

research conducted by _____
(Principal Investigator)

Section 2:

Category of Potential Surrogate	**Check ( ) the category that best describes your relationship to the potential subject:**	**For the categories listed above yours, provide the name(s) of other relatives. *(For example, if you are the adult son or daughter of the potential subject, provide the names of adults, if any, who are best described by categories 1-4 only)***
1. Agent named in the potential subject's advanced health care directive.		1. _____
2. Conservator or guardian of the potential subject, with authority to make health care decisions for the potential subject		2. _____
3. Spouse of the potential subject.		3. _____
4. Domestic partner of the potential subject		4. _____
5. Adult son or daughter of the potential subject		5. _____
6. Custodial parent of the potential subject		6. _____
7. Adult brother or sister of the potential subject		7. _____
8. Adult grandchild of the potential subject		8. _____
9. Adult whose relationship to the potential subject does not fall within one of the above listed categories and is best described as: _____ (Example: cousin, aunt, etc.)		9. _____

Section 3:
The following section information must be completed only for surrogate consent to participate in research in non-emergency settings:
(Check the statement which best describes the basis of your knowledge of the potential subject)

_____ I live with the potential subject and have done so for _____ years.

_____ I have discussed participation in research with the potential subject and believe that I can carry out his/her preferences.

_____ Other (please describe): _____
_____

Section 4:
Potential Surrogate's Contact Information:

Name: _____
Address: _____
_____

Home Phone: ( ) _____
Work Phone: ( ) _____
Cell Phone: ( ) _____
E-mail: _____

_____ ___/___/___ _____ ___/___/___
Signature of Potential Surrogate Date Signature of Witness Date

UCOP Office of Research Policy & Development

Source: University of California, San Francisco.

Further Resources

Sample forms and policies:

- http://irb.ucsd.edu/UCOP_SurrogateConsentGuidance.pdf
- ors.bsd.uchicago.edu/HS/surrogate_certification.doc
- www.va.gov/publ/direc/health/handbook/1004-1hk1-29-03.pdf
- www.hsrd.research.va.gov/publications/internal/consent_primer_final.pdf
- www.va.gov/publ/direc/health/handbook/1200-5hk7-15-03.pdf

Suggested readings:

- National Library of Medicine. *Current Bibliographies in Medicine* 99-3**:** Ethical Issues in Research Involving Human Participants and covers articles and books through 1998. www.nlm.nih.gov/pubs/cbm/hum_exp.html.
- Bramstedt KA. Questioning the decision-making capacity of surrogates. *Intern Med J* 2003; 33(5-6):257-259.
- Luce JM. California's new law allowing surrogate consent for clinical research involving subjects with impaired decision-making capacity. *Intensive Care Med* 2003; 29(6):1,024-1,025.
- Luce JM. Is the concept of informed consent applicable to clinical research involving critically ill patients? *Crit Care Med* 2003; 31(3 Suppl):S153-160.
- Chen DT, Miller FG, Rosenstein DL. Enrolling decisionally impaired adults in clinical research. *Med Care* 2002; 40(9 Suppl):V20-9.
- Rich BA. The ethics of surrogate decision making. *West J Med* 2002; 176(2):127-129.
- Koppelman ER. Dementia and dignity: Toward a new method of surrogate decision making. *J Med Philos* 2002; 27(1):65-85.
- Stineman MG, Musick DW. Protection of human subjects with disability: Guidelines for research. *Arch Phys Med Rehabil* 2001; 82(12 Suppl 2):S9-14.
- Sugarman J, Cain C, Wallace R, et al. How proxies make decisions about research for patients with Alzheimer's disease. *J Am Geriatr Soc* 2001; 49(8):1,110-1,119.

"You really just have to make sure you pay special attention when you are dealing with any vulnerable population," he says, whether they are those with diminished capacity, children, prisoners, or those who are economically and educationally disadvantaged. ■

FDA says off-the-shelf should be on the record

More should be filing IND applications

Too many research studies in this country are using experimental substances in human subjects without the oversight required by federal law and now can expect to undergo heavier scrutiny, say authorities with the U.S. Food and Drug Administration (FDA).

"Any substance that is not already marketed and is used in such a way as to affect the structure or function of the body is an investigational drug, and should have an application filed with us. That includes a lot of stuff that we know now we are absolutely not getting," advises **Robert Temple**, MD, associate director of the Center for Drug Evaluation and Research (CDER) at the FDA.

"We realize there is a lot of confusion in this area, and we are in the process of writing guidelines to clarify and make the regulations less confusing," he points out.

Following the death of a study subject at Johns Hopkins University in Baltimore, the FDA cited researcher Alkis Togias, MD, for ignoring basic safety rules during the trial and for not filing an investigational new drug (IND) application for the substance used.

In June 2001, Ellen Roche, a healthy 24-year-old, died after inhaling the chemical hexamethonium during a study designed to help researchers better understand the underlying causes of asthma attacks.

Roche was told to inhale the chemical — a known lung poison — so that researchers could see how her lungs reacted. Instead, the chemical severely damaged her lungs, leading to her death.

In its March 31, 2003, warning letter to Togias, federal officials said the study's consent form did not adequately warn Roche of the risks involved — two prior subjects had experienced adverse reactions, and the chemical involved was known to have toxic effects on the lungs, was not an approved medication, and was a chemical grade labeled for laboratory use only.

The agency also cited Togias for failing to notify the IRB and obtain its approval for changing both the dose and method of delivery for the experimental substance. (The full text of the

warning letter is available on the web at: www.fda.gov/cder/warn/ 2003/02-hfd-45-0303.pdf.)

Of interest to many other institutions, however, was the agency's ruling that Togias and colleagues should have obtained IND approval from the FDA before proceeding.

Currently, many researchers are using unapproved substances in human subjects without such oversight at all, says **Adil E. Shamoo**, PhD, a professor at the University of Maryland School of Medicine in Baltimore and co-founder of Citizens for Responsible Care and Research, a nonprofit group dedicated to improving protections for human research subjects.

"They are doing it when they think it is required, I don't doubt, but there are situations where it is not clear what is required and there is a lot of confusion," Shamoo adds.

When you need an IND

Researchers frequently take familiar substances off the shelf — chemicals not previously thought of as drugs — and use them in human research subjects without filing an IND application.

Sometimes, the experimental substances are ones that occur naturally in the human body and are thus thought of as safe, Temple explains.

However, a plain reading of the federal regulations enforced by the FDA stipulates that these substances should be considered experimental drugs when used by researchers to alter the functioning of the human body, Temple says.

These substances are, in fact, covered by the regulations governing experimental drugs, regardless of what researchers inform participants about in consent documents.

Medications already approved by the FDA and marketed are exempt from the rules — but this exemption only applies to the version of the drug that is actually on the market, Temple emphasizes. The same substance, or medication, in a different form, is an investigational drug.

"We know that not everyone realizes that and we know that we haven't really pushed hard in the past," he adds.

The death at Hopkins convinced the agency the time had come to crack down on this practice.

"We don't want to disrupt the whole research enterprise, and we know that many academic centers are going to be troubled if it turns out that every one of their studies should have had an IND application," he says.

"But we don't want to see any more disasters. We really didn't like what happened at Hopkins. A person died, for goodness sake. That is where we are. That is why we are looking at it," Temple explains.

Shamoo says federal laws governing use of substances in human subjects should be even stricter.

Under current federal law, only studies receiving federal funding or those covered by an IND application are subject to federal rules governing protection of research subjects.

Studies not involving investigational drugs or supported with federal dollars are subject to no federal oversight and do not have to be approved or monitored by an IRB.

"My attitude is that all chemicals introduced in human subjects ought to go to the FDA," he says.

"If I were advising IRBs and research universities, I would say that whenever they are using a chemical in human subjects, they should get FDA approval by filing an IND."

Shamoo notes that the FDA has sufficient authority under current federal law to require this level of compliance, but his opinion is not universal.

The CDER currently is drafting guidance for research institutions about when it is necessary to apply for an IND permit, Temple says.

The agency wants to find a way to offer maximum protections for research subjects without a massive interruption in critical medical research, he adds.

"There are some kinds of things that you don't worry much about. Already, for example, there is a separate rule that relates to radioactive tracers," he explains.

"There is a whole section of the regulations that allow people to test those, because they are not expected to have any pharmacologic effect on the body at all. You can run those through radioactive drug review committees, and never send it to us.

That is because we have concluded that if the appropriate criteria are met, there is really no risk. One of the things we are thinking about in this instance is, are there various categories of substances that might be treated the same way?" Temple asks.

In the meantime, CDER has a hotline that researchers and institutions may call to inquire whether a proposed protocol requires IND approval. The compliance number at CDER is (301) 594-0054.

The confusion over investigational substances is just one in a long list of dangers faced by human research subjects, Shamoo says.

He says he hopes that the attention generated by the Hopkins case will lead not only to increased IND scrutiny, but also to reform of federal law.

One set of rules should apply to all research studies involving human participants, whether federally funded or not, Shamoo adds.

"This is already the case, believe it or not, with animals. Any research involving animals is regulated by one law, the Animal Welfare Act of 1966, regardless of the source of the funding.

"Whereas, in humans if it is federally supported or if it is an IND application, the rest is unregulated, which doesn't make any sense. And that is what I would like to see changed," he points out. ■

Budget pitfalls can lead to monetary shortfalls

Don't underestimate trial's true costs

Before any clinical trial gets under way, the principal investigator and study coordinator must prepare the trial budget, ensuring not only that the investigators and staff have spending guidelines, but also that the site can support the work the trial will require.

Too many times, say experts, sites sign a contract to conduct a trial for a rate far less than what the trial actually costs.

"Most people budget for the best-case scenario, when they should budget for the worst-case scenario," says **Curtis Meinert**, PhD, director of the Center for Clinical Trials at Johns Hopkins Bloomberg School of Public Health in Baltimore.

"People are afraid to budget for that because they're afraid the sponsor will tell them to go fly a kite. They think, 'We'd better not ask for what we need; we'd better ask for what we can get.' But I keep telling people, they might give it to you for what you're asking for, and then you've got to do it. Ultimately, the world doesn't care whether or not you had enough money, they care whether you did a decent job," he explains.

Underestimating the amount of clerical and administrative support a trial will require, and miscalculating the costs of research staff and follow-up are just some of the common mistakes researchers make when preparing a budget.

Examining the pitfalls

The key pitfalls in clinical trial budgeting are as follows:

• Performing a less-than-substantive review of the study protocol.

Sure, participating in a multicenter trial of a promising new drug may seem simple, but what does it really involve?

Study coordinators and the principal investigator (PI) must get together and read over the protocol thoroughly to determine exactly what the trial will entail.

Ask these questions:

— Will the study be short-term or long-term?

— Is there one application of treatment or several?

— What kind of follow-up will be required?

— What kinds of tests, procedures, and lab work will be required, and who will conduct the collection of samples and the clinical assessments?

— How much should each staff person be paid for the time spent on the trial?

— How much time will each assessment take?

— If it is a multicenter trial, how much of the data analyzing and processing will be done locally and how much at a central location?

— Will any lab tests be performed at a central lab, or is your facility responsible for them?

Budgeting is an art, not an exact science, Meinert points out. It's important to get information and input from both the coordinator and investigators.

The study coordinator

Although the PI will be aware of the costs of the clinical aspects of the trial, it is the study coordinator who is responsible for the logistics, he notes.

After reviewing the protocol, the coordinator and / or study team needs to calculate the trial's direct costs.

Those include: patient visits, procedures, and lab tests, transportation of specimens and reports to other locations, and the personnel compensation for researchers and other staff.

A comprehensive method for determining the

cost of all services and procedures will help ensure nothing gets left out.

In developing the budget, the study team should make a list of all the procedures, assessments, and tests that will be needed for each subject. The coordinator can obtain a per-item cost for each service or procedure, then multiply by the expected number of times the test or service will be offered to each enrollee, and then by the number of enrollees.

Hospitals and other facilities usually have reference guides listing the itemized prices for each lab and patient care procedure.

Patient billing and laboratory management personnel are also sources of cost information. The totals for each procedure, test, and service should then be added up to determine a total.

Too much is as bad as too little

• **Underestimating administrative costs.**

If a PI primarily prepares the budget, he or she may underestimate the costs of providing the needed data processing and analysis, Meinert explains.

"Most people, when they think about budgeting, think about what they need in order to enroll a person, see a person, examine a person, collect data on a person, and get the lab tests done, and various other procedures," he says.

"But they often forget what else is needed to support a trial. A rule of thumb I use is that you have to think of 10%-20% of the overall budget will be related to aspects of processing: data processing, harvesting of data, assembling of data into databases for analysis, editing of data, and so on," Meinert continues.

The study coordinators should prepare a budget that includes compensation for the principal investigator and study coordinator at a minimum, and then a research assistant or data management support staff, if possible, he adds.

• **Overestimating the number of subjects.**

Meinert recommends always planning for a lower number of subjects than a site feels that it is likely to enroll, he adds.

"Sometimes, it seems that you start a trial and all the patients disappear," he says. "In the planning stages, you expect to find all kinds of people — you say, 'We see these cases all the time, of course we can enroll people.' But you start the trial, and that number is a lot lower because of all the exclusion criteria."

If, as is often the case, the research contract calls for a per-subject payment rate, then low enrollment will obviously hurt the site's ability to support the study.

• **Underestimating the time it will take.**

Obviously, the coordinator should consider the amount of time each clinical encounter with each subject will take and include the costs of the visits and the clinician's time in the budget. But what if, as inevitably happens, the visits take longer than expected?

"If the PI gives an estimate of spending one hour with a patient, I go ahead and usually budget for 1½ hours to make some breathing room," says **Ramesh Gunawardena**, manager of clinical research operations at Beth Israel Deaconess Medical Center in Boston.

Depending on the type of trial, different subjects may require a different number of visits. A patient enrolled in an oncology trial will go through the cycles of receiving the study drug until his or her disease progresses past a certain point. Different subjects will require more or fewer treatment cycles to reach the same endpoint.

Aside from budgeting for the time the actual subject visits will take, coordinators also often forget to consider the amount of time it may take to provide all of the documentation needed.

For example, some studies have complicated patient encounter forms, or long forms for reporting adverse events. When the coordinator reviews the study protocol, he or she should pay attention to whether these forms are simple and easy to understand and fill out, or whether they look like they will consume a significant amount of time.

Study coordinators also often don't budget enough time to follow the patients after treatments have ended, adds Meinert.

Is your personnel budget sufficient?

• **Skimping on personnel.**

Of course the biggest expense in any clinical trial will be the personnel — physicians, nurses, and technicians who see and manage the subjects, and the coordinators who manage the trial and data. If a trial gets into financial trouble, it will be this area that will be hit the hardest.

"Whenever there is a budget problem, it seems they always think they can balance the budget with the equivalent of reducing photocopying or not spending so much on postage," Meinert says.

"But if you are ever going to reduce a budget,

you're in the clinical trials business, you've got to reduce people, that is where 90% of the cost is," he adds.

Many clinical trials determine personnel compensation based on the number of patients expected to be enrolled. For example, the trial could be scheduled for a year, notes Beth Israel's Gunawardena.

"The PI gives a number of patients he can see over that time and the percent effort he and his staff will be spending on that trial," he explains.

"He informs us that he can enroll and complete 'x' number of patients that year. Then we take the total personnel cost of running the trial and divide it accordingly to get a per-patient amount that is related to personnel compensation. The PI and staff would be compensated on that amount of patients."

If over the course of the study they realize that the number of patients is going to be less than anticipated, they try to make adjustments at that point, he says.

"Sometimes, we catch it early and are able to negotiate with the funding company;, and sometimes, it is not caught until the end of the trial. By then, the trial is running in the red and is not beneficial to the hospital," Gunawardena points out.

One way to circumvent this is the PIs' willingness to take a pay cut because the study is of important scientific merit.

Some budgeters, however, prefer to calculate the coordinators' compensation separately from the PI's, by calculating the percentage of the coordinator's time that is expected to be devoted to the trial and calculating a percentage of the coordinator's total salary.

Don't forget about the costs of benefits

However, our experts warn, it is essential to also calculate the cost of any fringe employee benefits. The trial budget must absorb these as part of the compensation due to the coordinator and other personnel.

This can be accounted for by calculating the percentage of the coordinator's total time devoted to the trial, taking that percentage from his or her overall salary, then calculating the value of the coordinator's benefits (accrued vacation time, holidays, sick leave, etc.) and determining what percentage of the coordinator's overall salary this amount represents.

Adjusting for the time spent on the clinical trial, the percentage of the coordinator's benefits should be added to the base salary for the clinical trial to arrive at a budgeted amount for coordinator compensation.

For example, say a coordinator's base salary is $50,000. Adding up all of the coordinator's duties for the trial and the time it is expected to take over the course of a year, subtract that time from the total number of hours the coordinator works (40.0 hours per week, 10 hours each week devoted to the trial).

You should be able to calculate a percentage of the coordinator's salary that will be covered by the trial budget (in the above case, 25%). The salary attributed to the project would be $12,500. If the employee's annual benefits amounted to the equivalent of $10,000 compensation, then $2,500 would be attributed to the trial budget. Total coordinator salary for the trial would be $15,000.

Insurance issues

• Not knowing what procedures are billable to third-party payers and which come out of the budget.

The Centers for Medicaid & Medicare Services (CMS) has solid guidelines on what procedures are considered medically necessary and able to be billed to third-party payers and which are not and must be paid for by the study if performed.

Procedures and services that the subject would receive in the normal course of treatment for his or her illness can be billed to third-party payers. But experimental drugs, procedures, or extra visits or tests that are part of the clinical trial must be paid for separately.

"There are certain things that you do for subjects that are independent of the trial, that you would do as a normal part of caring for that person, so a lot of those things are billable," Meinert explains. "You don't have to budget for treatment, but you budget for things that are over and above what you do to care for them."

Coordinators must go over the trial protocol and determine what evaluations, tests, services, and procedures are included in the normal care of patients with the specific condition.

The definition of normal care is what CMS and the patient's payer determine. They must know and budget for the patient encounters, test, and procedures that are outside the scope of normal care.

It's important to note that even a covered

medical service might not be covered for the trial if the protocol requires that the service be performed at a specific time or more frequent time intervals, he adds.

Travel and incidentals

• **Forgetting about travel/transportation.**

If a site is participating in a multicenter trial, the coordinators and investigators must meet at some point during the course of a trial, and the travel costs (hotel, food, air, etc.) will come out of the trial budget.

A single-site study is no problem — all participating staff can get together in the office.

"If you've got 18 clinics participating in a study, then you have to have someplace where you can all meet," Meinert adds. "You have to travel; you've got to see the whites of their eyes."

The budget should also include items such as transportation costs for subject follow-up visits, parking stickers, cab vouchers, etc., and the costs of transporting some study information to other sites (e.g., X-rays obtained at other sites and sent to your location, or information collected at your facility that needs to be sent out).

For example, studies of pulmonary function may require that chest X-rays be sent to a central radiologist to be interpreted. There may be additional charges — above the cost of the X-ray itself — for copies to be made and sent out.

• **Not calculating indirect costs.**

Coordinators must also remember that part of the overhead for their facility should be included in the budget for the clinical trial as indirect costs. Indirect costs of the trial cover such things as use of office space, telephones, computer time, electricity, etc.

Overhead charges are normally set by policy at each institution and are calculated at a percentage of the direct costs of each project.

The study coordinators need to know what their institution's policy is and what percentage of their direct costs to add to the budget to cover indirect expenses. ■

Privacy requirements give researchers fits

Confusion in research circles over privacy requirements under the Health Insurance Portability and Accountability Act (HIPAA) is evident in a flap at the Johns Hopkins Medical School in Baltimore, which sent a letter to the Department of Health and Human Services (HHS) asking whether it could request patients' permission to use their medical records for research.

The *Baltimore Sun* reported that the university was seeking a waiver to the privacy rule for its research, even though the rule does not require researchers to inform patients whose personal health information they are looking at, as long as an institutional review board backs the research.

Two days later, the newspaper backed away from its story, saying the medical school was not asking patients to yield any privacy protections.

Officials of the medical school say they contacted HHS because they wanted to ask patients up front for their permission to view their medical information.

They said they decided to approach the government agency in response to a growing number of complaints from patients who had been called by researchers and asked to participate in a study.

The school's leadership thought that in light of the increased patient sensitivity to privacy concerns, it would be better to ask them for authorization up front.

Observers of the confusion say Hopkins is to be commended for trying to find the best way to manage the situation, and note that the rule has a lot of ambiguities and institutional review boards may be taking an overly cautious approach. ■

COMING IN FUTURE MONTHS

- Recruiting trial subjects
- Special handling of student volunteers
- Financial conflicts of interest
- Data safety monitoring boards/Data safety monitoring plans

CE/CME objectives

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

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*

For more information about the CE/CME program, contact customer service at (800) 688-2421. E-mail: customerservice@thomson.com.

9. Illinois law allows for surrogate consent in which of the following circumstances?
   A. A protocol has been approved for emergency use, and the subject may benefit from the research.
   B. The subject has a terminal condition for which all other treatments and therapies have been unsuccessful, and an experimental program may or may not help them.
   C. The protocol is a last resort to save the life of the subject, and there is no advance directive.
   D. All of the above

10. Federal regulations stipulate that off-the-shelf substances should be considered experimental drugs when used by researchers to alter the functioning of the human body?
   A. True
   B. False

11. University IRBs have jurisdiction over off-campus investigators recruiting students in what situations?
   A. They have the same jurisdiction as the study IRB.
   B. They have limited jurisdiction to review recruitment tools.
   C. They have no legal jurisdiction
   D. None of the above.

12. According to our article, administrative costs for a clinical trial will be what percentage of the total budget?
   A. 15% to 30%
   B. 10% to 20%
   C. 30% to 40%
   D. Less than 5%

Answer Key: 9. D; 10. A; 11. C; 12. B.