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An essential resource for managers of clinical trials

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Improve public knowledge and trust through communication

Clear info about benefits needed

In these days of negative headlines about research and the pharmaceutical industry, it's essential that clinical trials offices, IRBs, and research institutions join together to improve public education and trust about how research is conducted and the benefits it brings to society, several experts say.

Bad news is cyclical, and it appears the research industry is entering another period of increasing public distrust. Consider these recent events:

• After Merck & Co. recalled its best-selling painkiller Vioxx (rofecoxib) because of cardiac risks, newspapers reported a safety reviewer at the FDA had warned the pill was too risky. *The Lancet* reported in early November that a cumulative meta-analysis of rofecoxib studies demonstrates it was evident in 2000 that the drug had unacceptable cardiovascular risks.

• There have been a number of books recently published that are critical of the pharmaceutical industry: For example, Marcia Angell, who worked at *The New England Journal of Medicine* for two decades, wrote a book titled *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*, published by Random House in August. Another book that finds fault with the pharmaceutical industry is *The $800 Million Pill: The Truth Behind the Cost of New Drugs*, written by Merrill Goozner, and published this year by the University of California Press.

• *The Washington Post* reported Oct. 30 that the Environmental Protection Agency (EPA) has accepted $2 million from the American Chemistry Council to help fund the Children's Environmental Exposure Research Study (CHEERS) to investigate the impact of household pesticide exposure on 60 infants and toddlers in Duval County, FL. According to the newspaper, some EPA officials are concerned about the ethics of the study since it essentially will pay families $970 plus children's clothing and a camcorder to purposely expose their young children to pesticides, which may have no potential benefit for the subjects. EPA officials defend the study, saying that while it's acknowledged that pesticide exposure has been linked to neurological problems, birth defects, and lung damage, the impact of how the

bodies of young children absorb harmful chemicals is little known.

• The CDC announced in October that there would be a shortage of doses of influenza vaccine this year because the Chiron Corp. announced that none of its product would be available this flu season. News reports claimed this would cut the expected supply in half and make the United States one of the only industrialized nations to have fewer than the number of necessary doses. Some reports blamed the FDA's regulations regarding vaccine trials and the approval process and vaccine manufacturers' fear of lawsuits for the conditions that led to a shortage.

Every few years, there are media reports of a research project that has failed in some way or may have betrayed public trust; these can affect how the research community is perceived by the public. When this happens, it puts more pressure on researchers to educate the public about their work, experts say.

Statistics measuring public trust of information received from clinical research professionals show a trend in the wrong direction, says **Roni Thaler**, president of the Center for Information & Study on Clinical Research Participation in Boston.

"Over the last six years, the public's trust of information from the research community has decreased dramatically," Thaler says. "There also has been a lot of negative press about clinical research and public health issues like Vioxx and the flu vaccine."

The research community has done too little to counter the negative publicity, Thaler and others say.

"What continues to happen is that researchers come into a community, wanting something from that community, but they aren't interested in a dialogue with that community," says **Deborah Collyar**, president of Patient Advocates in Research in Danville, CA.

Some researchers have done a good job of connecting with communities, including the African American community, by visiting with churches and identifying community leaders and health advisors, she notes.

"They need to identify those people and engage them in dialogue so they can tell researchers what are the needs of that community," Collyar suggests.

Research institutions and IRBs should employ this type of strategy and others even when it's not for the purpose of recruiting subjects among a certain community, the experts note.

"What we believe is it's important to increase awareness about clinical research and the role it plays in our national health, as well as to educate and inform the public and patients, so when they are given the option of taking part in a trial, they're more informed and educated about the

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process and can make the best decisions for themselves, along with their physician," Thaler says. **(See story on specific strategies for educating the public, right.)**

Groundwork needs to be laid to better inform the public because the old methods of simply worrying about education during the informed consent process do not work very well, she says.

"What we have seen is the education part seems to take place during the informed consent process when data show 45% of people either don't read it or understand it," Thaler notes. "Many times, people are asked to sign the informed consent document when they are ill, and it's a difficult time to achieve a general awareness of the process."

Meantime, statistics show that when people are asked why they don't participate in clinical research, 41% say it's because information about research is difficult to access or is not available, and another three in four people say they have no real knowledge of the clinical research process, she adds.

"So we want to close this gap through education and outreach to the public," Thaler says.

Another good reason for educating the public about research has to do with subject recruitment, which has slowed the clinical trials process in recent years, others say.

"By some measures there are claims that virtually every kind of clinical trial has some sort of time delay directly related to patient recruitment," says **Jeffrey Trunzo**, RPh, MBA, CIP, vice president of Chesapeake Research Review Inc. of Columbia, MD. "These involve two sets of realities: Are expectations set by sponsors realistic to begin with and, secondly, is the public willing to participate?"

Get investigators to go public

The research community has not honed its message well enough, Trunzo notes.

"Part of the message the public is missing is that there's a safety net in terms of what sponsors do to formulate studies and what regulators do to oversee them and what the IRB does to mitigate risk," he says. "I think there's not enough information out there, laying out the system of human research protection in the United States."

For example, clinical trials staff and researchers could speak before public groups about how clinical trials have changed and how there's an important emphasis on prevention, quality of life issues, screening subjects, and, ideally, to identify better treatments for people who have a disease, Collyar notes.

"I really think with the public the only way they're going to be receptive and get used to clinical trials is to let them know there's a spectrum of clinical trials, and these are helping to get better answers more quickly," she says. ■

Strategies for educating public about research

Act locally and nationally, experts advise

Clinical trials offices shouldn't leave the public education work to IRBs and investigators. There's room for everyone to get involved, according to leaders of groups that assist in communication between the research community and the public.

"There are issues in the system that we have to fix," says **Deborah Collyar**, president of Patient Advocates in Research (PAIR) of Danville, CA.

"That's why going to local communities and targeting various populations could be effective," Collyar says. "People need to know more about medical research and what it's about."

Each community is different and so educational approaches should be tailored to the community that is being addressed, says **Roni Thaler**, president of the Center for Information & Study on Clinical Research Participation (CISCRP) in Boston.

She and Collyar offer these suggestions for improving public knowledge about research:

- **Use web sites:** Some research institutions include public information about research on their web sites, and this trend should be increased, they say.

CISCRP has its own web site (www.ciscrp.org/) with many facts and information about the clinical trial process, including information about subjects' rights, benefits, and risks, Thaler reports.

The web site has a revised version of the group's brochure, which is filled with answers to key questions people have about research, and it includes a way for people to sign up if they'd like additional information, such as a quarterly update called "The Participant," she says.

The organization will send distribution material, including brochures and other information about research, to any research institution that supports its work, Thaler adds.

• **Visit health fairs, community events:** "Go to health fairs and community fairs to provide basic education — not to recruit for a specific trial," Thaler suggests. "Also, visit senior centers, speak at the local Rotary Club meeting, speak on local cable television, and make yourself available to local newspapers, which would be happy especially if they have a health section."

Particularly for minority communities, it could be helpful to meet with ministers or to speak on local cable television programs, she adds.

And it's always a good idea to meet with disease-specific societies, professional societies, and support groups, which usually are looking for monthly speakers, Thaler says.

• **Hold seminars, meetings:** Clinical trials offices could hold a series of meetings or speakers bureau events with titles such as "How to decipher the news about cancer." These would attract some members of the community, Collyar suggests.

"This tells people they'll hear about the latest and greatest, and while the solutions rarely are available to someone who goes to the doctor tomorrow, they're important because of leading us to better answers through cancer research," she says.

When speaking about cancer research, for example, clinical trials professionals could highlight some examples of clinical trials that have helped with imaging technology, prevention work, and screening for early detection, Collyar adds.

• **Address physician audiences:** Another strategy is to better educate physicians about the value of research, Collyar says.

Patients most trust their community doctors, and these same doctors sometimes are good sources of information about potential research populations, so clinical trials professionals and research institutions could do considerably more to teach these physicians about the benefits of research and to improve their understanding of human subjects protection, she notes.

Nearly eight out of 10 people surveyed said their personal physician is their No. 1 source of medical information that they trust, Thaler reports.

"So it's important to involve community physicians as much as possible," she says.

Also, clinical trials offices could address a common concern among community physicians about keeping track of their patients when they are referred to a clinical trial, Collyar says.

"Most community physicians want to keep their patients and they want to follow their patients' care," Collyar says. "But if they refer them to a clinical trial, then a lot of times that's the end of their communication with that patient, and so that's an issue that needs to be addressed."

• **Provide educational material in Spanish and other languages as well:** "If your community has Latinos then they'll need materials to be in Spanish," Thaler says.

Likewise, communities with sizeable Asian populations should have research education materials printed in the common languages that are spoken and read in that area, she adds. ■

Improving communication between researchers, IRBs

Recent IRB conference highlighted problem areas

If there was one thing that most people in the research industry can agree upon, it's that communication channels between each part of the industry need to be improved.

IRB members, researchers, sponsors, and others attending the 2004 Annual IRB Conference, held Oct. 28-31 in San Diego, discussed how communication problems contribute to the problem of delayed clinical trials and misunderstandings among people who sometimes fail to remember that they're working toward the same goals. The Boston-based Public Responsibility in Medicine and Research (PRIM&R) sponsored the conference.

"I think the bottom line in terms of sponsor relationships is communication," **Philip Rubin**, PhD, chief executive officer and vice president of Haskins Laboratories in New Haven, CT, told *Clinical Trials Administrator*. Rubin also is a professor adjunct in the department of surgery, otolaryngology at the Yale University School of Medicine in New Haven and a research affiliate in the department of psychology at Yale University.

"It's important to have good communication in the process and to make sure that this communication is nonadversarial," he says. "I have been a researcher, so I know how because of delays and potential misunderstandings, people can get very frustrated and worked up about issues, and the situation can degenerate."

Investigators and clinical trials administrators may believe strongly in protecting their interests during the research process, but simultaneously fail to consider what's most important to the others involved in the process, the experts say.

"Given the different priorities and reward systems in different institutions and companies, negotiators can, understandably, take strong positions on issues, such as confidentiality and data ownership, that get in the way of reaching a win-win agreement," says **Ronald S. Newbower**, PhD, senior vice president for research and technology at Massachusetts General Hospital and vice president for research management at Partners HealthCare System Inc. of Boston.

"The examples that come to mind of situations where communication slowed progress all involve the front-end work of reaching agreement on terms of sponsorship that both the commercial sponsor and the academic institution can live with," Newbower says. "And occasionally, the delays can simply exceed the window of opportunity for participation and enrollment."

Rubin, who had served as director of the Division of Behavioral and Cognitive Sciences at the National Science Foundation (NSF) from 2000 to 2003, has found that researchers often misunderstand the role of government sponsors.

"The first thing the researcher or institution needs to understand is that the role of the sponsor is often constrained because of policy set at the institutional level," he says.

"Say, for example, you're having trouble with your IRB and someone calls the National Institutes of Health to intervene," Rubin says. "That's not something NIH is allowed to do, although you might think NIH can."

Improving IRB relations

Researchers and clinical trials staff also need to make certain they understand the regulations and practices that are relevant to their studies, Rubin says.

It's a good idea to use the university's sponsored research office as a resource for information and guidance, he adds.

Another strategy for improving communication would be to provide formal training in negotiation skills to clinical trials staff, Newbower suggests. "This can be very helpful in preparing staff to see the issues of the other party and to develop creative solutions, or to recognize when they are simply negotiating with the wrong person and need to seek connections with someone more empowered to modify the terms of standard agreements," he says.

Clinical trials administrators and investigators also could improve the process through better communication with IRB staff and members and through a better understanding of what IRBs do, the experts say.

"The major burden of education falls to the IRB staff who have to do a lot of explaining to new investigators to help them understand what an IRB is in the first place and how to interact with the IRB," says **Matthew Whalen**, PhD, co-founder of Chesapeake Research Review Inc. of Columbia, MD.

"When it comes to communicating with IRBs, I think it helps to have a process where nothing ends up in a black hole — there should be some transparency of expectation," says **Jeffrey Trunzo**, RPh, MBA, CIP, vice president of Chesapeake Research Review.

"Too often IRBs don't make their requirements clear, what materials they need to review, what the review process will look like, so folks don't know what to expect and this sets up an uneven dynamic," he adds.

From a purely social standpoint, it's important for clinical trials staff and investigators to make certain their interactions with the IRB are pleasant ones, Rubin notes.

"Try to frame them in a way that sounds conciliatory and brings entities together to see if they can solve a problem instead of just complaining about it," he says. "The ultimate goal is to do good research that protects participants in research."

Also, if there are unexplained delays during the IRB process and an investigator or clinical trials administrator wants to contact the sponsor, it helps to know the appropriate person to contact at the sponsoring agency, Rubin says.

"They'll tell you whether or not there's specific guidance addressing this issue," he adds.

However, the point, once again, is to frame the request in a problem-solving and conciliatory fashion, Rubin suggests.

"Instead of say, 'Wow, I have this problem and you guys have to do the following,' which will never work, you should say, 'Here's the situation, and is there anything we can do to make it better?'" he says.

Federal sponsors often have little flexibility for offering advice or assistance but occasionally there may be gray areas they can help interpret.

For instance, the NSF sometimes saw problems with informed consent among special populations, Rubin recalls.

"There is lot of latitude and flexibility in the Common Rule, but not everybody is aware of it," he says.

Communication also needs to be improved between clinical trials offices and research institutions and physician investigators.

"Research is not easy to conduct; you need a steady stream of investigators. And with them, you need study coordinators," Whalen says.

"The greater problem is turnover: At any given point in time, 60%-70% of all investigators do only one trial and don't do a second one," he notes. "They do one trial and then say, 'I can't do this — it negatively affects my practice,' or, whatever the reason might be, the burden falls to clinical administrators."

Clinical trials offices could try to reduce this turnover rate by assisting in training new physician investigators that a clinical trial involves some different tasks and skills than their patient practice, Trunzo says.

For example, a clinical trial investigator needs to keep up with a considerable amount of paperwork and know research and human subjects regulations, as well as know basic details, such as what a case report form is and how to report data on serious adverse events, he explains.

"Often, these folks look at participating in a clinical trial as a way to supplement their income or reduce their reliance on insurance reimbursement, but they don't realize you have to make an investment in your infrastructure to do it well," Trunzo adds. "You can't just dive in and hope for the best."

Likewise, research coordinators often are overburdened and could use additional personnel help and training, he says.

One industrywide change that may have help improve training and communication is the new focus on credentials for clinical investigators, IRBs, and others, Trunzo adds.

Also, accreditation processes are contributing to better communication, he says.

"Accreditation of human research protection programs is a programmatic effort to make sure all parties understand what is going on in other areas and that they're communicating effectively," Trunzo explains. "And through the accreditation process there will emerge best practices, which will be more widely shared than they have been in the past."

Besides accreditation, another strategy for improving communication and training is to hold educational meetings at which federal research staff are invited to speak, Rubin suggests.

These meetings could include all interested parties, including researchers, participants, IRB members, administrators, community leaders, and institution directors, he says.

Another communication problem area involves IRBs, which need to pay attention to the social impact of proposed new medications, devices, and vaccines, Whalen says.

"So if the clinical trials office and sponsor and IRB could share information along those lines, then that would help us fight the criticism of the me-too drug and device and, 'Why do we need it?'" Whalen says.

Clinical trials offices, along with researchers and IRBs, should make it a goal to improve public trust by discussing their work to the public and educating people about human subjects research protection whenever possible, the experts say.

"The whole purpose of the human research protection program is to improve communications throughout the research enterprise," Whalen says. "The whole notion is to enhance and systemize communications." ■

Brush up on the IRB submission process

Education specialist offers tips

Clinical trials staff and investigators could easily improve the IRB submission process by maintaining a good relationship with the IRB office and members, according to research education specialist.

It's always a good idea to build rapport with the IRB office and to think of the IRB as a service provider that can assist clinical trials staff and investigators in conducting good research and keeping subjects safe, says **Sarah Frankel**, PhD, education specialist at the Human Studies Committee of Washington University School of Medicine in St. Louis.

"Sometimes the way people look at the IRB process and its documentation is that it's just one more hurdle they have to jump through in order to conduct their research," Frankel says. "And yes, it's part of a process, but the real goal of the IRB is to protect the participants in the study, so it's not being done to prevent research."

Keeping this in mind, there are a number of ways the clinical trials office can improve the IRB submission process, including the following:

1. Be proactive. "Call the IRB and ask questions,"

Frankel advises. "Don't wait until you get a letter from the committee."

Clinical trials staff also should familiarize themselves with the entire IRB review process and learn what the board is looking for in a protocol, she points out.

"Here, we're happy to help people understand the process and why there are different processes in place," Frankel says.

"If you have any questions about a trial that may be submitted, the IRB staff are available and willing to talk to you about how to submit through their system," she says. "At Washington University, we spent a lot of time developing forms to guide the submitter through the process."

It's preferable to give IRB staff a quick call with a question than to submit a proposal that may be incomplete or inaccurate, Frankel adds.

It's also a good idea to observe an IRB meeting, which will help clinical trials staff and investigators gain insight into why certain questions arise and who the IRB members are, she adds.

2. Develop a good foundation in research ethics. Clinical trials staff who have a good foundation in research ethics and clinical practice will understand better why things are done the way they are during the IRB review process, Frankel notes. "Having that foundation helps you to know what to expect," she says. "We're fortunate at Washington University because we have workshops and course offerings by the IRB."

And human subjects protection and ethics courses need to be taken by study coordinators, as well as researchers, Frankel says.

"This is so they will understand their role and what's happening and help the investigator that much more," she says.

3. Build bridges between IRB and study coordinators. The IRB should have a lot of contact with study coordinators since this is part of building rapport between the research team and IRB, Frankel says.

This bridge includes an open-door policy in which study coordinators can call the IRB whenever there's a question or concern.

"Principal investigators [PIs] are not always available and many have other duties besides research, so that's why it's important that the study coordinator is well trained," Frankel says.

Also, it helps if a protocol is written with a lay audience in mind, since some IRB members are not scientists and may end up asking more questions if the technical writing of a protocol is too complex, she suggests.

4. Make certain study coordinators do not serve as PI substitutes. One common mistake is that busy PIs will send a study coordinator to the IRB meeting, and this could lead to inadequately answered questions and a delay in approval, Frankel says.

"When the committee invites the investigator to speak, they really want to see the investigator," she explains. "It's all right to invite a study coordinator to come along with the investigator, but occasionally an investigator will send a study coordinator instead."

When the IRB begins to ask questions about the fundamentals of the study including design and methodology, the investigator is the person who will need to answer these items, Frankel says.

"The study coordinator may give an answer, but maybe not give as in-depth an answer as the committee is looking for," she says. "Usually, if the investigator is asked there's a point of contingency that needs to be qualified, and they may need background to clarify a contingency point so they can move forward."

5. Check IRB application to make certain everything is included. Another common mistake is that PIs sometimes forget to include a minor point in their description of a study; this could lead to more paperwork down the road.

For example, a study designed as a retrospective chart review for the years 1999 and 2000 should include both years in the proposal, but perhaps also include 2001 if there's a possibility researchers will want to analyze those data as well, Frankel says. "That's something minor, but any change to your protocol you will want to get IRB approval first."

6. Be very familiar with regulations regarding expedited review and exempt research. "It helps if research staff understand the types of studies deemed minimal risk," Frankel says.

It also helps if research staff understand the policies the IRB has for using the categories of expedited review and exempt research, she adds.

"At some institutions, everything goes to the full board, and other institutions like ours have an expedited review mechanism," Frankel explains. "We have individuals who sit on the full board and are designated to do the review."

Another benefit to learning the regulations is that when research staff begin to look at the types of studies that fit expedited and exempt, they have a better understanding of the study's level of risk, she adds. "Maybe someone expects a study to be a minimal risk study, but the protocol is much more complex than the other ones in that category," Frankel says. ■

Avoid audit trouble by improving processes

Strict accounting system is needed

Investigators sometimes will rely on the old and less detailed way of handling expenses during a clinical trial, so it might be up to the clinical trials staff to make certain everything is done correctly and documented to avoid audit red marks.

Bruce Steinert, PhD, CCRA, director of the clinical trials administration at Children's Mercy Hospital in Kansas City, MO, offers these suggestions for avoiding process snafus that might result in an unfavorable audit:

• **Accurately document all time spent on federal grant studies.** Investigators often are juggling trials sponsored by industry and those sponsored by the federal government, but requirements for keeping track of costs are very different between the two, Steinert notes.

"We deal with commercial sponsors where there's no effort reporting," he says. "They don't care whether you spend one hour or 20 hours because you are reimbursed whatever the agreement says."

However, on the federal grant side, an investigator can only receive up to 100% of the grant, but every penny of time and effort must be documented, Steinert adds.

"Part of your 100% research effort on the NIH side is going to be on the NIH project; but if you spend 25% of your time on this project and 75% of your time doing other things, then all of this has to be accounted for," he explains.

"So if you have an FDA-, industry-sponsored study where you see one patient every few months, how does that get reported back on the NIH grant side?" Steinert says. "And there's another wrinkle: The FDA-type, industry contracts have nondisclosure clauses that prohibit us from acknowledging the existence of the trial, so you are having the conflict of being required to report something you can't report."

The way to circumvent this problem is by naming the industry-sponsored trial in general terms such as saying it's a diabetes study and then naming the amount of time that was spent on it, he notes.

The real problem is that many physicians have no idea how much time they're putting into a particular project because many research institutions do not have a tracking mechanism for breaking down their time between projects, Steinert says.

"Nothing says that on this day you spent five hours working on this project, which went into this account," he says.

So investigators will swipe in a time sheet when they arrive in the morning, but they don't do any other time documentation the rest of the day, Steinert notes.

"We send out forms to them, and they certify how much they did on such and such a thing, but it's only traceable back to their word against anybody else's word," he says.

Steinert once worked with an administrator who used a system where investigators could allocate sections of time to different cost centers on a paper form. Then at the end of the pay period, these forms were scanned into the computer program where administrators easily could see who had worked on which project and for how long.

However, this novel approach didn't last long, he says. "People didn't like coloring in the dots when they could just swipe a card and be done with it."

So the old system prevailed in which investigators often put in the same amount of time for each project each month, Steinert notes.

"It looks funny to auditors, but all we can do is say that's how they reported it," he says.

Although the NIH hasn't made a major issue of accurate effort reporting thus far, every time an NIH official speaks on the topic, the message is that clinical trials offices need to keep track of time and effort, and if an organization is having trouble, that's an area that will be examined, Steinert says.

• **Consider regulatory rules if electronic record keeping is used.** "The NIH doesn't have too stringent a requirement on electronic records," Steinert says. "Whatever works for your hospital system, they're willing to accept, and most do a fairly good job."

However, on the FDA side, clinical trials offices have to contend with CFR 21, Part 11, regarding electronic records and electronic signatures, he notes.

"And at the present time the FDA has pulled their guidance on how to comply with that," Steinert says. "The regulation still is there, but they don't tell you how to enforce it."

And the regulation itself is somewhat intimidating with terms such as "adequate validation and certification," he says.

"I'm logged into a discussion group that does nothing but Part 11 compliance, and every day

there are e-mails about people discussing picky things like page formatting and anticipating what the FDA might want to see at some point," Steinert says. "Our general patient record doesn't have to be Part 11-compliant because that's how hospital general records are set up."

But they do have to meet current needs for Medicare, Medicaid, and industry standards, he says.

"So when the research comes along, it adds another layer of complexity," Steinert adds.

Children's Mercy Hospital has one study subject to Part 11 compliance, and the sponsor has provided the computer, which is totally separate from the rest of the hospital's computer system, he says.

"At the end of the study, the computer goes back to the sponsor," Steinert says. "I'd hate to think that for every study, we'd have to have a [new] computer on site."

On the positive side, Part 11 compliance has been such a problem for the FDA that the agency pulled its guidance and came out with the critical path initiative in which it was intended to adopt more electronic records standards, he reports.

"The original Part 11 regulation was to make electronic records function like paper records," Steinert explains. "The recording data never posed a problem; the problem was tracking changes."

For instance, on a paper form, a person will initial each change so the FDA can come back and see who made the change and at which date and for what reason, he says.

Hospital records, however, don't provide that level of detail. Once a change is made, the old notation is gone, Steinert adds.

To meet Part 11 compliance, there has to be a way to verify that a person had access to the record, changed an item on this date, and this becomes very complex, he says.

• **Keep up with hazardous shipping training requirements.** "In the federal government's regulations, dry ice is considered a hazardous material, and there are hundreds of these shipments on dry ice going across country," he says.

The regulations governing these shipments have training requirements with stipulations that the training be documented and repeated every two years, Steinert notes.

"We talk to people on the loading dock and say, 'We'd like to participate in your training program, and we get a deer-in-the-headlights look,'" he says.

So the solution might be to buy a computer training course and modify it for research coordinators and others who might handle the occasional dry ice or other hazardous shipping material, Steinert says.

Everyone who packs or signs the shipping form needs to take this training, he adds.

"Research coordinators usually are the ones doing this, and it's been a requirement only for the last four or five years," Steinert says. "The regulations do allow for the training to be job-specific, so they don't have to study regulations about shipping on freight cars." ■

Budgeting trouble? Try a budget template

Research institution works toward best practice

One of the more challenging tasks for investigators and clinical trials offices involves developing an accurate budget that captures all that is needed.

Convinced that this process can be turned into a best practice, staff in the Clinical Trials Office of Thomas Jefferson University of Philadelphia have developed a budget template that is intended to help the office achieve three main goals, says **Roseann Talarico**, associate director of the Clinical Trials Office.

The three goals are as follows:

1. Implement a systematic budget system.
2. Ensure proper identification of study-related costs.
3. Facilitate the processes involved in negotiating the sponsor's budget and payment schedule.

"Our budget process was very ad hoc in the past," Talarico says. "Everyone kind of did their own type of budget; or rather, the sponsor presented it, and they just accepted it."

With a systematic budget system, the objective is to negotiate the sponsor's budget and payment schedule, she adds.

Since developing and implementing the new budgeting process, clinical trials administrators have begun to see a more standardized approach to budgeting among investigators as well as other improvements, Talarico says.

It was introduced in September, so it's too soon to note any financial improvements, but anecdotal evidence suggests it's been well received, she adds.

"It's still not mandatory, but what I'm finding is that people are gravitating to it more and more," Talarico says. "Before we began this process, research staff had no idea about all of the start-up

costs, time, and effort that go into the regulatory, administrative, and informed consent processes, and they had no idea they could get reimbursement for their time and work in these areas."

She describes how the institution has created a best practice for creating clinical trials budgets:

• **Begin with a pre-study checklist.** Talarico began by creating a pre-study checklist that assesses the feasibility of doing a pre-study trial. Here are some of the considerations on the checklist:

— Do we have a previous relationship with the sponsor?

— What is the sponsor's reputation with colleagues?

— Do we have access to the right population?

— Is the proposed enrollment goal realistic?

— Is the proposed enrollment period realistic?

— Will enrollment compete with other studies seeking the same patients?

— Are vulnerable populations involved, which take more time?

— Do we expect a significant number of adverse events?

— How ill is this population?

— Is the protocol well designed?

— Is the protocol ethical?

— Is the study question itself important?

— Is the protocol in its final form and how many amendments can be suggested?

— Will the sponsor be open to suggestions or modifications if the protocol is not feasible as written?

— Do we have qualified staff available and training available?

— Is the workload manageable?

— Does the principal investigator have the appropriate time to devote to the protocol and are specialists needed?

— Are there adequate clinic and office space available?

— Does the sponsor expect to audit the study?

— Will electronic or remote data systems be used?

— Will the sponsor's site visits be frequent?

— Is the necessary equipment available to do the study?

— Is the study unusually long in duration?

— Are the case report forms complex?

— Is there a large number of case report forms per subject?

— Are drug eligibility requirements complicated?

"These are hidden costs, and these all fall under the feasibility assessment," Talarico says.

The checklist also would need to assess whether inclusion/exclusion criteria are overly restrictive, resulting in a high screen failure rate, she advises.

• **Develop a budget template.** Talarico developed a one-page budget template that begins with fixed costs and nonrefundable costs, and includes the feasibility assessment, study initiation, capital equipment costs, special supplies, pharmacy, and other fixed costs, Talarico says.

"The facilities and administration rate of 25% goes on top of that," she says. "That's the standard rate you'll find."

Then the template goes into other fixed costs, such as the PI effort, advertising, record storage, monitor visits, post-study coordinator charges, etc., Talarico says.

These costs are refundable, and, again, the facilities and administration rate of 25% is calculated on these costs, she says.

Exempt from the facilities and administrative fee are the $2,000 IRB fee and any other study costs designated by the institution.

The next part of the budget template illustrates the study costs per patient, including the PI effort, clerical effort, coordinator/research nurse effort, pharmacy, radiology, etc., Talarico says.

"On some clinical trials you have to dedicate a clerical person specifically to the trial," she explains.

Finally, the budget template provides a row for the total study budget costs and total study budget per patient costs and a summary of the total fixed costs, study costs, study budget, per-patient cost, direct costs, and facilities and administrative costs.

The budget most be signed by the PI.

• **Present new budget process to investigators and staff.** One of the reasons the clinical trials office staff began to develop a new budget process was because investigators and clinical trials staff too often failed to designate that certain costs were nonrefundable, and this left the research institution to pay for costs that were incurred before a sponsor decided to cancel a study, Talarico says.

"We were burned so many times because sponsors would say they wanted to cancel the study, and we'd have to return all the money," she explains.

So a new budget process was developed to standardize costs across departments and assist the institution in developing and negotiating successful budgets, Talarico says.

"You have to anticipate the unexpected and know what's in your protocol," she says. "This is something that I try to get across to researchers and staff initially — that we have to gather information

and review the protocol in detail to make a complete list of all required procedures, tests, patient visits, etc., regardless of budget types."

Staff training in the new budget process is essential because so much of the success of the budget template is determined by a researcher's or research coordinator's ability to understand what will be required at each patient visit, she says.

"An important indirect cost is actual personnel time and effort extended, and they need a clear understanding of the scope of the study to determine these," Talarico adds.

For instance, there are the PI's time and effort, document reviews, informed consent, study coordinator's time, patient screening, shipping of specimens, vital signs, patient visits, and scheduling to consider when reviewing the protocol, she says.

Talarico developed a study coordinator's time and estimate sheet to help clinical trials staff and researchers determine these staff and procedures.

• **Teach investigators and staff to consider hidden costs.** Examples of hidden costs include unplanned visits or missed visits with subjects, Talarico says.

Also, copies of radiology scans, X-rays, FDA regulations, clinical and nonclinical supplies, such as catheters, office supplies, fax use, telephone calls, mailings, etc., need to be considered, Talarico says.

"You think you put together a budget, but it's extremely complex, and you need to consider fringe benefits, verifying prices," she says.

One way to assist clinical trials staff and researchers with determining hidden costs is to post costs for certain standard items on a research institution's web site, Talarico suggests.

"This way, budget people can extract pricing costs as they are doing their budgets," she says.

Also, researchers and clinical trials coordinators should call various hospitals and university departments to ask about costs of various tasks and services.

One of the most common areas of hidden costs is personnel costs, Talarico reports.

"Even if it's a six-month, double-blind study, the study staff will spend considerable time with start-up costs and will also consider closeout costs, such as data cleanup and queries," she says. "For the closeout, you need to consider the case report entry and filing."

Other hidden costs involve the subjects, such as paying subjects stipends or reimbursement to cover travel and parking costs, Talarico notes.

"Look closely to see how much the sponsor pays for screen failures, because screening may involve expensive tests," she says.

"Sometimes if sponsors come in and present a budget and say it's a fixed budget, I always encourage coordinators to go back and renegotiate if the budget seems inadequate," Talarico says. "Look at their track record of success: If the budget truly is inadequate, then you might have to step away from that study."

• **Analyze proposed payment schedule and its impact.** "Read the proposed payment schedule and understand it and analyze the impact it will have on your study," Talarico says. "If it seems impossible to understand, then start writing your own payment schedule because the sponsor may not understand it either."

She says her philosophy is to ask for an upfront payment payable upon execution of the agreement, which is when both parties sign it.

"This helps you to cover start-up costs, patient recruitment and screening, and to carefully consider the size of upfront payment that you'll need to keep you afloat until the interim payments are due," Talarico explains. "If you don't request this then you're incurring start-up costs before being given reimbursement."

Also, the payment schedule should include details about reimbursement for early termination and interim payments and milestones, she adds.

For example, are payments made when a specific number of subjects are enrolled or when they have been randomized or evaluated, Talarico explains.

"Usually, you have to negotiate these payments to fit the protocol and situation," she says. "About 90% of the work is done in the first few months of a study, and you should be paid accordingly so you have to consider the impact of cash flow."

Also, Talarico stresses to PIs that they should not overestimate their enrollment for the purpose of ensuring successful cash flow because if they

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overestimate, they will lose credibility with sponsors.

Other tips she offers are to keep document tracking and keep track of records that the study monitor reviews to make sure everything is paid correctly.

"And discuss when the final payment will be triggered because the sponsor may want to withhold a substantial portion of the budget until the case report forms are approved, and this could take months," Talarico says. "There would be less motivation for them to pay promptly, so we want to make sure we have that final payment when we complete case report forms and send them to sponsors." ■

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.

The semester ends with this issue. 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. ■

21. What percentage of the public says they have no real knowledge of the clinical research process?
A. 29%
B. 43%
C. 61%
D. 74%

22. According to an education specialist, one of the most important ways research staff could improve the IRB submission process is by doing which of the following?
A. Take a course in human studies protection
B. Be proactive and ask the IRB questions before submitting the protocol
C. Sit on the IRB for a year to learn more about the process
D. All of the above

23. Which of the following is not a best practices goal for a clinical trials budgeting process?
A. Implement a systematic budget system.
B. Ensure proper identification of study-related costs.
C. Facilitate the processes involved in negotiating the sponsor's budget and payment schedule.
D. All of the above

24. Federal regulations require research staff individuals who package and sign shipping items to be trained in hazardous material shipping rules largely because of which hazardous material?
A. Dry ice used in packing items
B. Tissue samples
C. Blood specimens
D. None of the above

Answers: 21-D; 22-B; 23-D; 24-A.

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