THE INVESTIGATOR IS A CRUCIAL PLAYER in helping pharmaceutical companies bring their products to market. BUT SITES, AND THOSE WHO WORK WITH THEM, SAY SPONSORS DO NOT ALWAYS FULLY APPRECIATE THE VALUE OF THEIR INVESTIGATOR RELATIONSHIPS. As a result, more top investigators may be driven out of the industry.

BY KIM RIBBINK

Site Unseen

Uncovering the Concerns of Investigators

Investigators, one of the industry's most valuable assets, face pressures with regard to time, money, and manpower, making their jobs that much harder to perform.

A 2003 Thomson CenterWatch study found that investigative sites are typically taking on clinical projects that require about $4,000 to $6,000 in hidden costs per study that are not being reimbursed by sponsors and CROs. Since then, Thomson CenterWatch's research indicates that there has been some improvement with regard to the costs and profits at sites, with estimated site profits for 2004 up 7.3% from 2002. At the same time, however, many sites are still reporting shrinking margins.

Experts say the problem is, in part, a one-size-fits-all model for reimbursement, which fails to take into consideration site and principle investigator (PI) cost variations. The fact is that in some areas of the United States it costs more than three times as much to profitably build and maintain site infrastructures capable of meeting sponsors requirements.

"Clinical reimbursement is patterned after a model that insurance companies use to compensate physician practices, and that's not necessarily a good model for research," says Dan Ulrey, president and CEO of Midwest Clinical Support Inc.

Additionally, the degree of difficulty in enrolling and retaining patients can differ dramatically in the same disease state, depending on a number of economic factors often overlooked by sponsors and CROs during their investigator identification, selection, and study conduct processes.

Craig Pfister, research program manager at Temple University Office of Clinical Trials, says the degree of difficulty of a trial can dictate different staffing needs and study start-up timelines for an investigative site.

"Industry timelines for investigative sites are aggressive, and consideration is not often given for the complexity of the trial," he says. "An investigative site may need to coordinate and provide training for multiple departments before IRB submission. Yet the timeline is often presented similarly to an outpatient trial."

Experts say problems with the setup and the timelines are causing costs to rise and are forcing many trials to be extended and amended.

"About 90% of the problems that arise could be avoided with clear communications and expectation setting up front," says Thomas Sellig, VP of business development at Ventana Clinical Research Corp.

Those with experience on the sponsor side say improving communications so sites are well informed about a trial and its complexity in advance is an area for improvement.

"From the sponsor's perspective there's an awful lot riding on this," says Frank L. Douglas, Ph.D., M.D., executive director for the MIT Center for Biomedical Innovation. Until his retirement, Dr. Douglas was executive VP, drug innovation and approval, and chief scientific officer of Aventis SA, now Sanofi-Aventis. "At the end of the study, the FDA will select sites that it will audit; and if reviewers find either the investigators or sites did not follow the protocol or there were major deficiencies, then the whole program could well be disqualified. The company stands to lose hundreds of millions of dollars."

The relationship between the site and CRO presents challenges. Since a CRO is entrusted with the stewardship of the clinical trial, CROs tend to be more conservative than sponsors in their decision making with investigators, which can create challenges between sponsors and sites, says Tom Wardle, senior VP of clinical research operations at i3 Research.

"The CRO is likely to approve deviation from the approved protocol to a lesser degree than the sponsor would, but in the real world of clinical-trial practice, investigators need some latitude in managing their subjects," he says. "Recognition of this perspective by investigators and sponsors will allow improved alignment of expectations between sponsors, CROs, and investigators."

Uncovering Pain Points

As in any business partnership, investigative sites expect their interaction with the sponsor and the CRO to be one of mutual benefit in which they are regarded more as a client or partner as opposed to a commodity.

"Sponsors and CROs must recognize that sites have to make a profit on each study to remain viable," Mr. Ulrey says. "Operationally, the sponsor's primary objective is to achieve patient enrollment within established study timelines. If a site turns down a study because of budgetary or payment cycle issues late in the sponsor prestudy process, it can create an adversarial relationship. The tendency is to accept each study opportunity without access to a complete protocol or budget. This can result in a lose-lose economic and clinical relationship."

The amount of reimbursement and the time it takes to receive that money is a major cause of contention for sites.

A 2005 report from Thomson CenterWatch notes that sites spend a lot of time up front on study-related tasks for which they rarely receive reimbursement. These include attending start-up meetings, preparing regulatory documents, engaging in presite visits, laboratory preparations, source document review and comparison with the CRF, or making new source documents and learning a new protocol, as well as actively recruiting for a new study. The time spent on study preparation impinges on the physician's ability to see patients, which means a further financial hit.

"All of the things that sites have to do just to get initiated on a trial are never itemized on a budget, and very rarely are sites compensated for these tasks," says Daniel Manak, director of business development at PharmaSEEK LLC. "It costs a site between $4,000 and $7,000 to get to the point where it can bring the first person into the trial. Rarely, a budget will contain a nonrefundable start-up fee, and that's meant to cover the costs that the site has to pay."

Some experts say sponsors do not always appreciate some of the critical factors that go into conducting a clinical trial under the current regulatory and ethical landscape.

Thomas Sellig

About 90% of the problems that arise could be avoided with clear communications and expectation setting up front.

"Regulatory compliance initiatives — AE and SAE reporting, protocol amendment changes, CRF changes, IRB communications, multiple protocols, and blood draws for pharmacogenomics — cost sites additional time and resources," Mr. Pfister says. "Not all sites work with a central IRB, and those sites have a tremendous burden of regulatory communication and documentation."

Mr. Sellig says to ensure compliance with 21 CFR Part 11, there are increased requirements for system validation as it relates to quality assurance audits, and these naturally add to start-up costs.

"Sponsors are starting to question some of the start-up costs associated with the requirements for system validation," he says.

Lisa Grimes, R.Ph., a member of the executive advisory group at Campbell Alliance, says protocol changes made by sponsor companies are one of the primary causes of pain for sites.

"These changes create additional paperwork and a loss of time for sites and are often not reimbursed at a level that covers the sites' incremental costs," she says.

Investigators say the sponsor often sets overly aggressive timelines, putting undue pressure on investigators, who are forced to change schedules on short notice while trying to run their clinic. Rarely are these factors accounted for in the study budget.

According to recent data, on average, 75% to 90% of the time that a site spends on a study is not in the study budget as a direct or even overhead cost.

Kathy Carter

An open line of communication and increased familiarity between the site and sponsor boosts enrollment and provides for more accountability.

"It is important for sponsors to recognize the activities required outside of the medical/clinical skills necessary to conduct a clinical trial without jeopardizing the integrity of the process," Mr. Pfister says.

Dr. Douglas says investigators have a responsibility to reject a study because they don't have the resources or they think the timelines are unrealistic.

"The problem, of course, is that occasionally an investigator believes that he or she should do the study to keep his or her operation running," he says. "But investigators have to make those tough decisions, and if the study is not right for them or they don't think the study is suited to their site and patients, they need to be very clear with the sponsor and perhaps pass on the particular study. Certainly in my experience in the pharmaceutical industry, those are the type of individuals to whom we pay special attention, to avoid unwelcome outcomes in study conduct."

Those who work with sites, however, say turning down a study is a double-edged sword.

"The site is a really small fish in the sea of clinical research, so how often can that site

afford to say no, and what are the ramifications for that?" Mr. Manak says.

Sites also face large salary commitments. A recent Thomson CenterWatch survey indicates that total salaries now consume two-thirds of revenue, up from one-half in 2002. Investigator salaries alone now consume almost 26% of revenue, up from 11% in 2002. (See chart on page 36.)

Sound Bites from the Field

PHARMAVOICE ASKED EXPERTS TO COMMENT ON WHAT NEEDS TO HAPPEN TO ENSURE THAT THE OBJECTIVES OF BOTH THE INVESTIGATIVE SITE, OR INDIVIDUAL INVESTIGATOR, AND THE SPONSOR ARE MET.

STEVE CUTLER, PH.D., is Senior VP Clinical, Medical and Regulatory Services, at Quintiles Transnational Corp., Durham, N.C., which helps improve healthcare worldwide by providing a broad range of professional services, information, and partnering solutions to the pharmaceutical, biotechnology, and healthcare industries. For more information, visit quintiles.com.

"One of the ways of improving the relationship between investigators and sponsors/CROs is through site alliances in which a firm commitment is made by both parties to provide mutually beneficial outcomes to each other. CROs and sponsors need to be able to provide an ongoing stream of good trial opportunities to the investigator, while the investigator needs to be able to consistently deliver on the agreed patient-recruitment target with a high level of data quality. We all know that 60% to 70% of alliances fail for one reason or another. Both parties need to be prepared to allocate resources to develop and actively manage an honest and open relationship to make certain that any issues are confronted and dealt with proactively. We'd rather have investigators refuse a study than agree to participate and then fail to enroll any patients.

In addition, sponsors and CROs need to be adequately staffed with competent and responsive clinical research associates, clinical managers, medical advisors, and project managers who are experienced in managing and monitoring clinical research projects and who are able to set targets and expectations and manage unexpected situations rapidly, consistently, and effectively.

Finally, the processes and procedures by which the trial is conducted at the site need to be streamlined and efficient. This particularly applies to procedures such as reporting SAEs, generating and answering queries, or ensuring suitable patients are randomized efficiently as well as ensuring that study medication is available on an ongoing basis. While most sponsors and CROs follow SOPs that are based on ICH GCP, the development of appropriate project-specific procedures to communicate decisions or handle key situations, such as protocol waivers, with sponsor or CRO medical advisors, is critical to ensure an optimal outcome for the trial."

MICHAEL JAY is Contract and Budget Manager for RxTrials Inc., Elliott City, Md., a multispecialty clinical research organization that conducts clinical trials in the Washington, D.C., Maryland, and Virginia medical communities. For more information, visit rxtrialsinc.com.

"Sponsors and CROs can acknowledge and pay for the work that has to been done by the site to put a study in place, manage the subjects to completion, close the study, store the documents, and pay the sites on a schedule consistent with the payment structures to which the sites have to abide. Most experienced sites will agree that the budgets are not increasing to match study complexity and the payment terms are archaic holdovers from the institutional era. Clinical outcomes will be improved when sites can concentrate on subject enrollment and data collection instead of making payroll. Investigators are receiving payment (less withholding) in May for work they did in January, and the result is that 75% or so of investigative sites only do one study and then get out of research — meaning that the majority of sites participating in a study are inexperienced. This definitely affects outcomes."

ELAINE KUCERA is Director of Clinical Research Services, Bismarck, N.D., a medical center serving central and western North Dakota, northern South Dakota, and eastern Montana. For more information, visit st.alexius.org.

"Well-written protocols and informed consent templates are steps that could be taken to improve the success of the study. Our investigative site spends a lot of time making sure they are written at the appropriate 6th or 8th grade reading level, accurate to the protocol, and easy to read. Kudos to the sponsors/CROs that put the time into developing good informed consent forms.

Another issue is the development of strategies for enrollment. One approach would be sharing information from other sites about strategies that have worked or have been tried and have not worked. Investigative sites want the trial to be a success. Sometimes we need help with enrollment when issues come up that were not anticipated with the initial protocol review. There needs to be honest, up-front information about the protocol as far as screen failure percentages and anticipated snags. A lot of work goes into study start up to find that there is an unanticipated number of screen failures or another glitch that causes slow enrollment. Providing as much information as possible will assist investigative sites in meeting enrollment goals. When a budget is submitted, if it is non-negotiable that should be stated at that time before a lot of work is put into developing a budget or knowing that the budget will not be acceptable to the site. Low budgets do not motivate physicians to make enrollment a priority."

LAWRENCE MEINERT, M.D., MPH, is VP, Medical and Scientific Affairs, Late Stage Development Services, at Covance Inc., Princeton, N.J., one of the world's largest and most comprehensive drug development services companies. For more information, visit covance.com.

"Optimistic projections of site performance variables, such as time-to-activate, patient accrual, and frequency of adverse events, can drive significantly lower projections of overall program cost, which can 'win out' over more realistic projections. Unfortunately, once the study begins, reality returns with lower-than-

Yet sites often have to wait months for payment or reimbursement, some industry experts say.

"It's rare that a site will get compensated on a monthly basis," Mr. Manak says. "Payment should be either biweekly or at least monthly, with a hold-back of no more than 10%. The reality is more like the milestone payments come quarterly, and then the actual payment somehow doesn't arrive for another 30 days or 60 days from when it's scheduled, which can mean investigators are only getting paid every five and a half months."

According to Ralph F. Munyan, managing director of PharmaPayments Inc., one reason for late payments can be because sponsors' payment systems are not up to the task.

"Payment processes can easily get bogged down at multiple points in the system, especially in larger trials," he says. "Improved internal investigator grant payment systems are available, but putting them in place is usually not easy or cheap."

In Thomson CenterWatch's survey, investigators also cited challenges involved in finding and competing for appropriate studies, the difficulty recruiting patients, increased EDC requirements, and contract negotiations. (See chart on page 36.)

According to Jeffrey A. Green, Pharm.D., president and CEO of Datatrak International Inc., the most critical aspect to any clinical development program is the timely availability of the required patient population. But he notes that poor planning by the sponsor and the CRO often prevents this from happening.

"Back when I was functioning as a principal investigator at Case Western Reserve University's Division of Cardiology from 1984 to 1992, the biggest disappointment with the pharmaceutical industry, and with the CRO industry as well, was the haphazard method by which access to patient populations was approached," he says.

According to Mr. Wardle, the lack of adequate feasibility studies on patient populations and investigator capability can lead to lower-than-expected-subject enrollment rates, which can lead to a strain in relationships with the investigator, CRO, and sponsor.

"Since subject enrollment is the single-

projected site performance or higher adverse-event rates being encountered. The resultant change orders and budget over-runs are explained away as due to 'factors beyond control.'

Experience indicates that investigators who make optimistic assertions are more likely to be selected than those offering candid realism. Breaking this cycle has proven very difficult. During our site feasibility assessments, we use independent ways to predict the capabilities of individual sites. We will then select those investigators whose performance projections are in line with our independent predictions, rather than 'over optimistic' sites.

Both sponsors and CROs should listen carefully to the feedback from the professionals at the study sites. In our experience, successful relationships are built on a shared agreement with the sponsor that change is required in clinical-trial operations. The change is based on the premise of increased allocation of budget funds to the support of primary site performance and quality, balanced by subsequent decreases in expenditures on central management and oversight."

MARK ROSEMAN is Executive Director of Clinical Operations at PPD, Wilmington, N.C., a global contract research organization providing discovery and development services, market development expertise, and compound partnering programs. For more information, visit ppdi.com.

"The goals of investigators are in many ways in line with the goals of clients: to recruit patients, conduct a study, determine if a new drug or new indication works, and, ultimately, get a new and beneficial drug to market. Investigators want to get involved in research, and clients want investigators involved. As a CRO, PPD acts as a broker in bringing these two groups together to push their shared goals forward. On a practical level, we conduct site assessments to ensure investigators have the necessary resources to participate in a clinical study. Depending upon the nature of a proposed study, we may conduct other assessments, such as feasibility studies for clients that also may ultimately help define what may be required of investigators including their expertise, experience, and access to technical services or equipment. Clients are better served when investigators are better informed. That's good business and good research."

A Dual Commitment

IMPROVING THE OUTCOME OF CLINICAL STUDIES REQUIRES EFFORTS ON BEHALF OF BOTH THE STUDY AND THE SITE.

The sites

- Capture data to the best of their abilities
- Meet sponsor-set timelines
- Be considerate if a need of the sponsor is presented
- Don't take studies unless enrollment can be reached
- Communicate with the sponsor regularly
- Remember that it takes a team to accomplish what is expected
- Be prepared and available for monitor visits
- Provide monitors with an area conducive to review the data
- Ensure staff are properly trained, including GCP and ICH guidelines
- Be prepared so extra work is not put on the sponsor, lab, ECG facility, etc.

The sponsors

- Need to pay in a timely manner
- Base budgets on today's cost, not on those of five or more years ago
- Compensate for those things that are not part of the site's normal cost of doing business
- Be more aware of the actual time that the site spends on conducting the study, such as the time to train subjects in the use of electronic equipment
- Provide good source documents and definitions, for example mild, moderate, possibly related, not certain, etc., on the AE form
- Provide good guidelines for the site to reference
- Make study information, especially for the study visits, clear and precise
- Outline priorities and due dates
- Maintain consistency of study information
- Have a help line available, taking into account the time differences of the sites

Source: Cyndi Serpico, Owner, Clinical Trials Specialists, Phoenix, an investigative site.
For more information, e-mail cserpico@ctsofaz.com.

Investigator-Initiated Studies

TRADITIONAL CLINICAL TRIALS HAVE ALWAYS BEEN UNDER INTENSE REGULATORY SCRUTINY, AND INVESTIGATOR-INITIATED STUDIES (IISS) ARE NOW COMING UNDER CLOSER WATCH. IN RECENT YEARS, INSTITUTIONAL REVIEW BOARDS (IRBS) AND REGULATORS HAVE BEGUN PAYING GREATER ATTENTION TO THESE RELATIONSHIPS BETWEEN PHARMACEUTICAL COMPANIES AND PHYSICIANS. THIS MORE INTENSE LEVEL OF REVIEW HAS LED PHARMACEUTICAL COMPANIES TO RETHINK THEIR APPROACH TO IIS SPONSORSHIP.

Benefits of Sponsoring IISs

Sponsoring IISs gives companies an opportunity to enhance relationships with good investigators and key opinion leaders, as well as identify and become familiar with new potential investigators. These studies also provide an excellent forum for meaningful scientific discussions between physicians and pharmaceutical companies. Proposals often represent interesting research concepts that have not been explored for a specific product, and results may provide valuable safety information, such as greater clarity on adverse events.

Identifying and sponsoring studies that are more likely to produce such promising results have become increasingly important in recent years. Building relationships is still part of the equation, but this is taking a back seat to selecting proposals with the potential to deliver useful results. This is largely because IISs are smaller in scale and hence less expensive to conduct than traditional clinical trials. If the outcome of the IIS is positive, then the sponsor can leverage those results in deciding to launch a full-blown clinical trial. Even if the outcome is negative, sponsors have saved a considerable amount of money when comparing the cost of IIS sponsorship with the expense of conducting a traditional clinical trial.

Regulatory Scrutiny

The potential for new discoveries and cost savings makes IIS sponsorship attractive, but the challenges associated with navigating the current regulatory environment take away from that allure. The lack of clear guidance about IISs from the FDA causes confusion and leaves pharmaceutical companies with questions regarding the appropriate level of involvement with IIS projects.

Companies are most concerned about the role of medical science liaisons (MSLs) and sales representatives because inappropriate involvement on their part could lead to violations of the FDA Modernization Act. It is the responsibility of the pharmaceutical companies to ensure that their MSL involvement in IIS support could not be considered promotional or marketing-related. Any mixing of the MSL and sales representative responsibilities could trigger FDA inquiries.

Part of the solution is to strategically position the MSL role within the company. MSLs who report to medical affairs are better equipped to maintain the necessary balance than those who must function as part of the sales and marketing team.

Recognizing Greater Benefits

Standard guidelines are a major part of recognizing greater benefits from their IIS investment. Building standard operating procedures (SOPs) around those guidelines is also important. SOPs bring clarity to the process and help companies address difficult IIS-related issues, such as measuring IIS success and determining appropriate allocations of the overall clinical development budget. SOPs are also useful in improving IIS-related communications. Clear and consistent communication leads to cost savings. Sponsors can reduce costs by sharing their specific areas of clinical interest with the investigator community. This reduces the likelihood of receiving unwanted applications and, in turn, reduces the resources required to conduct due diligence, review IIS applications, and respond to investigators.

A related method for making the process more productive and less time-consuming is using an abbreviated, electronic IIS proposal process. This begins by posting high-level criteria for funding IISs to a specific area on a pharmaceutical company's Website, which enables an investigator to determine whether or not to apply for funding. A typical application form includes basic information, such as the goal of the proposed research study, the study timeline, and the required resources. A draft protocol synopsis is also required to outline the study design, rationale, and target patient population. In addition to these areas, the applicant is often asked to address feasibility issues, dosing information, any comparator or blinded groups, and the amount of funding being requested. Capturing and managing this information electronically saves the pharmaceutical company significant application processing time.

The use of technology to improve the IIS process can be taken a step further by using electronic data management (EDM) in the studies. This would allow the data to be consistently captured and reported.

A well-managed process for collecting and disseminating data is important at all stages in the IIS process. Most companies currently lack a consistent system for disseminating data both within the company and to healthcare professionals. Often, the results of the IIS are submitted to the pharmaceutical company and are rarely seen again. To achieve greater benefit from the IIS expenditure, sponsors need to develop and follow a standard process for sharing results.

Such measures are part of an overall effort to not only recognize greater benefits but also measure those benefits against the actual investment. Given the large sums of money being expended on IIS sponsorship, it is important for pharmaceutical companies to track and measure their disbursements. Some companies choose to make milestone payments based on timelines, patient enrollment, or the achievement of other targets, while others choose to make payments at the beginning and end of the studies.

Source: Excerpt from Investigator-Initiated Studies: A White Paper, by Lisa Grimes, a member of the executive advisory group at Campbell Alliance, Raleigh, N.C. For more information, visit campbellalliance.com.

most important rate-limiting factor in the overall project life cycle, improved feasibility studies will provide all stakeholders with more accurate planning and projection of timelines," he says.

Another issue of contention that industry experts raise is the tendency by sponsors to over-recruit sites because of research that shows one-third of sites will fail to enroll a single patient, another third will perform adequately, and the top third will exceed enrollment objectives. At the same time, however, budgets are allocated uniformly to all sites.

"The top third of investigators, who are performing well and coming up with the evaluable and timely patient enrollment, are allocating almost 300% more time than the bottom third to achieve those results, yet are reimbursed the same," Mr. Ulrey says. "Past performance is not necessarily indicative of future performance. Sponsors should do more thorough assessments to determine present and future capabilities to meet objectives over the course of a study. As important, sites have an obligation to themselves and to sponsors to carefully review each protocol, their budget, and their patient resource pools before accepting any study."

Ms. Grimes notes that some sponsors try to enroll as many sites as possible up front and then limit the number of subjects that can be enrolled at a given site.

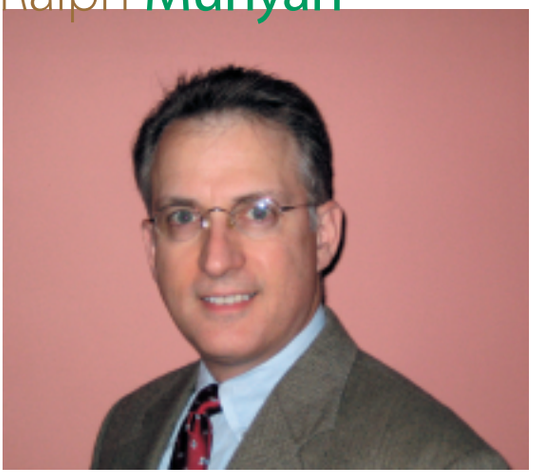
"Given that site start-up costs are included as part of grant payments, enrollment limitations constrain the opportunity to recoup those costs; that is, there are fewer subjects across which to spread start-up costs," she says.

Assessing the Fallout

Failure to improve the relationship and the economics between sponsors, CROs, and the investigative sites continues to have huge ramifications for the industry, including continued delays in bringing products to market, increased costs of clinical trials, and a further dwindling of investigators. According to the Tufts Center for the Study of Drug Development, the total number of FDA-regulated U.S. principal investigators declined 11% from 2001 to 2003.

"Top investigators are being replaced by sites with far less experience and with inadequate infrastructure," Mr. Ulrey says. "Because there are so many trials taking place, sponsors are forced to use sites that perhaps they would not otherwise use."

The fact that so many trials with similar enrollment criteria are being conducted does put top investigators in a position to pick and choose, some say.



Ralph **Munyan**

Sponsors may fail to pay investigators on time because they do not truly appreciate the value of their investigator relationships. While hard data are not available, it just makes sense that satisfied investigators are likely to enroll more subjects and write more prescriptions.

Craig **Pfister**

Investigators must be true to themselves on what their motivation is for conducting industry trials. This motivation can often be very different from the sponsor's perspective.

"When approached by different sponsors to conduct similar studies, such as studies that involve recruiting similar types of subjects, sites will choose to work with the sponsor that offers the most attractive grant, makes timely grant payments, has a streamlined contracting process, and is the easiest with which to deal," Ms. Grimes says.

The different goals and perspectives of the investigator and site representative also often are not taken into consideration, which can lead to conflict, Mr. Pfister says.

"Investigators are recruited for their medical training and patient populations, while the site representatives are more expert in the regulatory environment and study operations," he says. "This can create a disconnect in investigator/sponsor communications. Often this can be resolved by a qualified study nurse trained in both areas, but this is not always feasible for a new investigative site or a site where there is coordinator turnover during the trial. Sites need to develop contingency plans for coordinator turnover, but this is difficult to do with the current system."

Mr. Ulrey says sites would like greater involvement in the study design or at least the CRF and have earlier access to protocols and budgets during the sponsors' process of identification, evaluation, and selection.

"They don't have much input as to what case report forms look like, and, unless they're opinion leaders and are asked to consult, they have no input as to the design of the trial," he says. "As a result they unfortunately accept studies usually with little or no idea of the complete trial design and the budget that is offered."

According to Kathy Carter, owner of the Horizon Research Center Inc., problems could be addressed by having a panel of investigative sites involved in the development of the protocol and the CRFs.

"The sponsor knows the data they want captured; but the site personnel know how practical or impractical some requirements are," she says. "By including sites in the protocol development process, it may reduce the number of amendments and post study start-up changes."

But Dr. Douglas points out that widespread input from investigators isn't always practical.

"All companies have a clinical investigator advisory group made up of lead investigators who help design the trial, and then there are investigator meetings when the protocol is presented to the investigators," he says. "But a trial may involve 80, 100, or even 200 sites, and it's not possible to involve all of these investigators directly in the design of the trial."

Mr. Wardle says the investigator meeting should not be used to develop or finalize the protocol; it should be used as a training session and to provide for an enthusiastic launch of the well-designed protocol.

Some say investigators have the additional burden of taking responsibility for the business and regulatory aspects of running a trial.

"Investigator training is now readily available through different associations," Mr. Pfister says. "But many investigators have not completed this training. It is no longer accept-

able to be a medical expert with a patient population without being keenly aware of the ethical and regulatory considerations."

During his years of overseeing the research, development, and regulatory activities at Aventis, Dr. Douglas says he and his team ensured good clinical practices at a site. So, when the FDA audited a site, the FDA could recognize that the company had worked with the investigator to identify and correct potential problems that could have negatively impacted the conduct of the trial.

"Investigators often fail to realize that if they develop a history of doing poor studies, it's not just that a particular sponsor may not use them again, it's also that they may become disqualified by the FDA as an active site," he says.

Improving the Outcome

With the time it takes to get a drug to market averaging 10 years or more, there is a pressing need for sponsors to improve the prestudy timeline.

According to Mr. Ulrey, the average time in the United States from first contact of a site to first patient in (FPI) is 9.2 months for a Phase II or III study.

"In that time, a lot can change; study coordinators can leave and more studies can come aboard for a particular investigator," he says. "Data clearly show shortening the time between first contact to FPI, and providing the site with a complete protocol and budget, would dramatically improve the site/sponsor/CRO relationship."

From an investigator's perspective, there is currently minimal priority planning regarding the most important aspect of clinical development, which is access to the right patient populations.

For clinical research to be an efficient process, sponsors must be actively engaged in fostering the interest of clinical investigators, Mr. Wardle says.

"They can do this by focusing on several key initiatives, such as supporting investigator training and education, supporting certification programs for physician investigators, expanding the network and use of investigators as key opinion leaders in clinical development programs, and increasing collaboration with investigators in publishing clinical-trial results," he says.

Being up front with the sites and ensuring fairness in all contracts, including indemnification and study subject injury protection, as well as fair insurance and IP statements, would dramatically reduce the time from point of contact to execution of the contract, Mr. Manak says.

"If there were a more consistent body of language — and there is an effort being made to this effect — and items such as indemnification and insurance were incorporated into the contract early on, it would save a significant amount of time during negotiations," he says.

Dr. Jeffrey Green

A planning method that is trial-by-trial is a symptom of the larger problems within the industry, Dr. Green says.

"Long-term access is rarely established for a consistent site and repetitive patient tributaries but is dealt with on a case-by-case basis, necessitating this process to be repeated multiple times over and over again with minimal efficiencies resulting," he says.

Mr. Munyan notes that a standard grant agreement would dramatically reduce the time and cost of negotiating each investigator agreement, ultimately enabling more compensation for investigators.

More realistic trial protocols in terms of

Investigative Challenges

WHAT IS THE BIGGEST CHALLENGE YOU FACE TODAY?

2004

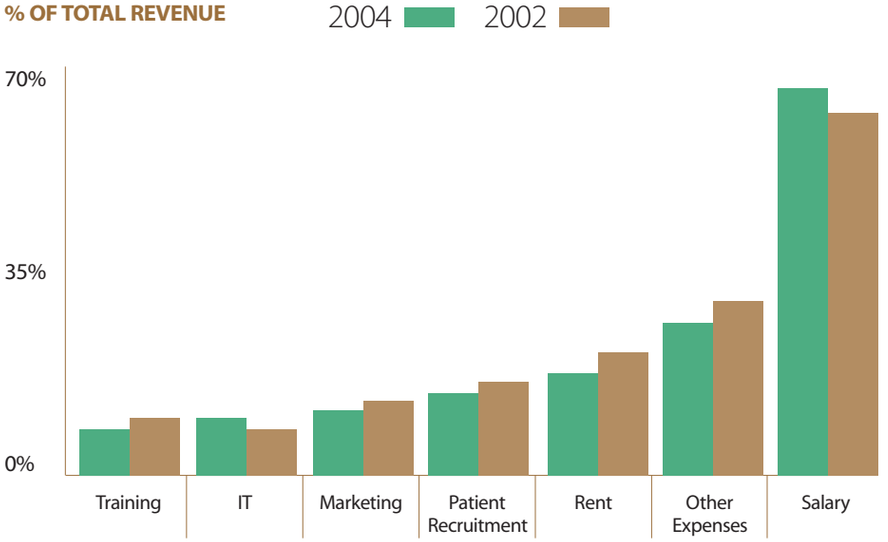
Finding/competing for appropriate studies	25%
Budget doesn't cover hidden costs	21%
Difficulty recruiting patients	10%
Increased EDC requirements	9%
Negotiations of contracts	9%

2002

Slow reimbursements from sponsors	35%
Rising operating costs	19%
Hiring and retaining staff	18%
Difficulty recruiting patients	12%
Intensifying competition	8%

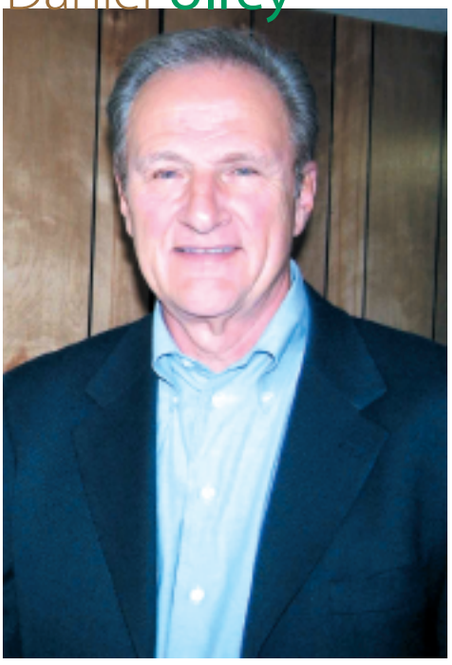
Source: Thomson CenterWatch, Boston, survey of 61 investigative sites in 2004 and 111 investigative sites in 2002. For more information, visit centerwatch.com

Average Site Expenditures



Source: Thomson CenterWatch, Boston, survey of 61 investigative sites in 2004 and 111 investigative sites in 2002. For more information, visit centerwatch.com.

Daniel Ulrey



Since patient enrollment and retention in clinical trials is controlled 100% by clinical sites, the need to improve investigator and site reimbursement, as well as ensure prompt payment for performance, has never been greater.

inclusion/exclusion criteria and subject enrollment timelines would enable sites to avoid unnecessary work and expense caused by later changes, Ms. Grimes says. Sites also could take steps to improve outcomes.

"Many sites could significantly improve their relationships with sponsoring pharma companies by providing more accurate estimates of subject recruitment/enrollment within given timelines," she says. "To improve their ability to make these estimates, sites could do a better job of keeping track of the numbers of subjects enrolled within specific timelines in similar protocols. Sites could also know when to decline the opportunity to participate in specific studies based on inclusion/exclusion criteria if they had better records of their previous enrollment rates in similar studies."

Mr. Manak says it would be to the advantage of sponsors if they were to provide sites with information well in advance, as well as gather information from the sites.

"Sponsors send out a site questionnaire to help identify appropriate sites, which is a good first step, and that is then followed by a clinical-trial agreement," he says. "After the questionnaire, sponsors should provide the sites with the protocol and a two-way questionnaire, which would be a platform for the sites to give feedback to the sponsor. The end result would be that sponsors would likely end up with better qualified sites."

Sites also could improve their own situation with regard to compensation by itemizing their costs and providing that information to the sponsor, Mr. Manak says.

"When sponsors receive itemized per-patient costs, they may give more consideration to the budget than just pushing back a request for more money per patient," he says.

Forming a Bond

Industry leaders say developing better and more stable relationships with the sites can go a long way toward saving time in the development process rather than scrambling to find the right sites for a trial at the last minute.

Dr. Green suggests setting up a community of investigative sites appropriate for each priority development program.

"This makes far more logical sense than having a clinical trial approved one day and then scrambling to find the sites the next, which is how most programs function today," he says.

The CRO can play a central role in this, Mr. Wardle says, as long as the sponsor has selected a CRO that has demonstrated commitment to therapeutically focused research.

"The CRO must demonstrate this commitment by hiring employees at all levels who have abundant expertise in clinical-trial operations within the therapeutic area of the compound being developed," he says. "The result will be sponsors, investigators, and CRO personnel benefiting from their collective experience in the design, execution, and analysis of the clinical trial."

Maintaining consistency with personnel throughout the study would also improve relationships and ultimately productivity, Ms. Carter says.

"An open line of communication and increased familiarity between the site and sponsor boosts enrollment and provides for more accountability," she says. "By developing the relationships early and building upon them, there is a more cohesive bond, which in turn makes everyone perform at a higher level because they know who they are working with."

Dr. Frank Douglas

What investigators often fail to realize is that if they develop a history of doing poor studies, it's not just that a particular sponsor may not use them again; it's also that they may become disqualified by the FDA as an active site.

Dr. Douglas says before going into industry his own experiences as a researcher made him aware of the value of building relationships with physicians.

"When I was the director of the hypertension clinic at the University of Chicago, sales reps would come by periodically to tell me what was in the pipeline relevant to the category," he says. "When a company had something of interest, I wanted to participate in the study because the reps had done a lot to cultivate my interest.

"When I left and went into industry, I tried to do the same," Dr. Douglas continues. "I had my people identify investigators and develop their interest in the science of our projects and the compounds that were advancing in our pipeline. It might be three or four years off, but we'd periodically drop by and let them know what in their research we found of interest and that we looked forward to an opportunity to engage them in a study in the future, if they were interested."

The essence of a good partnership is to have agreed-upon objectives, mutual benefits, and some shared risk, Mr. Ulrey says.

"The primary mutual benefit to sites is the same as the sponsor's: enrolling and retaining the requested number of evaluable patients well within the timeframe," he says. "Anything the sponsor or CRO can do to make sites successful is mutually beneficial. The multitude of challenges are not going to be easily solved; to move forward, sponsors need to restructure their processes to ensure success. Sites are not commodities; they are entities and need to be treated more as partners from a clinical and business perspective." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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