BY DENISE MYSHKO

Drugs in the REAL WORLD

A greater regulatory focus on safety means companies are under pressure to provide more information about a prescription drug, as well as about the characteristics of patients, once a product becomes available to the larger marketplace. **COMPANIES ARE BEING ASKED TO PROVIDE INFORMATION TO PHYSICIANS, PATIENTS, PAYERS, AND REGULATORS ABOUT HOW PRODUCTS ARE USED, THE EFFECTIVENESS IN CERTAIN PATIENT POPULATIONS, AND WHETHER THERE ARE SAFETY CONCERNS.** Phase IV trials have become important vehicles for postapproval risk management and drug-safety assessment. Additionally, Phase IV studies can be used to assess comparative efficacy, health outcomes, and health economics — all of which can be important data for marketers looking to exalt differentiation in the marketplace.

THOUGHT LEADERS

CAROL COLLINS. Corporate VP, Peri-Approval Clinical Excellence (PACE) Global Group, Parexel International Corp., Waltham, Mass.; Parexel is a global biopharmaceutical services organization, providing a broad range of knowledge-based contract research, medical marketing, and consulting services to the worldwide pharmaceutical, biotechnology, and medical-device industries. For more information, visit parexel.com.

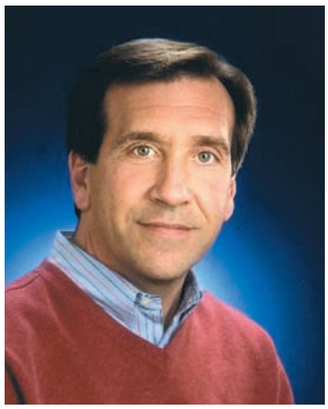
PAUL COLVIN. Director, Clinical Operations, Eli Lilly and Co., Indianapolis; Lilly is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. For more information, visit lilly.com.

WILLIAM H. CROWN, PH.D. President, i3 Innovus, Basking Ridge, N.J.; i3 Innovus, a division of i3, provides health economics and outcomes research solutions that use thought-leading analyses and the largest, most complete longitudinal database available to support market access and reimbursement of healthcare products. For more information, visit i3innovus.com.

MARIO EHLERS, M.D., PH.D. Chief Medical Officer, Pacific Biometrics Inc., Seattle; PBI provides comprehensive laboratory services in support of pharmaceutical and diagnostic product research. For more information, visit pacbio.com.

BRUCE FREUDLICH, M.D. Assistant VP, Musculoskeletal Clinical Research and Development, Wyeth Pharmaceuticals, Collegeville, Pa.; Wyeth is one of the world's largest research-driven pharmaceutical and healthcare products companies. For more information, visit wyeth.com.

RICHARD GLIKLICH, M.D. CEO, Outcome, Cambridge, Mass.; Outcome is a provider of



Dr. Donald Therasse
Eli Lilly and Co.

ONE OF THE CHALLENGES WITH A GLOBAL PHASE IV TRIAL is to get harmonization of the protocol.

Cynthia Verst-Brasch
Kendle

Because there is more intense competition in the marketplace with me-too products as well as shrinking patent lives, **THERE IS A REAL PUSH FOR LIFE-CYCLE MANAGEMENT; AS SUCH, COMPANIES REALIZE THAT THEY HAVE TO GET OUT THERE WITH PHASE IIIB/IV STUDIES**.

Dr. Bruce Freudlich
Wyeth Pharmaceuticals

WE BELIEVE THAT IT TAKES A LARGE NUMBER OF PATIENTS STUDIED IN THE POSTMARKETING PERIOD to create a strong safety database for our products.

Phase IV **TRENDS**

There is much more emphasis on — and more postmarketing requirements for — Phase IV studies, especially to learn more about the safety of a drug and how it is used in clinical practice.

CROWN. More emphasis is being placed on Phase IV studies than ever before. The types of studies vary widely from analyses of health insurance claims data — primarily in the United States — to patient registries, prospective patient surveys, and large, simple clinical trials conducted globally. Changes in the marketplace for pharmaceutical products are creating the need for much more information about the characteristics of patients and less emphasis on physician information. Companies must be proactive in monitoring the performance of their products in actual clinical practice. In the case of safety-related issues, for example, it is important to identify safety signals as soon as possible to limit adverse patient outcomes. In addition to being good for patient care, it is a smart business decision to limit any liability that might result from serious adverse events.

SCHRAMMEL. The overall science behind Phase IV trials has come a long way. Patients, providers, and payers are making sure that science leads development and ultimately supports effective marketing. Interest in using patient registries as a late-phase tool continues to increase. Patient registries are larger, more observational studies designed to determine

strategies and solutions designed to meet the unique needs of the postapproval market. For more information, visit outcome.com.

DOUG KURSCHINSKI. VP, Market Development, AtCor Medical Inc. (USA), Lisle, Ill.; AtCor Medical develops and markets cardiovascular technologies for risk assessment and patient management. For more information, visit atcormedical.com.

PEGGY SCHRAMMEL. Executive Director, Late Phase Development Division, PharmaNet Inc., Blue Bell, Pa.; PharmaNet is an international drug development company offering a complete range of clinical development and consulting services to the pharmaceutical, biotechnology, and medical-device industries. For more information, visit pharmanet.com.

DONALD THERASSE, M.D. VP, Global Medical Affairs, Eli Lilly and Co., Indianapolis; Lilly is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. For more information, visit lilly.com.

GARY TYSON. VP, Clinical Development Practice, Campbell Alliance, Raleigh, N.C.; Campbell Alliance is a specialized management consulting firm serving the pharmaceutical and biotechnology industries. For more information, visit campbellalliance.com.

CYNTHIA VERST-BRASCH. VP, Late Phase, Kendle, Cincinnati; Kendle is a global clinical research organization, delivering innovative and robust clinical-development solutions — from first in-human studies through market launch and surveillance — that help the world's biopharmaceutical companies maximize product life cycles and grow market share. For more information, visit kendle.com.


Phase

patient outcomes in a natural setting. These registries go hand-in-hand with another trend: pharma's commitment to using Phase IV tools for risk-management purposes. Certainly with some of the guidances that have been issued by the FDA and the European regulatory bodies, pharma is looking at what the risk-benefit ratios are for products on an ongoing basis. Long-term safety endpoints are rising to the top of importance in late-phase studies. Some of the data that we have seen show that up to 80% of the drugs approved in the United States are required to fulfill some type of postmarketing obligation, whether it is evaluating the impact of the drug in a special population or tracking the long-term safety associated with the drug. Pharma companies have to step up and meet those commitments.

A Case Study: Phase IV Can Impact Product Positioning

Doug Kurschinski
AtCor Medical Inc.

By documenting specific mechanisms of action, **PHASE IV STUDIES HAVE THE POTENTIAL TO CREATE PRODUCT DIFFERENTIATION AND EXTEND PRODUCT LIFE CYCLES, INDEPENDENT OF PATENT LIFE AND GENERIC DRUG DEVELOPMENT.**

Phase IV trials have become increasingly important as competition has intensified in the pharmaceutical industry. By documenting specific mechanisms of action, these studies have the potential to create product differentiation and extend product life cycles, independent of patent life and generic drug development. This is especially true when a Phase IV trial can document an advantage that is not known — or has not been demonstrated — to be a class effect.

In one of the more dramatic developments in recently reported major drug trials, Pfizer was able to demonstrate product differentiation for its calcium channel blocker, amlodipine, by using new technology to noninvasively demonstrate differential reduction of central blood pressures.

The Conduit Artery Functional Evaluation (CAFE) study — a 2,199 patient substudy of the Blood Pressure Lowering Arm (BPLA) of the 20,000-plus subject Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) — was designed to assess whether central blood pressure effects were different from those measured in the arm by the traditional blood pressure cuff. The ASCOT BPLA compared the amlodipine with the beta blocker atenolol to assess effectiveness of blood-pressure reduction and improvement in cardiovascular outcomes.

The CAFE study took on added importance when the ASCOT study was stopped early because of the significant reduction in adverse cardiovascular outcomes in the amlodipine arm as compared with the atenolol arm. The two study arms showed no statistical difference in brachial cuff blood pressure reduction, which therefore provided no clue as to the difference in outcomes. Central aortic pulse pressure (the average of which was 4.3 mmHg less in the amlodipine arm than in the atenolol arm <.0001) proved to be the sole independent predictor of outcomes and thus explained the mechanism of improved cardiovascular outcomes.

Central blood pressure is that which is present in the ascending aorta and is, therefore, the pressure that the heart works against. From a physiological standpoint, central systolic and pulse pressure are more relevant to cardiovascular outcomes than the brachial cuff pressures traditionally measured in the arm, and these recent trial results were consistent with this thinking. As a result, documentation of these effects through the use of novel technology has created a potential marketing advantage in this instance.

Source: AtCor Medical Inc., Lisle, Ill. For more information, visit atcormedical.com.

FREUDLICH. It is encumbant upon us to understand how our products are being used and if there are differences in safety or efficacy in different populations. For example, we want to know if medicines work differently in patients who are being treated for early-stage diseases, late-stage diseases, or in patients with comorbid conditions. It is also important at times to examine specific patient subsets, such as elderly patients. We occasionally are interested in making comparisons with other medications on the market, which can help give authorities and consumers some indication of differences in value. We're very attuned to safety. We believe that it takes a large number of patients studied in the postmarketing period to create a strong safety database for our products. This may be useful, for example, to uncover adverse events that are rare, which may not be evident from the few thousand patients who have been studied for drug registration.

CROWN. Because Phase IV is the first opportunity to observe a drug's use in standard clinical practice, it also is the first chance to observe the impact of a product upon medication adherence and switching patterns, use of healthcare services, and drug safety in large numbers of patients who often have other comorbidities and who are being treated with concomitant medications.

SCHRAMMEL. Where Phase IV can really shine is looking at nontraditional endpoints, such as economic value, treatment satisfaction, quality of life, compliance, and caregiver burden, as well as more intangible benefits that are important to patients but are very hard to get in a Phase III environment.

COLVIN. Phase IV trials extend the work that has been done leading up to registration. The registration package is broad, but it certainly is not complete in defining appropriate use of that molecule in practice. There are a number of activities that we look at depending on the product, such as combination therapies, sequential therapies, and comparative efficacy; additional health outcomes or health economics; safety studies; and new populations. This expands the database that helps us define appropriate use and guide physicians.

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Dr. Richard Gliklich
Outcome

THE BEST WAY TO COMPETE FOR SITES FOR A PHASE IV PROGRAM IS TO increase the value of what is delivered to the sites.

SCHRAMMEL. There has been more continuity between Phase II, Phase III, and Phase IV trials in the last couple of years. There used to be silos in those sectors, but those walls are coming down. Events of the last couple of years have forced us to look at development and life-cycle management in a different way.

THERASSE. We are focusing on high-quality medical studies. We're doing more safety studies, but the trials really depend on the product and what the FDA's postmarketing requirements are. There is better life-cycle planning in general for molecules — extending to the global medical planning and the coordination of what was done in Phase III and what needs to be done in Phase IV.

GLIKLICH. One of the big changes is more focus on credibility and standardization; the evolution of standards in this arena is happening very quickly. With regard to investigational studies, there's more clarity on what's necessary in certain protocols involving human subjects. But there are still open issues regarding how to select sites, how to select investigators, and how to determine sampling criteria. On the observational side, there's currently work going on under the Agency for Healthcare Research and Quality (AHRQ) to create a reference handbook from a broad group of stakeholders to guide how to evaluate information from these types of programs. The quality from these studies needs to be much more consistent.

Paul Colvin
Eli Lilly and Co.

Phase IV trials extend the work that has been done leading up to registration. **THE REGISTRATION PACKAGE IS BROAD, BUT IT CERTAINLY IS NOT COMPLETE IN DEFINING APPROPRIATE USE OF THAT MOLECULE IN PRACTICE.**

Achieving **OPTIMUM OUTCOMES**

Experts interviewed for this Forum stress that companies can achieve positive outcomes in Phase IV by designing appropriate studies, asking relevant medical questions, and increasing the value to the sites.

FREUDLICH. As a company, we don't believe in study designs that only aim to place more patients onto our product. Instead, we expect to enhance our knowledge of the clinical science behind our products and to understand how the drugs work in the different populations. Getting the study design right is an important first step. We seek outside expert advice to test and develop our ideas. We may have what we consider great ideas about a study concept or design; but if the best opinion leaders in the field think that they don't make sense or are inconsequential, we won't go forward. It is also important to keep an eye on the study as it's proceeding, which involves having an excellent clinical-operations team that is well trained and is in close contact with all study sites. Additionally, there needs to be

Status of Postmarketing Studies

	NDAs/ANDAs (% of total)	BLAs (% of total)
Applicants with open postmarketing commitments	54	44
Number of open postmarketing commitments	1,231	321
Status of open postmarketing commitments		
Pending	797 (65%)	118 (37%)
Ongoing	231 (19%)	94 (29%)
Delayed	28 (2%)	53 (17%)
Terminated	3 (<1%)	0
Submitted	172 (14%)	56 (17%)
Conducted studies (Oct. 1, 2004 through Sept 30, 2005)	156	56
Commitment met	136 (87%)	41 (73%)
Commitment not met	5 (3%)	0
Study no longer needed or feasible	15 (10%)	15 (27%)
Applications with open postmarketing commitments with annual reports due but not submitted	170 (47%)	37 (50%)

Note: Information current as of Sept. 30, 2005.
Source: U.S. Food and Drug Administration, Bethesda, Md. For more information, visit fda.gov.

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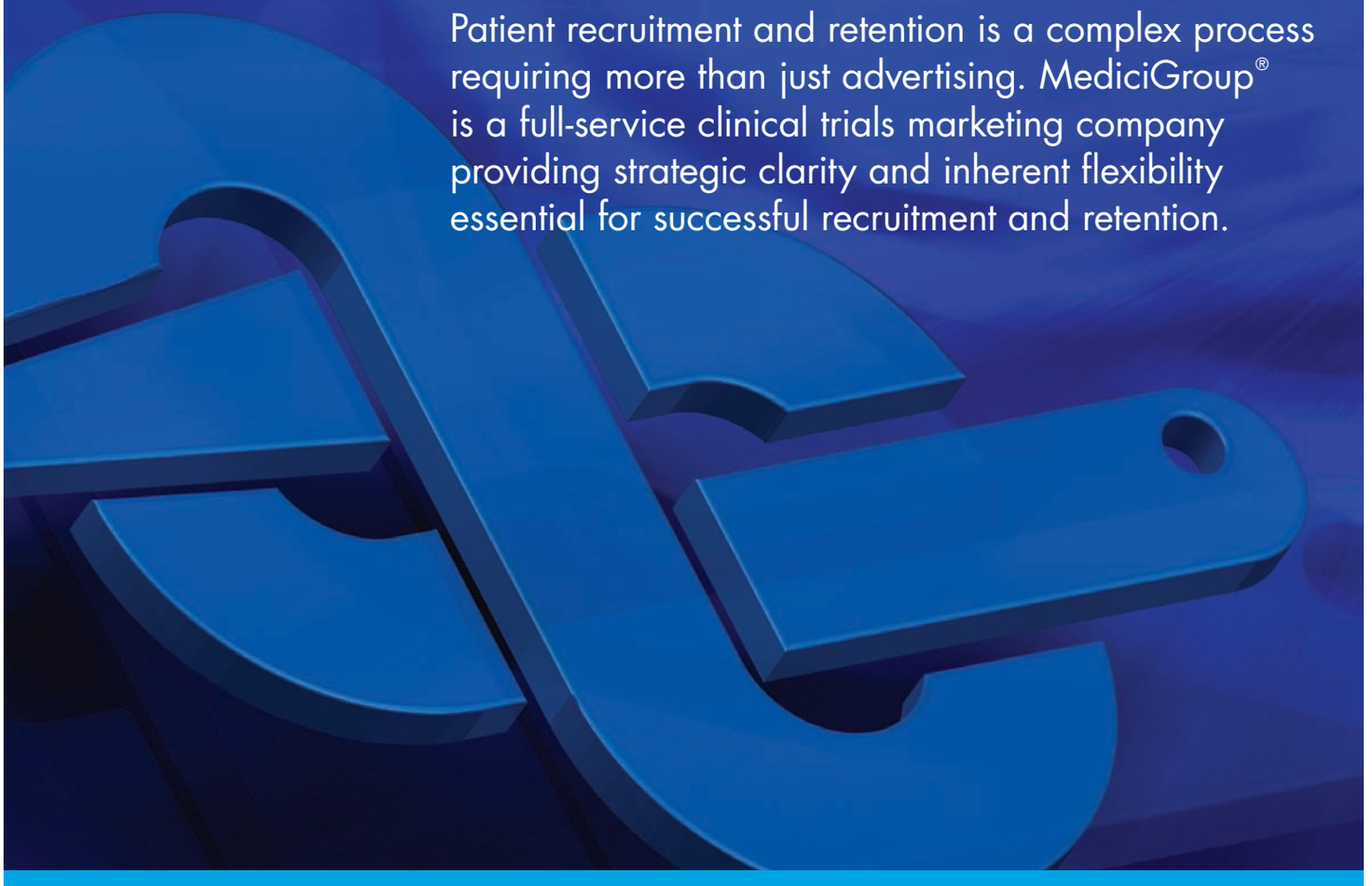

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Dr. Mario Ehlers
Pacific Biometrics Inc.

frequent feedback; this way if any difficulties arise along the way, adjustments can be made.

VERST-BRASCH. If the resultant clinical data are for a nonregistrational purpose, in other words, the intended recipients are not regulatory authorities, we can offer creative study design and operational elements to render high-integrity data that are compliant.

COLLINS. It is important to have a joint team with all of the different stakeholders within the company involved — not only the R&D group but also the marketing group, outcomes research, pharmacovigilance, and so on, who meet around the table to understand the products and the markets. Everyone needs to agree on the protocol design, with a focus on what is needed rather than collecting unnecessary data.

SCHRAMMEL. Companies should take the time to think through the issues and define them so that when the study is designed, everybody has a solid understanding of what it can and can't do. People have different perspectives and expectations; so before the study begins, it's important that all of the stakeholders understand what they'll get back.

INCREASINGLY, THERE WILL BE THE NEED TO INCORPORATE TESTS FOR GENOMIC AND PROTEOMIC MARKERS IN PHASE IV STUDIES to better understand pharmacogenomic and proteomic properties of drugs.

There is more continuity of Phase III and Phase IV as part of life-cycle management.

THERASSE. Another challenge is getting investigators to take Phase IV studies seriously. Sometimes when the shine wears off of a new product, investigators may not be as interested in doing the work, particularly if the research does not address an important medical question.

GLIKLICH. The best way to compete for sites for a Phase IV program is to increase the value of what is delivered to the sites. There has to be value brought back to the sites.

COLLINS. Technology is one reason why the Phase IV area is growing at the rate that it is. After many years, electronic data capture has finally been accepted as the most efficient method when conducting large studies with thousands of sites in multiple countries.

Peggy Schrammel
PharmaNet Inc.

THE OVERALL SCIENCE BEHIND PHASE IV TRIALS HAS COME A LONG WAY. Patients, providers, and payers are making sure that science leads development and ultimately supports effective marketing.

TYSON. Technologies such as EDC can be helpful in large-scale registrational studies. There are some very specialized EDC vendors that focus on these large-scale registrational studies, making their products extremely easy to use and requiring minimal training for clinical staff. That significantly improves the overall efficiency of the entire registrational study.

Phase IV **CHALLENGES**

Recruiting physicians and patients, managing large global studies, and collecting and managing data are some of the challenges sponsors face.

EHLERS. Conducting large Phase IV studies can require thousands of patients and can take many years. Some mortality and morbidity studies can be as large as 20,000 patients over five years. This can exhaust the supply of patients willing to participate in the United States and Europe, and the length of the studies can consume a significant portion of the drug's patent life post approval.

There are more postapproval studies as a requirement of market approval.

GLIKLICH. These programs tend to use sites that are potentially the customers of the sponsor, so there are more dynamics in play. The biggest challenge is that, as these programs get larger, they need to compete with each other for sites to participate.

EHLERS. Increasingly, there will be the need to incorporate tests for genomic and proteomic markers in Phase IV studies to better understand pharmacogenomic and proteomic properties of drugs. This will present challenges in terms of how to deploy such tests on a big scale and how to interpret the results.

CROWN. A major challenge with Phase IV studies is the need to control for the myriad other factors, besides drug treatment, that can influence

patient behaviors and outcomes. Large, simple Phase IV trials that are specifically designed to measure health-economics and outcomes-research endpoints probably do the best job in this regard. But because such trials are expensive to undertake, nonrandomized study designs are more common. These can provide reliable evidence, particularly with careful use of sophisticated multivariate

Sound Bites from the Field

PHARMAVOICE ASKED INDUSTRY LEADERS ABOUT THEIR KEY STRATEGIES FOR MAINTAINING REGULATORY COMPLIANCE IN PHASE IV CLINICAL TRIALS. WE ALSO ASKED HOW THEY OVERCOME THE CHALLENGE OF PATIENT/PHYSICIAN RECRUITMENT FOR THESE TRIALS.

MAINTAINING REGULATORY COMPLIANCE

ANTHONY F. ABRUZZINI, PH.D., is Senior VP of Regulatory and Analytical Services at INC Research Inc., Raleigh, N.C., which provides pharmaceutical and biotechnology companies with central nervous system, oncology, and pediatrics drug-development expertise worldwide. For more information, visit incresearch.com.

"The key to maintaining regulatory compliance in Phase IV trials is to approach them as one would Phase II studies. Like Phase II studies, the Phase IV studies should be designed to answer significant questions about potential uses of the product that may not have been addressed completely in the Phase III program. This should hold true regardless of whether the Phase IV studies were required by the FDA as a condition for product approval. If the study data are important, the care and attention required to ensure the validity of the data will ensure that regulatory compliance is maintained throughout the study."

JOHN CLINE is CEO of etrials Worldwide Inc., Morrisville, N.C., an e-clinical software and services company offering pharmaceutical, biotechnology, and contract research organizations worldwide a suite of technology-based tools, including electronic data capture, electronic patient diaries, interactive voice response, and reporting. For more information, visit etrials.com.

"Building a sound scientific design for a Phase IV study is of utmost importance to avoid the appearance of being a commercial program. Technology that can allow a cost-effective method to capture common Phase IV study designs quickly and easily is important to implement. Critical information, such as quality-of-life outcomes and treatment-satisfaction data, can be collected using electronic patient reported outcome tools, for example, interactive voice response and electronic patient diaries directly from the subjects' homes. This causes less impact on the patients and sites, as the outcome data are collected directly from patients rather than being transcribed by sites. It also provides a powerful vehicle for sponsors to monitor data and track the course of the study in near real time."

SCOTT FREEDMAN is President of MonitorForHire, Conshohocken, Pa., a Web-enabled resource management company providing qualified, regional, independent clinical monitors to the pharmaceutical, biotechnology, medical-device, and contract-research industries. For more information, visit monitorforhire.com.

"The cornerstone of any study is clean data. Up front, the best approach is good study design; great training at the site level; and a solid, well-experienced team of clinical monitors."

GAIL L. KONGABLE is Executive VP of Research and Development at The Epsilon Group LLC, Charlottesville, Va., an international healthcare research and consulting firm specializing in formulating evidence-based strategies for identifying market opportunities. For more information, visit epsilongroup.com.

"When introducing the study to the investigators and study team, we stress the importance of postmarketing safety surveillance and cite the more recent examples of approved compounds that have been found to have serious safety profiles requiring further examination or withdrawal from the market. It is important to have the appropriate reporting documents and to identify the critical pathways for adverse events and regulatory documentation. We require the same regulatory practices and documentation as we would if the study were a Phase II or III trial."

DARREN MCDANIEL is CEO and Managing Member of Coast IRB LLC, San Clemente, Calif., which provides central international review board (IRB) services for Phase I-IV pharmaceutical, medical-device, and repository trials in the United States and Puerto Rico. For more information, visit coastirb.com.

"Diligent IRB review and oversight are the keys to ensuring compliance within Phase IV trials. Phase IV sites, for the most part, are new to research; so pivotal aspects for protecting human subjects are often neglected. Thus, an IRB needs to aggressively oversee the research by providing educational tools and training to the sites so the sites know why and how to report protocol deviations, continuing review reports, and so on. Secondly, an IRB should audit sites at random to ensure compliance with ethical principles of conducting research. In a study we are currently overseeing, a research site that had not applied to our IRB for approval enrolled two research subjects after hand-writing a consent form. The CRO shrugged off this major violation by simply informing our board and telling us it had "re-educated the site." This gross negligence forced our IRB to aggressively audit the overall research study to ensure this occurrence is not being replicated at other sites. This level of IRB oversight ensures compliance with ethical principles of conducting research as outlined in the Declaration of Helsinki, the Belmont report, and federal laws and guidelines."

statistical methods. In general, the more robust the data-collection effort, the better the job that such methods can do in controlling for confounding factors, such as unobserved disease severity, that may be the real reason behind variation in patient outcomes.

GLIKLICH. More than 50% of Phase IV programs are global, and more than 50% involve more than one language. Those challenges are

STEVEN PASHKO, PH.D., is VP, Scientific Affairs, Late Phase Studies, at Icon Clinical Research, Philadelphia, a global contract clinical research organization. For more information, visit iconclinical.com.

"In the Phase IV arena, a number of midsize and large pharmaceutical companies are developing study operations requirements that conform to the more stringent regulatory requirements associated with pre-approval studies. For example, some companies have made corporate policy decisions to conduct non-IND studies under IND regulations despite what the GCP guidance suggests. This probably has been decided because GCP requirements have a consistent historical precedent in Phase II and III, but this degree of consistency is lacking in Phase IV due to its wider variety of study types and purposes. Pharma may end up spending significantly more money on these studies than necessary since the incremental level of quality may not be worth the incremental study cost. Of note, however, is that one welcomed addition to the regulatory guidance concerning Phase IV has recently come out in the form of the use of patient-reported outcomes to support label claims. Using this guidance, additional costs may be incurred, but the quality achieved is probably worth the money spent. Guidance around these factors is critical since many important treatment effects, such as pain intensity/relief, are known only to the patient, and today the patient's view of treatment is taking on a more important role. Measurement properties for properly created and appropriately validated instruments are important aspects of the burden on the patient. Our view is that the guidance supports the proper psychometric standards for tests already approved by psychologists and will minimize the use of inadequate and inappropriate testing of patients in clinical trials."

STEVE RAYMOND, PH.D., is Cofounder, Chief Scientific Officer, and Quality Officer at PHT Corp., Charlestown, Mass., a provider of electronic patient reported outcome (ePRO) solutions. For more information, visit phtcorp.com.

"Phase IV data-capture technologies are getting ahead of regulations for adverse-event reporting. Using e-clinical systems, we can now capture subject reported data in real time and use it to track symptoms or snoop for adverse events. Most agree that this capability could make a big difference in safety monitoring of subjects in all types of clinical trials; yet regulations and standard practices seem to be stalled. We hope to see regulators and sponsors take advantage of timely information to make Phase IV trials better and safer by working out such issues, including time of notification and liability."

MICHAEL ROSENBERG, M.D., is President and CEO of Health Decisions Inc., Chapel Hill, N.C., a full-service CRO. For more information, visit healthdec.com.

"Two key — and little appreciated — elements of postmarking work include being able to cast a wide net and enabling a study to shift in response to information as it becomes available. The focus is marketing and performance, especially compared with other therapeutic options, in a real-world context. This way studies can both get a broad picture by being able to collect a lot of information fairly inexpensively, then zoom in on areas of particular interest. The adaptive nature means that results are continuously monitored as data are collected and the study can be shifted, supplemented, enlarged, or otherwise altered to focus on findings of interest. This adaptive strategy is based on newer technology and rapid decision making."

MARY STEFANZICK is Manager of Office Operations at Criterium Inc., Saratoga Springs, N.Y., a full-service, global contract research organization that offers a mix of high-quality clinical-research services, real-time data acquisition, and personalized communications processes. For more information, visit criteriuminc.com.

"First, the goal of Phase IV studies needs to be defined. Phase IV cannot be used anymore as a tool for marketing to drive prescriptions; these studies must be conducted to the same standards as earlier phase studies. Comparative trials or large safety trials in the approved indication can be logistically and economically prohibitive. By using cost-effective, real-time technologies, such as 21 CFR Part 11-compliant IVRS applications or automated fax scanning, one can manage the site, collect data, and determine site payments from a central location. Travel and monitoring costs are minimized with procedures that meet regulatory requirements."

RECRUITING PATIENTS AND PHYSICIANS

SCOTT H. CONNOR is Director of Marketing at Acurian Inc., Horsham, Pa., a full-service provider of patient-recruitment solutions. For more information, visit acurian.com.

"Phase IV teams face a double challenge with regard to patient recruitment. First is the collective set of issues that surround any recruitment initiative regardless of phase — namely, competition for patients, timely enrollment, and site motivation. Second is the fact that most postapproval studies don't get the attention or budget that critical path Phase III trials receive. Companies will have to focus on recruitment techniques that maximize a very limited budget or offer risk-sharing with the vendor."

LANCE CONVERSE is CEO of ePharmaLearning Inc., Conshohocken, Pa., a provider of clinical site activation and online training services for the pharmaceutical industry. For more information, visit epharmalearning.com.

"Some of the challenges sponsors face in recruiting sites/patients for Phase IV trials is the cost and time of activating and educating physicians who may be inexperienced in conducting clinical trials. The larger Phase IV ▶

obviously different from those of a small Phase IV trial at a single site in Ohio. There are cultural differences; there are regional differences. The relevance of the data is going to differ slightly from country to country; maybe subsets of data will be of particular value in France or China. Companies need to be able to produce and manage these studies with different flavors for the different regions and yet still be able to do them in a centralized way for cost efficiencies.

More and more Phase IV work is done to monitor and track long-term safety of prescription drugs.

THERASSE. One of the challenges with a global Phase IV trial is to get harmonization of the protocol. Practice patterns differ around the world. In that way, Phase IV trials are just like Phase III trials.

Gary Tyson
Campbell Alliance

THE GOAL OF PHASE IV STUDIES IS NOT TO GATHER MARKETING DATA. These studies are conducted to gain additional scientific knowledge.

COLLINS. Very often when doing Phase IV there will be a core protocol with local adaptations. These studies are more complex. There are more stakeholders involved; it's not just the local marketing company, the opinion leaders, and the physicians in that region. Central headquar-

Sound Bites from the Field (CONTINUED)

studies may need more than 1,000 clinical study sites, which makes the feasibility and activation process used in earlier phase research unacceptable from a time and cost perspective. Sponsors are starting to use technology to accelerate and improve this process. The use of study workspaces allows sponsors to reach out to a large number of potential sites and conduct site feasibility, self-paced study training, regulatory document completion, and activation online, which streamlines and systematizes the process for sites and study teams. It also allows for something I call a "stagger-start" for study launch, allowing the sites to commence enrollment as soon as they complete their online training and study documents without waiting for other sites to get caught up to have an investigator meeting. This process saves more than 50% in both time and cost compared with traditional methods."

JOANN DZENIS is Head of Global Late Phase Operations at Omnicare Clinical Research, King of Prussia, Pa., a full-service CRO. For more information, visit omnicarecr.com.

"Low public awareness in conjunction with a lack of clinical research understanding by family physicians are, in combination, huge obstacles for enrollment into late phase trials. Many physicians invite their patients to actively participate in clinical trials, yet surveys show that perhaps even more patients would be interested if proactively approached by their physicians. Further, many Phase IV protocols frequently target research naïve sites, therefore, the study design must adhere to a "keep it simple" philosophy. Site ease of use will help to ensure success by making the study nonintrusive to the patient-recruitment efforts since Phase IV longitudinal studies can be challenging because they require a long-term commitment from patients. Select clinical sites are in various stages of establishing a patient database and initiating patient participation. There are many publications to educate the physician community on conducting clinical research. An ideal strategy to overcome these issues involves a comprehensive public-awareness campaign. Companies may also want to consider creating a study Website with access to educational materials, links to related information, and forums for patient awareness and motivational support. Further, keeping the trial design simple from the beginning, with the end in mind, and focusing efforts on collecting only the data needed will minimize the process at the site level. Next, educational programs attached to the study, for example CME credits for GCP training, would assist the process. Lastly, by branding the study, patients will feel that they are joining a group that has a common bond."

DENISE KRAPF is Senior Director of Business Development for LifeTree eClinical, Temecula, Calif., a member of the FFF Enterprises Inc. family of companies and a provider of clinical electronic data capture and analysis systems. For more information, visit lifetreeclinical.com.

"Some of the key challenges to successful Phase IV clinical-trial site recruitment are screening, training, and communications. Extensive screening for sites that are highly motivated and have a strong interest and experience in the clinical area of focus will result in more successful outcomes. Screening sites for training experience — records and documentation — will result in more effective and efficient training. It is also important to have a clearly defined site-training program that includes ongoing and spot training, so training is consistent and quality is maintained. Companies should also offer training certifications to motivate site staff. Screening sites for communications capabilities will also result in more productive sites. A comprehensive communications plan, instituted before trial launch, is essential."

LIZ MOENCH is President, CEO, and Founder of MediciGroup Inc., King of Prussia, Pa., a provider of comprehensive clinical-trial marketing services. For more information, visit patientrecruitment.com.

"One of the most vexing challenges is recruiting patients for Phase IV studies when the product is available commercially. In these cases, patients must weigh the complexities of the clinical study and what it offers against the simple convenience

ters is involved; different regulatory authorities are involved; and there may be other bodies, such as NICE in the United Kingdom, that are looking for more evidence-based medicine.

FREUDLICH. Recruitment is sometimes a challenge because the product is already on the market. Patients can get the product from their doctors, and if it is covered by insurance they are often reluctant to enter a study, especially if a placebo is involved. It is advantageous to spread Phase IV studies out over multiple countries and involve multiple doctors' offices. This increases the heterogenity of the study population and allows for better generalization regarding conclusions. Data gathering is another challenge but is continually improving with updated technology. EDC is changing our lives. Instead of having hundreds of thousands of pages per study, the entire data set can be viewed in an electronic file. This is a tremendous advantage.

Phase IV
OUTSOURCING TRENDS

More Phase IV trials, as well as the individual components of those trials, are being outsourced. Experts say this trend is likely to continue.

SCHRAMMEL. In the last five years, we have witnessed an increase in outsourcing of, as well as spending on, postmarketing studies. Some statistics indicate that there has been an increase of between 20% and 23% in the outsourcing of this sector.

VERST-BRASCH. Many companies are continuing to outsource, and those companies that traditionally did not outsource their Phase IV trials are now doing so primarily because of resource crunches. This can be due to financial constraints as well as timing constraints and longer review periods around the globe. Additionally, because there is more intense competition in the marketplace with me-too products, as well as shrinking patent lives, there is a real push for life-cycle management. It's all about timing. As such, companies realize that they have to get out there with Phase IIIB/IV studies. They are turning increasingly toward CROs for advice and consultation regarding study design and creative operational solutions.

FREUDLICH. Wyeth does all of its Phase IV studies in-house. These studies are so impor-

of securing a prescription. This challenge requires sponsors to give sites the training and tools to detail the value of the study to individual patients. It requires well-executed study-support initiatives."

M. KAY PRICE is Director of Clinical Operations at Registrat Inc., Lexington, Ky., which focuses on strategic design, coordination, and applications of registries and peri-approval studies. For more information, visit registrat.com.

"Some physicians and/or patients may not see the value in participating in a long-term Phase IV trial that typically has fewer data requirements and lower remuneration than early-phase trials. Sponsors need to educate physicians and physicians need to educate their patients on how Phase IV trials can provide valuable efficacy, long-term safety, and patient reported outcomes data to support optimal care. To this end, value can be created through benchmark data reports, patient profiles, educational programs, and publication opportunities. Phase IV trials also can provide an opportunity for sponsors to involve research-naïve physicians to help them gain valuable clinical insights and research experience."

ED SEGUINE is CEO of Fast Track Systems Inc., Conshohocken, Pa., a provider of clinical-trial software and professional services to pharmaceutical and biotechnology companies. For more information, visit fast-track.com.

"Phase IV investigator grant payments certainly fall under the purview of the OIG Compliance Program Guidance because the relationship could easily be construed as having the potential to interfere with, or skew, clinical decision making. It is, therefore, imperative that pharmaceutical companies make a good faith effort to establish a reasonable fair-market value (FMV) payment to clinical investigators for the services required. Although FMV has not been specifically defined, sponsors can demonstrate their intent to comply by referencing comprehensive industry cost benchmark data and other objective third-party sources to determine an appropriate payment range."

ADAM B. SERODY is VP of Clinical Solutions at Dimensional HealthCare Inc., Cedar Knolls, N.J., which provides community-based research to the pharmaceutical and medical-device industries. For more information, visit dhcare.com.

"One challenge with large Phase IV trials is that they're often conducted in a community-based medical setting. Identifying and motivating the 'right' investigative sites sets the tone for hitting study milestones and ultimately the success of the study. Breaking through the daily noise to get the physician's attention and a commitment to attend live investigator training is crucial. Sites that attend these training meetings often demonstrate increased protocol compliance. Once launched, specially designed tactics and materials help keep the study on the radar, impacting the way the physician approaches patient enrollment and how responsive the site will be."

JEFF L. WILLIAMS is CEO of Clinipace Inc., Research Triangle Park, N.C., a clinical-research software company providing a single, integrated data-capture and study-management platform for postapproval research and registries. For more information, visit clinipace.com.

"The biggest challenge is workflow friction. As fewer than 5% of physicians in the United States participate in clinical trials, the need for attracting doctors to participate in Phase IV programs is significant. Unfortunately, physicians who have participated in Phase IV trials have become all too aware of the drag a trial can place on clinic workflow and patient throughput — the engines that keep the business side of care delivery humming. Among the causes of workflow friction: paper-based trials; hard-to-use and locally installed computer systems; nonintegrated platforms, such as separate randomization, EDC, and AE solutions; poorly designed protocols; and, ultimately, investigator payment latency. EDC via a Web-based, easy-to-use, and fully integrated clinical-trial platform that is designed from an investigator-centric perspective, not a sponsor perspective, can substantially reduce or eliminate the friction identified above in every case."

Dr. William Crown
i3 Innovus

CHANGES IN THE MARKETPLACE FOR PHARMACEUTICAL PRODUCTS ARE CREATING THE NEED FOR MUCH MORE INFORMATION about the characteristics of patients and leading to less emphasis on physician information.

tant to the company that we want to maintain as much control as possible to guarantee they are done right.

GLIKLICH. I see more components being outsourced. The rigor that is required, as well as the globalization and the changing technology, are all rarely contained within the medical affairs or even the clinical departments. Most companies typically don't have all of the components in-house to do these types of studies because of the number of different factors — from site recruitment to site management to data management — involved in Phase IV studies.

The objective of Phase IV studies is to answer important medical questions ...

COLLINS. Companies are looking to CROs that have developed expertise with Phase IV. Some have this expertise in-house, but we've been approached by a number of companies that don't.

VERST-BRASCH. Our operational staff members undergo training to understand the basic needs of community-based practitioners who are participating in clinical research. We train our project specialists to do the heavy lifting on behalf of these doctors. They prepopulate forms. They work collaboratively with the physicians and office staff to make it simple from study start up to data collection, data query, and finally site wrap up. They're trained personnel who become ambassadors and who liaise between the sponsor and the site. The underlying key to success is to ensure that the practitioner's daily routine is not interrupted while participating in late-phase research.

EHLERS. For contract organizations, including CROs and central labs, Phase IV studies offer significant revenue opportunities. Global CROs and central labs will benefit the most because Phase IV studies will mostly be global — increasingly in Eastern Europe, Russia, China, India, and South America — to recruit the patients needed to complete them. Specialty labs also will benefit because of the need for novel biomarker testing. As novel biomarkers are introduced there will be opportunities for vendors with expertise in development of such markers — not only for use in Phase IV trials but for further development and eventual approval of novel tests, such as *in vitro* diagnostics, that can be used to predict and monitor drug efficacy and safety in targeted populations.

Marketing **IMPLICATIONS**

Regulations now require Phase IV studies to address scientific questions, and those interviewed for this Forum say what is good for patients is good for marketing.

SCHRAMMEL. Up until fairly recently, it was quite common to see single-arm trials in which the unwritten goal was to get as much of the drug into the key prescribers' hands. Many times, there wasn't a protocol; there weren't any scientific research questions associated with the trial. Recently, a couple of things have have happened. Physicians have become more savvy, and patients are a lot more vocal. The scientific community as a whole has said the data that companies are culling through Phase IV have to be scientifically based. There has to be a research question; there has to be a protocol; there have to be metrics; and the data have to be analyzed correctly.

... and provide the healthcare community with real-world safety and effectiveness information to better treat patients.

VERST-BRASCH. Phase IV trials are no longer purely marketing studies. It is no longer permissible from both a local and global perspective to conduct seeding studies since ethics committees, such as MRAC, and regulatory guidelines, such as the EU directive, no longer permit them.

TYSON. The goal of Phase IV studies is not to gather marketing data. These studies are conducted to gain additional scientific knowledge.

SCHRAMMEL. The operative word here is "marketing." That word makes people uncomfortable when coupled with the words "clinical research." I look at Phase IV as a way to better characterize a product so it can be used in the most optimal way to benefit patients.

CROWN. Data collected in Phase IV enable the product to be compared with competitor products, as well as to examine stratifications of the market. For example, a manufacturer with a new product indicated for treating major depression could profile the characteristics of patients treated with its product versus patients treated with other antidepressants already on the market. Phase IV studies can answer a variety of questions. What are the medical and mental health comorbidities of patients treated with one product versus those of the competitor treatments? What is the pattern of healthcare use in the year before treatment and in the year following treatment? Is there evidence that sicker patients are being treated with the new product? The list of questions goes on and on. Answers to these questions help biopharmaceutical firms understand which patient subgroups are likely to benefit most from treatment with their products.

EHLERS. For pharma and biotech, successful Phase IV studies can considerably strengthen the drug or biologic in the market by enhancing the safety database, providing useful marketing data versus competitor drugs, and allowing for label extensions and expanded indications.

THERASSE. These studies are done to answer important medical questions. What's good for patients is good for business. The results of a good Phase IV trial, just like a good Phase III trial, can be used in the pursuit of advancing healthcare. ✦

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