BY DENISE MYSHKO

THE PATIENT PIPELINE

Unclogging the bottleneck in clinical-trial recruitment and enrollment must become a priority for pharmaceutical companies as a way to offset the costs and delays of drug development.

TO DO THIS, COMPANIES HAVE TO BEGIN THE PROCESS SOONER RATHER THAN LATER.

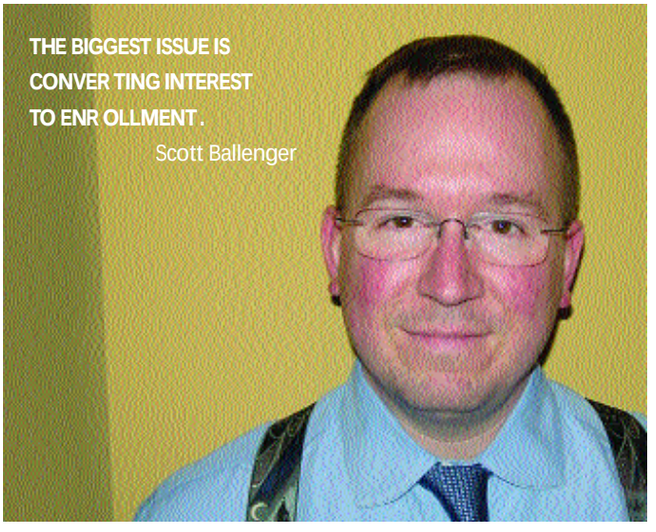
CLINICAL-TRIAL RECRUITMENT AND ENROLLMENT EFFORTS ARE OFTEN NOT GIVEN HIGH PRIORITY, causing costly delays in the development of new drugs. Unfortunately, there are no quick fixes, but companies are beginning to institute well-thought out and designed processes to bring the right patients to the right trials. Industry analysts intimate that one of the best ways to do this is for companies to take a page out of their marketing handbooks.

According to Janice Cruz Rowe, Martin E. Elling, Judith G. Hazlewood, and Randa Zakhary, authors of The McKinsey Quarterly, 2002 Number 2 report, by setting a target for the number of patients needed in a trial, the R&D team in essence creates a sales challenge: to get enough patients to buy the "product" — in this case, participation in the trial.

Planning for a clinical trial begins with the design of a protocol, which sets out the criteria for patients who can be admitted to the trial, maps the treatment they will receive, and establishes how they will be monitored.

With the demand for clinical-trial participants at an all-time high, sponsors have to initiate processes to more efficiently recruit "consumers" for their product. Last year alone, an estimated 80,000 clinical research studies were conducted in the U.S., and included between 5 million and 6 million participants. Even more patients will be needed in the future as new biotechnology products advance through the pipeline and as regulators demand additional studies to ensure safety.

The industry is struggling to keep the patient pipeline full. According to CenterWatch, 81% of all clinical trials are delayed at least one to six months due to difficulties in patient enrollment, with another 5% delayed six months or more. According to McKinsey & Co., failure to enroll enough patients in a timely manner accounts for 85% to 95% of all days lost during clinical trials.



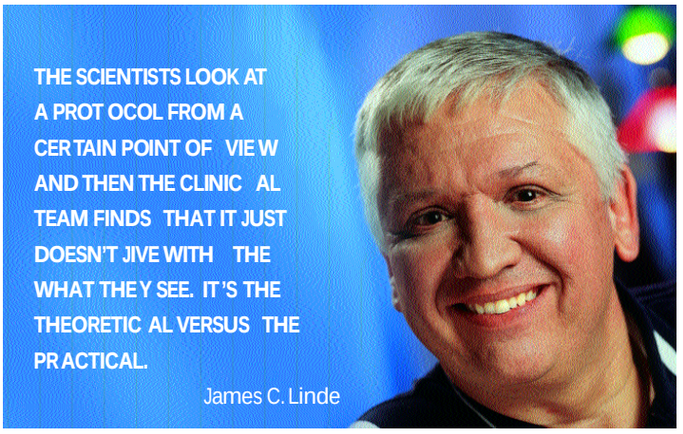
These delays have a direct impact on a company's bottom line. First, there is the direct cost of extending a study, which is estimated to be about $40,000 a day says John Yee, M.D., MPH, senior VP of medical affairs at BBK Healthcare Inc.

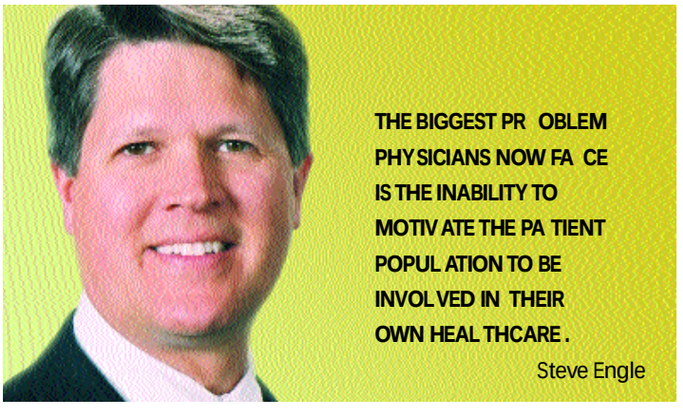
In addition, problems with recruitment delay the drug launch and creates a shorter window of market exclusivity, which could have an opportunity cost of $1 million to $5 million in revenue per day.

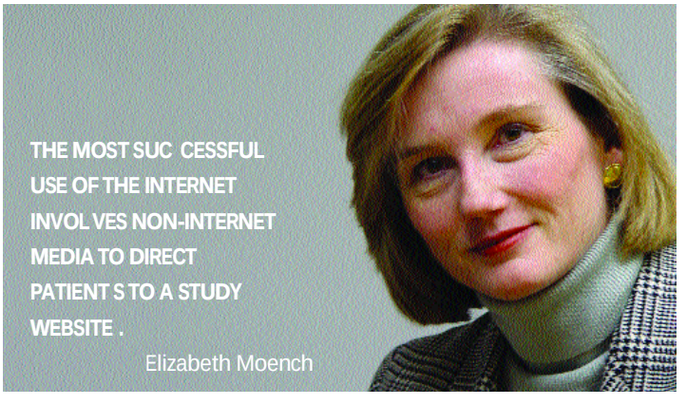
According to McKinsey researchers, opportunity costs stemming from lost revenue could be as high as $800,000 a day in lost sales for a niche medicine and as much as $5.4 million for a blockbuster drug. Reducing the length of a clinical trial by just one month by improving patient recruitment could generate an additional $40 million in sales for an average drug.

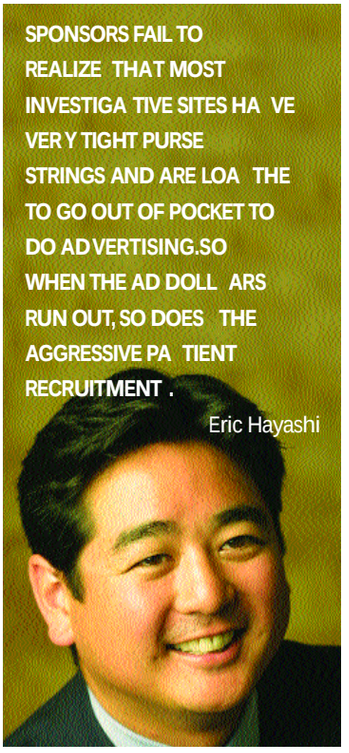
Third, delays can have an impact on investor confidence. With research and development for a new drug estimated at about $800 million, these are losses the industry can ill afford.

"Clinical trials, and specifically the patient









recruitment aspect, are the No. 1 delay in getting a drug to market," says Kathleen Drennan, chief of global marketing and strategic business development for Iris — Global Clinical Trial Solutions, a Corbett Healthcare Group company. "This always has been a problem, but it is progressively getting worse."

The difficulties with patient recruitment are a fact of life that plague clinical research organizations.

"The mathematics of this are well-understood, but not well-accepted," says G. Stephen DeCherney, M.D., MPH, executive VP of worldwide clinical operations at PRA International, a contract research organization. "We and our pharmaceutical sponsors get very eager and optimistic about every study we launch and sometimes overestimate our ability to recruit patients into these studies. We're both almost uniformly disappointed. If we looked carefully and changed our expectations about what enrollment rates should be, we would all be a little better off."

REGULATIONS, AWARENESS, AND TRUST

Industry experts have identified several mitigating factors that negatively impact on a company's ability to recruit, and subsequently enroll, qualified patients for trials.

The first is a changing regulatory environment, which requires more trials — and more patients for participation — than ever before. The average number of technical studies conducted to determine safety and effectiveness has doubled from 30 in 1983 to 68 today. The number of voluntary patients enrolled in these studies has tripled — from 1,300 in 1983 to 4,500 today — according to the Pharmaceutical Research and Manufacturers Association (PhRMA).

The second issue is a lack of awareness about clinical-research studies. In areas such as cancer — where industry-wide estimates point to more than 1.2 million new cases a year — just 2% to 4% of available patients enroll in studies. According to a 2001 survey by Harris Interactive, 85% of cancer patients are either unaware or unsure that participation in a clinical trial is an option.

"The biggest problem physicians now face is the inability to motivate the patient population to be involved in their own healthcare," says Steve Engle, chairman and CEO of La Jolla Pharmaceutical Co. "We need to get physicians, patients, as well as the govern-

ment, around a table to have a conversation about this. With an ever-increasing number of drugs in development, in two or three years we'll all be talking about patient enrollment as the No. 1 issue in some of disease areas."

A third area that continues to hinder recruitment efforts is the lack of patient trust in the clinical-research process, says Kenneth M. Borow, M.D., CEO of The Covalent Group.

The Web: Not a Magic Bullet

DESPITE THE HYPE, THE INTERNET HAS NOT PROVEN TO BE THE ANSWER TO THE PHARMACEUTICAL INDUSTRY'S PATIENT RECRUITMENT WOES. While the Internet is regarded as effective in recruiting some patients for some studies in some disease states, most in the industry agree that the Internet is an adjunct — although an important and often cost-effective one — to traditional methods for recruitment and enrollment.

"Five years ago, the Web was new and we thought it was the answer to the challenges of patient recruitment," says Elizabeth Moench, president and CEO of MediciGroup Inc. "We believed we were going to be able to target different groups of patients and we could do it very quickly and the patients would come. That has not been the case."

OTHERS AGREE. "My own experience as an investigator and as a practicing physician is that patients go to the Web after they've had a diagnosis and have initiated treatment," says G. Stephen DeCherney, M.D., MPH, executive VP of worldwide clinical operations of PRA International. "The window of opportunity to engage a patient in a clinical trial absent of investigators is very small. By the time a patient becomes aware of a trial and contacts the investigator and finds the center, they've already started therapy and may not fit the inclusion/exclusion criteria."

USING THE INTERNET CAN BE PROBLEMATIC, says Kenneth M. Borow, M.D., CEO of The Covalent Group. "The top of the funnel with the Internet is so large. The Internet can draw people who may be geographically too far away for a participating study site to take part in the trial or who may not be eligible. There is self-screening by the patient. The Web may draw patients who think that just because their blood pressure was elevated at some point in their lives when they were under a high degree of stress, that they have ongoing hypertension. Subsequently, resources are expended contacting the patient, talking to the patient, having the patient come to the study site to be seen by a nurse or physician, despite the fact that the patient may be totally inappropriate for the study."

"The Web's biggest strength also is its biggest weakness and that is the breadth of its reach," says Scott Ballenger, VP of sales at Acurian. "The biggest issue is converting interest to enrollment. The Web certainly is a broad net and can intercept a large volume of information about patients, but getting those individuals who expressed an interest to become an enrolled patient is the challenging part."

THE INTERNET, HOWEVER, IS NOT WITHOUT ITS ADVANTAGES, bringing clinical studies to the attention of patients with certain conditions.

"I have been impressed that with certain chronic conditions — diabetes, hypertension, ongoing depression, anxiety disorders, arthritis, some of the gastrointestinal disorders — radio advertising and Web advertising works because the investigator is going to intervene anyway in the course of ordinary therapy," Dr. DeCherney says. "In some of these instances, direct-to-patient advertising is successful."

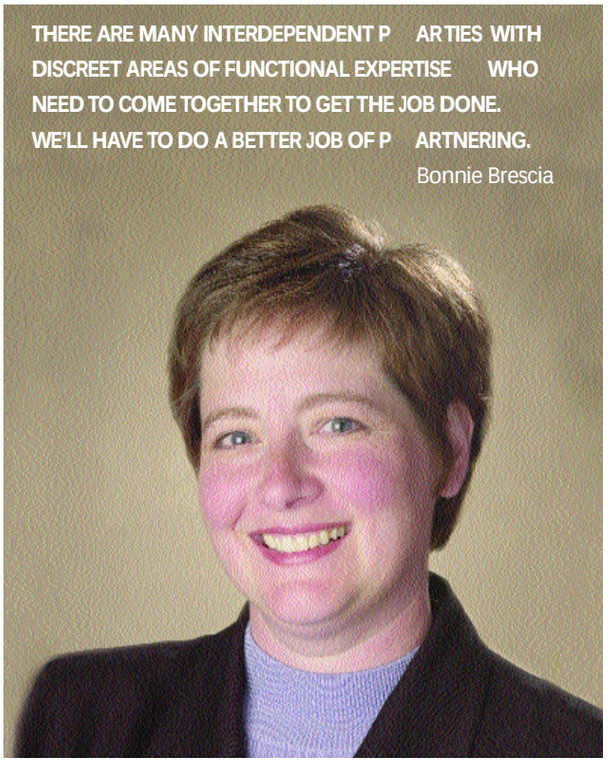
THE COST OF USING THE WEB IS MINIMAL, so even if only a few patients are enrolled through this method, it is cost effective, says Deborah Kniuksta, assistant director of patient recruitment at Kendle International Inc. "I don't think anyone would say that just using the Web as a stand-alone method is going to enroll all of the patients needed in a trial, but it is definitely a good adjunct to other types of media. The Internet has a place and we will see its use grow. It is not so much a failure of the Web but an absence of favorable publicity about clinical trials and the general public's lack of awareness about the necessity for trials."

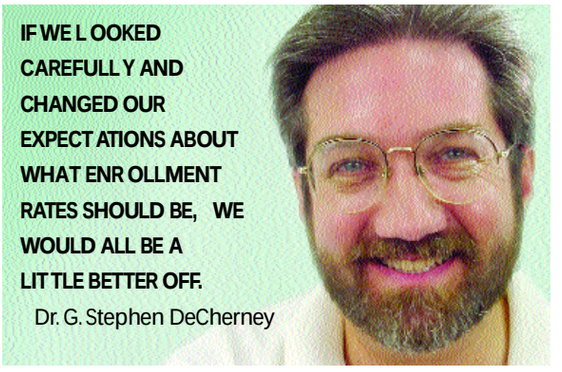
Ms. Moench says the most successful use of the Internet involves non-Internet media to direct patients to a study Website. "Hands down, this has consistently outpaced any other method," she says. "Our tracking shows that about 30% to 40% of referrals are coming through this method. About two years ago, we were tracking 20% of referrals coming from this method."

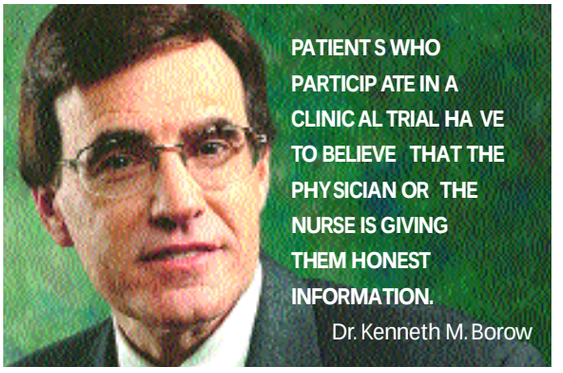
This model is succeeding, according to Ms. Moench, because people respond when they have a need and the information is readily visible.

"In a targeted (Internet) method, you're hoping patients have a need," she says. "You're sending information out to a mass group, hoping to find one or two might qualify. Instead of a push-through approach, it is a pull-through approach."

"WITH ONLINE METRICS, WE KNOW EXACTLY THE STATUS OF ANY STUDY AT ANY GIVEN TIME," ELIZABETH MOENCH SAYS. "WE CAN TAILOR OUR ADVERTISING SUPPORT AND RECRUITMENT SUPPORT TO SITE PERFORMANCE. THAT HAS BECOME AN INCREDIBLY SOPHISTICATED MANAGEMENT TOOL. WE HAVE MORE TECHNOLOGY THAN EVER BEFORE TO HELP US DO OUR JOB."







"Patients who participate in a clinical trial have to believe that the physician or the nurse is giving them honest information," he says.

A highly publicized death in one trial and isolated lack of oversight in a few trials have caused patients to be more cautious in the past couple of years. A survey conducted earlier this year by Harris Interactive found that only one-third of adults are confident that patients in clinical trials get good medical care.

"The negative media attention given to these events, which are far and few between, is what people hear," Ms. Drennan says. "We, as a country, have failed to promote the benefits and importance of participating in clinical trials for patients. Anytime patients see anything negative about clinical trials, they are going to be wary. The majority of the population does not understand what clinical trials are all about."

Trust is developed when patients are fully informed about the risks, Dr. Borow says. He highlights one of the most highly publicized clinical-trial deaths as an example of the potential dangers of not providing thorough information. According to a "Dateline NBC" broadcast from September 2002, one of the problems with the gene-therapy trial during which Jesse Gelsinger died was that neither he nor his parents were fully informed about what was known by investigators. If this is true, then it represent an example of why the informed consent process must be modified to improve patient safety.

An emerging barrier to recruiting qualified clinical-trial participants is the changing nature of the demographics of the American population in general.

"Recent data reveal that more than 50% of U.S. Caucasians are overweight or obese," Dr. Borow says. "More than 60% of African-American and Hispanics adults are overweight or obese."

These changes in overall U.S. demographics are likely to lead to greater numbers of patients who do not meet the inclusion criteria for many trial protocols, which often exclude overweight patients.

DESIGNING FOR RECRUITING

Industry sources say patient recruitment and enrollment issues often are not adequately planned for and brought into the process early enough.

"The majority of studies that come our way are rescue studies," Ms. Drennan says. "Companies invest large amounts of dollars into the study, but they fall short because they can't recruit enough patients through the sites' efforts alone. Until companies recognize that that they have to take the time to include proper recruitment planning as an integrated part of a clinical study, they will continue to go through rescue efforts and spend twice and possible three times as much money than necessary."

Because patient recruitment and retention often are not part of protocol development, companies continue to stumble, says Elizabeth

Moench, president and CEO of MediciGroup Inc. "Patient recruitment still is not part of the critical thinking process in up-front planning."

According to Ms. Moench, a prevailing problem is that patient recruitment is an afterthought for most companies, a component of the process that comes at the end of a long list of other requirements: finding a site, getting case report forms completed, writing the protocol, and submitting the protocol to the International Review Board (IRB).

"Sponsors often think about clinical development as a linear process," says Bonnie Brescia, president of BBK Healthcare Inc. "Companies design the protocol first and, based on the protocol, decide what doctors they are going to work with. They then negotiate the contracts with the doctors and after that is done, they start thinking about recruiting patients."

Another challenge is that pharmaceutical companies don't routinely correlate recruitment expenditures to cycle-time reductions, thus patient recruitment and enrollment efforts are left lagging.

"I think if sponsors gave this more thought, they wouldn't hesitate to invest millions in participant recruitment activities," says Eric Hayashi, VP of corporate development at Radiant Research. "The other thing that sponsors fail to realize is that most investigative sites, particularly the mom-and-pop research sites, have very tight purse strings and are loathe to go out of pocket to do advertising. So when the ad dollars run out, so does the aggressive patient recruitment. The result is that studies are dragged out. That makes the site less efficient, the sponsors less efficient, and overall costs are increased."

Pharmaceutical companies, according to industry experts, should work closely with their CROs and investigators to identify areas in protocols that may present recruitment challenges.

"Often we can identify the first time we read a protocol what problems we will encounter," says Deborah Kniuksta, assistant

Marketing to Patients

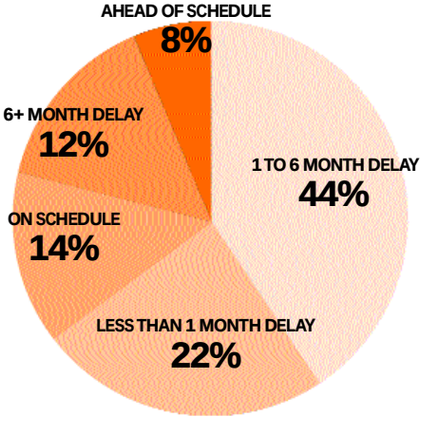
IN GENERAL, THE EFFORTS OF PHARMA COMPANIES TO MARKET CLINICAL TRIALS ARE HARDLY SOPHISTICATED OR EFFECTIVE. One company that was testing an arthritis medication, for example, gave participating physicians a budget for local advertising. Instead of buying ads aired during cable television shows viewed by the elderly or marketing the trial directly to them, the physicians purchased space in general-interest local newspapers and got marginal results for the money.

Both the message and the mass media in which it is disseminated must be chosen wisely if marketing money is to be well spent. First, a pharma company must create a clear profile of the target patient, including age, sex, and ethnicity. Parts of this profile might be implicit in the protocol, but a careful demographic analysis will usually make the profile more detailed. Once it is complete, companies need to know how target patients get information about clinical trials and what might serve as an inducement to take part in them.

An example of effective marketing comes from a U.S. company that was researching a drug for Type II diabetes, which disproportionately affects Hispanics. Using focus groups in Hispanic communities, the company set out to learn what would be most likely to motivate these patients to participate in a trial:free medical care, access to more effective treatment, or a chance to help find a cure for a disease. It found that since many patients in the target population lacked health insurance, free medical care and medication had the greatest appeal. With this marketing data in hand, the company's efforts at recruitment — and the trial — proceeded on schedule.

Indeed, segmenting the audience and targeting the groups with the highest value also can guide decisions about how to convey the message. Television spots, ads in local newspapers, and posters at bus stops, for instance, reach different demographic audiences.

PERCENT AGE OF STUDIES MEETING PATIENT ENROLLMENT DEADLINES



Source: CenterWatch, Boston (www.centerwatch.com)

Once pharma companies recognize that marketing skills are essential for bringing enough patients into clinical trials, it becomes obvious that organizational changes linking marketers with R&D are needed as well. Such changes do not mean substituting brash commercialism for scientific standards, but they do require a better understanding of what motivates people to participate in clinical trials.

To focus on recruitment for these trials, a few of the largest and most successful companies have recently established centers of excellence that include employees from clinical development, marketing, and market research. Marketers have insights that were often missing or overlooked when the trials were being designed: a knowledge of consumer behavior and the ability to track the progress of marketing campaigns. Such centers help companies complete their studies on schedule.

Source: Janice Cruz Rowe, Martin E. Elling, Judith G. Hazlewood, and Randa Zakhary, The McKinsey Quarterly, 2002 Number 2

director of patient recruitment at Kendle International Inc. "Sometimes recruitment is hindered when a protocol requires invasive procedures that are not 'standard of care' for disease management or subjects who don't fit the typical disease profile."

Ms. Kniuksta says sponsors seldom make a change to a protocol based on feedback, and time and money are wasted.

"It could take six months, eight months, or even a year for the sponsor to agree to let more typical sufferers of the disease into the study. By the time a protocol is amended, valuable enrollment time has been lost," she says.

This discrepancy often is a result of a mismatch between the scientific experts and the clinical experts, says James C. Linde, senior director of clinical services and trial support services at Kendle. "The scientists look at a protocol from a certain point of view and then the clinical team finds that it just doesn't jive with the what they see. It's the theoretical versus practical."

For example, tasks that are required by patients during a trial should be critical considerations.

"A clinical trial has to be 'reality-tested,'" says Dr. John Yee, senior VP of medical affairs at BBK Healthcare Inc. "If the task becomes too onerous for a patient, it may be very hard to recruit patients, as well as retain patients, even those who meet the criteria. If a protocol requires twice-weekly visits for 26 weeks, that's a major time commitment for a patient."

Dr. DeCherney says his organization works with advocacy groups to get input on what trials will work and which won't.

"I'm sometimes embarrassed by how often, as designers of protocols, we forget what impact our tasks have on an individual subject," he says. "For example, lunch hour visits work out for very few people."

OUTREACH EFFORTS

Many in the industry believe that enrolling the right patients depends on reaching the right physicians. But as the McKinsey report notes, a one-size-fits-all approach to recruiting physicians won't bring about the desired results. What is needed is to segment physicians according to how well their pool of patients fits the protocol required by a clinical trial, and their success in meeting recruitment targets in earlier trials.

But seeking trial participants through physician practices also presents its own challenges, since there are limited numbers of qualified investigators who want to participate in clinical trials, Dr. DeCherney says.

"Like the rest of the industry, we tend to approach the same investigators repeatedly because they're seasoned, because they fully understand ICH and GCP, and we trust them to conduct safe trials," he says.

Recruitment efforts have to go beyond just enlisting quality investigators and throwing money at advertising. The days of selecting an investigator who has every patient needed for a trial are gone. What is needed is an integrated, dedicated, and well-planned approach.

Both Dr. Yee and Ms. Drennan say effective patient outreach has to be based on market research about the patient population.

"Generally, sites do not do that," Ms. Drennan says. "A good market-research based plan that looks at initial recruitment, and subsequent enrollment, and retention is essential to successfully complete a critical study."

The most prolific research study sites are reaching out to patients directly through advertising, not through physicians, Mr. Hayashi says.

"Show me successful research sites, the ones that pharma loves because they produce quality data quickly, and I'll show you sites that derive the majority of their patients from advertising," he says. "Sponsors want to believe that they derive the majority of their patients from practice, but it doesn't work that way for the nation's most prolific sites."

Ms. Kniuksta points out that there seems to

Recruitment Standards On the Way

AN INDUSTRY INITIATIVE TO DEVELOP A STANDARD FOR BETTER PATIENT AND INVESTIGATOR RECRUITMENT IS CURRENTLY UNDERWAY. BBK Healthcare Inc. is developing what it calls Good Recruitment Practice (GRP), which would function as an adjunct to Good Clinical Practice (GCP).

"GCP does not address all of the aspects of patient and investigator recruitment that we're learning are important," says John Yee, M.D., MPH, senior VP of medical affairs at BBK Healthcare Inc. "The Good Recruitment Practice that we are initiating is an attempt to develop guiding principles, standards, and procedures for patient and investigator recruitment — raising the bar, if you will, to meet some of the unmet needs in the industry."

GOOD RECR UIT MENT PRA CTICE (GRP) IS AN ATTEMPT TO DEVEL OP GUIDING PRINCIPLES, STANDARDS, AND PR OCEDURES FOR PA TIENT AND INVESTIGAT OR RECRUIT MENT TO MEET SOME OF THE UNMET NEEDS IN THE INDUSTRY.

Dr. Yee, chairman of the GRP advisory board, says the initiative aims to accomplish a number of things, including increasing awareness about clinical research in general, as well as increasing participation of physicians and patients in clinical research. Most importantly, the initiative aims to empower patients to make better-informed decisions regarding study participation.

The model will stress the need for the pharmaceutical industry to consider recruitment issues earlier in the development process, as early as protocol creation and investigator recruitment.

"Through the dissemination and adoption of these good recruitment principles and standards, we hope to see a reduction in the delays in clinical development of new drugs and devices and other treatments and getting safe and effective treatments to market faster and making them more generally available to patients," Dr. Yee says.

A draft of GRP is expected to be available to the industry by the middle of next year.

be a growing trend to use more media and large recruitment firms as a way to enroll patients.

"This approach mush be used with discretion, however, because patient recruitment is not a 'one-size-fits-all' effort," she says. "Oftentimes, patients can be recruited successfully by using the site-developed patient databases that are built on good patient-investigator relationships. The key is knowing which approach to use when."

In the future, Ms. Brescia says synergy between site recruitment and patient recruitment will have to become better defined.

"I'm hopeful about the concept of patient communities, that each time a clinical trial is started a community is created," Ms. Brescia says. "There are many interdependent parties with discreet areas of functional expertise who need to come together to get the job done. We'll have to do a better job of partnering."

Mr. Engle says this partnering relationship will be critical.

"My suspicion is that in five years there will be a different system with the government more involved in trying to make sure that patients are more aware of clinical research," he says. "Everyone talks about the cost of healthcare, but what isn't understood is the hidden cost of patient recruitment and retention, which also is one of the biggest delays in getting drugs to market."

Mr. Engle says there is a need for a national effort to increase awareness for volunteerism in clinical research.

"We need a new Peace Corp, if you will, in the medical research area," he says. "This is consistent with the call by President Bush for increased community support. My prediction is that in two or three years we are going to be talking about this much more often than we are right now."

TECHNOLOGY SOLUTIONS

Making recruitment efforts more effective are newer technologies. Sophisticated customized software programs can provide the tools to enable sponsors, contract research organizations, and patient recruitment firms to create a model upfront, even before site selection, of where the patients are and how big the recruitment reach will need to be.

This insight also can be used to determine which media are likely to be the most effective for recruitment, and even how much this effort will cost.

This is important, Ms. Moench says, especially when a trial calls for specific patients.

"There are some conditions where patients are concentrated in specific geographic location," she says. "Constipation, for example, is one such condition. There are people who suffer from constipation in certain pockets of the country, for instance the cheese belt of Wisconsin, Maine, and parts of Texas, Nevada, and Arizona. For anorexia, a patient population pocket can be defined as middle-income to upper-income Caucasians, who live in certain suburbs such as Chicago or in parts of California."

Although results for using the Web to bring patients into studies have been mixed, Web-enabled (real-time) systems have been successful in tracking recruitment progress.

"With online metrics, we know exactly the status of any study at any given time," Ms. Moench says. "We can tailor our advertising support and recruitment support to site performance. That has become an incredibly sophisticated management tools. We have more technology than ever before to help us do our job." ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmalinx.com.

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