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Pharmaceutical industry has fat to trim — How will that impact CT sites?

Lean/Six Sigma may be next industry trend

In the future, clinical trial sites might have to prove their success in recruiting participants and meeting deadlines before they're offered new research contracts. At least that's what will happen if the latest trend in the pharmaceutical research business world takes hold.

Called Lean/Six Sigma, the process combines a Toyota production system with a Motorola technique designed to reduce manufacturing defects.

"After World War II, Edward Deming trained Toyota in new techniques or product development and manufacturing, which they perfected as they moved plants into the United States," explains **Douglas E. May**, MS, a solution partner in life sciences practices for BusinessEdge Solutions of East Brunswick, NJ.

"Two years ago, a book called 'Lean Thinking' [by James P. Womack and Daniel T. Jones] came out," May adds. "It was about how elements of lean manufacturing can be applied to any product development or manufacturing process."

Six Sigma refers to a process that tries to improve process quality, and combined, the Lean/Six Sigma model is a powerful technique for taking a look at the end-to-end clinical product development process, May says.

"It eliminates waste and puts in mechanisms for continuous improvement," he adds.

This model is ideal for pharmaceutical companies and the research process, especially as the industry's profitability has reached its apex and as sponsors increase their focus on outsourcing for clinical research, says **David T. Asher**, MBA, MBB, a pharmaceutical consultant with Asher Consultancy of Double Oak, TX.

Some of the largest pharmaceutical companies across the globe closed some facilities last year, Asher notes.

"They had workforce reductions, and this is a leading indicator that they're not as profitable as they once were," he says.

With the need to trim fat and become more efficient, many people in the clinical research industry are saying that the industry can't afford the same 40-50-year-old model anymore, Asher says.

Lean/Six Sigma is not about laying off workers, but it is about restructuring work to be more efficient, Asher explains.

"All pharmaceutical companies have open job postings," he says. "If we do a better job at what we're doing, then we can take people from within and repost them."

This requires rethinking the old business model and beginning major changes.

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"A lot of time and money is spent in clinical trial work," Asher says. "We're trying to better manage our costs as a business."

The old model and business practices no longer work, Asher notes.

For example, clinical trial statistics show that 30 percent of clinical trial sites never enroll one participant. Yet, pharmaceutical sponsors return again and again to these non-producing sites out of habit and the belief that the physician investigators are thought leaders in their fields, Asher says.

"This is an enabling process," Asher says. "How do we select our clinical trial sites using good data, or is it a purely emotional process?"

The Lean/Six Sigma process requires sponsors to look at this objectively and decide whether the current method of site selection has more or less benefits than risks. **(See story on how to market clinical trial site to sponsors, p. 100.)**

These are the questions both sponsors and sites will need to ask, Asher suggests:

- How do you get patient materials to sites faster?
- How do you collect information from sites faster?
- How long will it take to schedule the first participant visit?
- How is the organization performing on each of its core functions, including subject enrollment?
- How can the organization sustain the delivery of its strategy?
- How can the organization manage patients, document research, and close the site while delivering value to its clients?

There are societal pressures that make the current time for most research trials unacceptable, Asher notes.

The public wants safe and effective drugs as quickly as possible, and sponsors are finding that the current process is too expensive, as their investors express frustration over the length of time it takes to get a drug through the pipeline, Asher explains.

"We want to make these processes better," Asher says. "We can no longer take 10 years to get a drug to market."

For sponsors, the patent for a potential new drug is filed before clinical trials begin, which means that if the drug takes five to 10 years to make it to market, then the pharmaceutical company has lost that amount of time on its patent, Asher adds.

Also, the faster a drug makes it to market, the sooner patients can benefit from its use, he says.

"If we can get a drug to market three years earlier, you can imagine the impact that would have on patients — especially for cancer drugs," Asher says.

In the current clinical research model, the business processes create delays through oversight, inefficiencies, and breakdowns, he says.

"If we can fix these processes, then we wouldn't have to do the same thing over again," Asher says.

There typically are two types of waste in a process, May says.

The first type involves activities that add no value to the final outcome, and these can be eliminated by redesigning the process, May says.

"In other words, these are things we do for no good reason," May explains.

The second type of waste is one that adds activity but doesn't add value, he says.

"You have to do it because you're missing tools or other things," May says.

For example, in clinical research there are case report forms that need to be completed after patient visits. Often these forms are accumulated in a batch and then shipped back to the sponsor company for data entry and data cleaning, May says.

"The time spent accumulating the batch is a time where there's no value being added to the process, so the waiting time is a waste," May says.

The way to eliminate this waste would be to make the process electronic, perhaps through using a fax input system in which the case report forms could be continuously faxed and used at the receiver end, May says.

An even better solution would be to have an electronic data transfer in which the information from the patient chart is put directly into a tool where it is cleaned up by the tool and distributed in real time, May adds.

By switching to an electronic process, sites and sponsors would save time and money and have clean data to review on a continuous basis.

In the example of site selection, sponsors could improve the process by making the process entirely objective, using past data about sites' performance when making decisions about new sites to use.

Sponsors might object, saying they need to keep their thought leaders in the equation, but there are other ways to handle this, Asher says.

"Maybe we need to rethink where to apply the thought leader," Asher suggests. "Maybe the thought leaders shouldn't do clinical trials, but could serve as a consultant for how to structure the trial."

By finding a different way to use the thought leader, sponsors would change the cultural tradition and paradigms, but preserve their goals.

Another example of how the research industry can improve its process involves the handling of clinical supplies, May says.

"If you have a clinical supply chain that is not efficient then you could have patients visiting with now kit ready at the site," May says. "Or if you ship a lot of kits to a site, then you have inventory sitting there, and maybe nothing is being done with it."

A lean/Six Sigma intervention would have sites reduce the time spent in the distribution of the kits.

Other ways to improve the process might be to get investigators involved in the protocol process early on to make certain the protocol is suitable, May says.

"Sometimes the protocols have all kinds of exclusions/inclusions, and investigators say, 'I can't do this — you've made the criteria so stringent that I now have no patients in this population,'" May explains.

Sponsors could avoid this problem by setting up a secure Internet portal where investigators could review the proposed protocol and make comments. It would be done electronically and quickly, and would eliminate some problems during the start-up of a trial, May suggests.

"On average, the study start-up for a big trial takes about 26 weeks, and in the best cases, it may take 13 weeks," May says. "I know of one company where their average start-up took 39 weeks, so there's tremendous variability across the industry."

"Six Sigma says variability is your enemy," May says.

So when efficiency experts look at the clinical research industry and see tremendous variability, they know the process is messed up, May says.

For instance, clinical research organizations are known to develop drugs 30 percent faster than other companies, and this is because they operate on a different economic model where rapid cycles and efficiency are critical, May says.

"Sponsor companies have traditionally been insulated from the reality of the economics," May adds. ■

Patient adherence data is key to improve trial efficiencies

Nonadherence poses risks to study results, patients

Researchers and clinicians like to believe that patients will do as they instruct, taking their

Trial sites can attract more sponsors by learning 3 words: change, change, change

Put site performance info in electronic database

One of the hottest topics in clinical trial research these days is site selection, and the biggest obstacle to matching sites and sponsors is that people won't let go of the old ways, an expert says.

"There's resistance to change, and until some sort of burning platform appears that forces you to take action, companies don't change," says **Douglas E. May**, MS, a solution partner in life sciences practices for BusinessEdge Solutions of East Brunswick, NJ.

"To me it's perfectly reasonable that you would really examine your sites to make sure you get the ones that have experience as successful enrollers of patients and the ones that have experience in meeting deadlines," May says.

Instead, the traditional way of finding sites has resulted in sites that enroll zero patients being chosen repeatedly for reasons other than their efficiency, May says.

With the Lean/Six Sigma philosophy spreading throughout the research industry, the traditional way is giving way to change, and clinical trial sites can position themselves for the new trend by changing themselves.

"Clinical trial sites need to undertake methods to optimize patient recruitment or make it known to sponsors that they're willing to be early reviewers of protocols to assess how well it could be executed," May suggests. "Often sites are not involved, and it may be that the sponsor never thinks about involving them or thinks they wouldn't be willing to do it."

So if sites put a high priority on being early reviewers of protocols, then they'll be able to handle studies more efficiently and they'll be asked to be involved with more studies, May says.

Likewise, sponsors need to change the traditional practice of selecting sites based on what they perceive as opinion leaders, May says.

"I believe it's important to have influential physicians getting excited about the coming of a new product in their therapeutic area, but it has to be balanced because, at the end of the day, you have a business to run," May says. "If you don't hit the clinical trial deadline, the product will be delayed in coming to market, and that will hurt its marketability."

So, it makes no sense to continue using low enrolling sites, he adds.

"Some companies we're working with are waking up to that fact and are putting together tools that will help them be much more selective in choosing sites," May says.

Sponsors can easily find out this information by reviewing sites' past performances and by checking with on-line sources, such as clinicaltrials.gov to see where some of the industry leaders are initiating trials, May suggests.

"If Eli Lilly is going to one site time and time again, then chances are it's a good site, and you may want to get a study placed there, as well," May says.

Pharmaceutical companies already have site and investigator performance information that they've collected, but the information is not captured in a database that can easily be analyzed, May notes.

"There is very important site information captured in site-monitoring reports," May says. "Those are kept as documents rather than data, so it's not available to be analyzed to help you make better site selection decisions."

The solution would be to make the monitoring reports electronic so sponsors could easily see each site's performance on protocol deviations, violations, good clinical practice, and participant enrollment, May says.

"It would be simple to use electronic forms for monitoring reports or to routinely put these into investigator site databases so that you could use these in the future," May says. ■

medications, showing up for appointments, and keeping notes on symptoms, etc.

But the reality is that adherence can be far lower than imagined, even for a highly-educated population, experts say.

Thirty years ago, a study on glaucoma patients and adherence found that only 25 percent of university-educated patients with the eye disease would take their eye drop therapy as prescribed, says **John Urquhart**, MD, DrHC, FRCPE, FAAAS, FISPE, FBMES, FRSE, chief scientist with AARDEX Ltd. of Union City, CA, and Zug,

Switzerland. Urquhart also is an adjunct professor of biopharmaceutical sciences at the Center for Drug Development Science, University of California - San Francisco, CA, and an emeritus extra-ordinary professor of pharmacoepidemiology at Maastricht University in Maastricht, the Netherlands.

This adherence study was possible because of the use of a bulky electronic device in the eye drop bottle, and its results stunned ophthalmologists, Urquhart says.

"Nobody saw what real patients do with their medicine before that," he says.

In principle, research participants are supposed to follow the instructions in the protocol, but to what extent do they do this and what are the implications of deviations, asks **Carl C. Peck**, MD, an adjunct professor at the Center for Drug Development Science in the School of Pharmacy, department of biopharmaceutical sciences, University of California - San Francisco.

"Since this is a human activity, there is reason to expect that perfect adherence to the protocol will not happen," Peck says. "What's surprising is that deviations from clinical trials [involving adherence] are presumably known and measured, but in fact they are not."

Adherence is the missing link in therapeutics, Urquhart says. **(See story on how to improve patient adherence, p. 102.)**

Medications are developed with high levels of quality control in specifying content and dosage form, but once they're given to patients, it's like sending it down a black hole, he says.

The key in both clinical work and research trials is to monitor patients' adherence and use these data effectively.

Traditional methods for measuring adherence include pill counting and having the patient keep a diary, Peck notes.

For example, investigators would have patients bring in their pill bottles, and then they'd count how many pills were left, compared with how many pills should have been left if the patient had been taking his or pills as prescribed.

The problem with this method is that it was too easy for patients to dump out their pills before coming to the clinic, Urquhart says.

"If you don't believe they'll do that then give them 50 percent more pills than they need and see how many still come back with an empty bottle," Urquhart says. "So there's a false sense of security in the minds of most investigators because they've been lulled into that by a method that has been thoroughly discredited by both electronic monitoring and chemical marker data."

Likewise, when investigators ask participants to keep a diary, there's a bias for reporting good adherence, Peck says.

"Patients have a desire to please their doctors, and clinical trial participants have a desire to please investigators, so there's always bias in their reporting how much drug they took," Peck says. "The deviations are huge."

In the past decade, researchers have relied more heavily on other methods of measuring adherence, including the electronic pill bottle device called medication-event monitoring systems (MEMS® cap) and testing participants' blood for drug levels.

The MEMS® cap, which Urquhart's former company designed, has been used in many HIV medication trials, and it's designed to record the times and dates of when patients open the pill bottle to take their medication. Studies have shown that the MEMS® cap's data corresponds with biological markers, indicating the participants have adhered to their medication regimen as well as predicted by MEMS® cap data.

MEMS cap may even be a better measurement of adherence than some types of directly-observed therapy, Peck suggests.

"During the Vietnam period, I was a physician and did some research," Peck says. "All the men who went to Vietnam had to take once-a-week chloroquine pills."

The drill sergeant would put the pill in their mouths and tell them to swallow them, Peck recalls.

When the soldiers left, they'd find two-thirds of the pills on the ground. The soldiers didn't want to prevent malaria because that diagnosis could get them back to the states, Peck says.

Once investigators establish that adherence is low, what are the implications, Peck says.

"The results in clinical trials are believed and used for decisions," Peck explains. "So to the extent that deviations from the nominal description or regimen are occurring, there's opportunity for a lot of misinformation out there."

This is where researchers can turn the lemons into lemonade: "If you could actually know what a patient takes in a clinical trial, then you have powerful new information that permits greater learning and knowledge retrievable from a dataset," Peck says. "This is true so long as you take the deviations into account."

The trouble is that investigators, physicians,

and the FDA interpret clinical trial data without taking into account the participants' actual exposure patterns and drug-taking behavior, Peck notes.

Incomplete and inaccurate information obtained during a clinical trial can prove dangerous to patients taking the medication later, he says.

For example, in the 1980's, Peck saw a young woman patient who had potentially fatal cardiac arrhythmia. Her other doctors thought it was related to an antifungal medication she was taking, he recalls.

Peck was skeptical and didn't want to re-challenge her to the antifungal medication as the other doctors had advised. The case eventually led to an FDA investigation in which it was discovered that her allergy medication, a drug called Seldane, had caused the uncharacteristic arrhythmia, Peck says.

"They found that Seldane had low potential, but does slightly prolong the QT interval and can lead to fatal arrhythmia," Peck explains.

Investigators found that Seldane complications occurred when patients took both Seldane and either erythromycin or the anti-fungal agent ketoconazole. So the FDA issued warnings and label changes. Then in January 1997, the FDA announced that Seldane would be withdrawn from the market.

This case made the research community aware of QT prolongation and its connection to fatal arrhythmia, and led to the discovery of other drugs with the same problem, ultimately causing nine drugs to be withdrawn from the market, Peck says.

"Now, the FDA requires all drugs to undergo QT prolongation study in phase I with healthy volunteers," Peck says.

In these phase I studies, variations in participant adherence can impact the data about QT prolongation, he says.

"If you don't know whether patients are taking their medications or whether they're taking it at irregular times, it could lead to false positives or negatives," Peck says.

One theory for ignoring the patient adherence problem is that adherence is a real world problem, and so the trial data will more accurately anticipate how patients use the medication in the real world, Peck notes.

"But if the data are based on erratic compliance, how do you inform the patient who is compliant, and a small handful of patients actually follow instructions, that they're likely to have a greater safety problem," Peck says. "The safety information would be downward biased."

Also, drug efficacy could be downward biased and even lead to a drug being turned down when it would have been proven effective if it had been properly used, Peck says.

"So, if you have compliance data that are objective and reliable, and you use it, then you learn more," Peck says.

Investigators who use adherence data to assist with their studies could handle the information this way, Peck suggests:

- Ask what are the implications with regard to observed outcomes measures for having MEMS® cap data showing a variable exposure pattern for each patient?
- Switch from simple statistics to more complex statistics that take into account dose response and equate the compliance data with the actual doses taken.
- Use a more advanced statistical technique to determine whether the dose response is hidden in the data.

On the negative side, some drug developers worry that if investigators start to explain the actual patterns of the medications people take, it may slow down the review process, Urquhart says.

"Against that is the risk of failing to confirm the effectiveness of the drug," he adds.

"My advice to people doing trials is to be much more careful about patient selection than they have been traditionally, selecting people who will comply satisfactorily," Urquhart says. "The best predictor of a patient's future adherence is his/her past adherence. The more variance you have in a clinical trial, the less statistical power you have, and the number one source of variance in drug response is variable adherence." ■

Improve CT participant adherence with these tips

There are three typical adherence problems

Clinical trial coordinators and investigators could prevent the problems posed by study variability in trial adherence by taking measures to improve participant adherence.

There are three typical problems with medication adherence, suggests **John Urquhart**, MD,

DrHC, FRCPE, FAAAS, FISPE, FBMES, FRSE, chief scientist with AARDEX Ltd. of Union City, CA, and Zug, Switzerland.

They are as follows:

1. Patients never start the drug. "Sometimes patients who are prescribed a drug will never start taking it," Urquhart says. "That's called non-acceptance, and it can happen in clinical trials."

This is a variable that depends on incentives to patients, he says.

For instance, if people are recruited in the United States for a clinical trial that includes some doctor's check-ups, and the patients have no health insurance, then it's a big incentive to enroll simply for the check-ups, Urquhart says.

"Any trial participant can camouflage his/her nonadherence by discarding the trial medication and returning an empty container," he adds.

2. Execution can be a problem. Problems can occur in how well patients execute their drug-taking. More evening doses are missed than morning doses, and more weekend doses are missed than weekday doses, Urquhart says.

3. They quit early. Many patients have short persistence. There are many plausible reasons for quitting the medication early, but not much solid data on which reasons are most important, Urquhart says.

An example of these adherence problems was highlighted in a study of 4,800 hypertensive patients followed after being prescribed once-daily hypertension drugs of proven efficacy, he says.

"Fifty percent of the patients had quit within one year," he says. "The prescribed drugs had proven efficacy and no difference in recorded side effects from what was in the placebo group, so they were safe, effective, and convenient."

The first step in preventing adherence problems is to measure adherence, Urquhart says.

"It's okay for patients to miss an occasional single dose, but if they miss three or more in a row, then the drug action stops," Urquhart says.

The second step is to anticipate execution problems and take measures to prevent them. If clinical trial coordinators and investigators anticipate that participants will miss some doses, then they can give instructions up-front on how to handle it when they realize they've missed a dose.

For example, consider how women take low-dose, oral contraceptives, and the careful instructions they're given for how to handle missed doses, Urquhart says.

"There is labeling with instructions for what to do if you miss a pill," he explains. "It tells you that if you miss one pill you take the missed dose as soon as you recognize it, and continue on with daily pill-taking, but use back-up barrier methods for the next seven days."

If a woman misses two pills, then she must take one of the pills today and take the other missed one tomorrow with seven days of back-up barrier contraception, Urquhart adds.

"And if you missed more than two pills, you throw away the pill pack and institute back-up barrier contraception, waiting for the next period to come and a new cycle to begin," he says.

Another way to improve adherence is to use the research-proven measurement guided medication management, using the micro-electro-mechanical systems, which is an electronic device on pill bottles that collects data on how frequently and at what times the pill bottle is opened, Urquhart suggests.

"When you download data from the package, you receive in several minutes a series of graphs that show what the dosing history looks like," he says.

Clinical trial staff can show participants their graphs and explain what these mean. Where the graphs show times and dates when the participant missed the medication, the clinical trial coordinator can ask what he or she can do to help the participant change a pill-taking time or behavior to increase adherence.

For example, if the participant always bowls on Wednesday evenings and has a few drinks afterwards and then misses his bedtime dose, then the clinical trial coordinator can suggest a better time, perhaps before bowling, when the participant can take the medication, Urquhart says.

"Measurement and improvement are all part of the same package," he says.

It's a management task to bring the patient's actual dosing patterns closer to the prescribed dosing arrangement, Urquhart says.

"Think of adherence as an independent variable, and look at patterns," he says.

"When people take half as many pills as they're prescribed, and the drug is still working, they think they don't need as much," Urquhart adds.

And sometimes patients are right. One out of four recently-introduced drugs have had a 50 percent reduction in dose after marketing, he says.

This happens because the higher the price of the new drug, the more drive there is among

patients to see if they can get away with using less of it, Urquhart says.

Another pattern is negligence. People often forget to take their medications because they haven't incorporated it into their daily routine, he says.

"So they need some kind of external help to show them how to take their medication correctly," Urquhart explains. "They don't need Freudian psychoanalysis, they need a few practical pointers on how to integrate the dosing regimen into their daily routine." ■

System to reduce health disparities in community

Approach works to improve provider-patient trust

When Adventist HealthCare Inc. of Rockville, MD, asked community leaders what the health care system could do to better serve the community's needs, the answer was to form a center on health disparities.

So in late 2006, the health system opened the Center on Health Disparities, with the goals of assessing health care access among various demographic groups and assisting in improving health care access where it's needed, says **Marcos Pesquera**, RPH, MPH, executive director of the new center.

National numbers on health care disparities are available, but there's very little data at the local and county level, Pesquera says.

"We don't have data about what's happening in our backyard, and that's where the disparities are having a big impact," he says.

Too often, health care professionals will see the national data about minorities and ethnic groups and health care access, and they'll say that this problem isn't happening in their own community, Pesquera notes.

But when someone actually studies the issue of disparity at the local level, the numbers tell a different story, he adds.

"We're working on a disparities report card, and we're looking at data available throughout the county," Pesquera says.

For example, Pesquera looked at all of the hospitals in the county, reviewing their data on HIV/AIDS diagnoses, and he found that 75 percent of the patients discharged with HIV/AIDS diagnoses were African Americans.

"So we look at a county that's only 15 percent African American and see that 75 percent of the HIV/AIDS discharges are African Americans, then we know there's a disconnect," Pesquera explains. "The data tell us we need to come up with some program around HIV/AIDS education specifically geared to the African-American community."

The report will have useful information for health care facilities and research institutions, particularly when recruitment disparities are encountered.

"By creating this report and distributing it locally, we'll identify and put a light on areas we need to work on," Pesquera says.

For instance, there are clinics where Adventist HealthCare has a partnership with the county for prenatal care and child care, he says.

"When I sit in the exam rooms, I realize the majority of their patients are in the immigrant community, and there's very little data around immigrant health," Pesquera says. "So I will do a chart review one-by-one in terms of prenatal care."

Pesquera will review the different rates of gestational diabetes, infant mortality, and co-morbidity among the patients seen at the clinics. He'll also collect information about when, in their pregnancies, they first seek prenatal care.

"I'll do a manual chart review to get those data," he says.

Through this type of community-based research, he plans to look at the public health issues impacting various ethnic and minority groups and look at strategies for improving health care where disparities exist, Pesquera says.

"We're trying to improve the quality of care," he says. "We firmly believe that by improving the patient-provider relationship, that health care outcomes will improve."

When patients and providers have better communication and relationships, then trust develops, and patients are more likely to follow treatment recommendations and become enrolled in clinical research, Pesquera notes.

"The trust has to be there as a baseline so the patient will say, 'I'll join that research trial,'" Pesquera says.

Once the center has built a foundation in its work to increase patient trust and reduce care disparities, then investigators can build on that foundation for their work, he says.

"If you're my doctor and you trust me fully and I trust you, and you say, 'We need more Latinos for XY study, and you are a perfect candidate,'

then I'm going to enroll in the trial," Pesquera says. "But if I don't trust you, I won't."

By providing education to health care providers about the disparities that exist in their own communities and how they can help improve the quality of culturally, competent care, then they'll be able to build that trust, he adds.

The center's educational program will start with three modules about how to provide culturally competent care, Pesquera says.

These are as follows:

1. Health care disparities: "We want to make sure providers understand what is going on in disparities, what the diseases are, and what the issues that different communities have are," Pesquera explains. "This is not only in health care, but in the provision of health care too."

This module will focus on the local counties and their data regarding the languages residents speak and how to provide interpretation for them.

"We'll focus on how many encounters we have in health care with people who require Spanish interpretation or Mandarin or other languages," Pesquera says. "We need to make people realize the high numbers of our patients who request over-the-phone interpretation.'

2. Racial ethnicity of the county: This module will look at the countries patients come from and will help providers of care understand the health beliefs and practices of this population, Pesquera says.

"If health care providers tell me the majority of the limited-English proficiency patients are from El Salvador, then they can ask that I come up with a module addressing that population," he says. "I'll interview leaders at churches, etc. and come up with modules that help providers understand the patients' practices, beliefs, and health behaviors."

3. Stereotypes, biases, and assumptions: "I go under the assumption that if we live in this world, we all have stereotypes, biases, and assumptions," Pesquera says. "That's the premise I start with in this module."

The purpose of this module is to help people bring to the surface their own hang-ups, he says.

"Sometimes, without our saying a word patients can sense what we're thinking or feeling and what our apprehensions are," Pesquera explains.

Studies involving placing electrodes on people's heads showed that if someone is sitting at a table and someone walks into the room upset, the electrodes show that without either person saying a word, the person who is sitting at the table has the same neurons light up as the upset person, Pesquera says.

"The same thing happens with a happy person," he adds. "If the happy person looks at you in the eyes, then the same neurons in you light up as are in the happy person."

There's a human connection that takes place even without words, and until providers fully understand this, they will not be aware that they can walk into an exam room and jeopardize their relationship with a patient before they even say "Hello," Pesquera says.

The modules are presented as inservices to groups of no more than 20 physicians, nurses, and research professionals and include exercises and discussions.

Pesquera also offers these other suggestions on how to reduce disparities in health care and research:

• Hire diverse research and health care staff.

"Our providers of care are quite diverse," Pesquera says. "We have providers from every country you can think of, including nurses from the Philippines and Africa."

Having a diverse group of providers helps to reduce the need for medical interpreters, and it helps build trust more quickly.

"When you look at our staff, we do represent the communities we serve in terms of diversity," Pesquera notes.

• Make certain informed consent forms are translated appropriately.

It's best to hire organizations that are well qualified in medical translation to translate informed consent documents, Pesquera advises.

When the translated informed consent documents arrive, the next step is to provide a proper quality process check-up, he says.

"Give the translated document to another translator and have him or her translate it back into English to compare this document to the original English document," Pesquera says. "That's the quality process that will be required for consent forms, and any company that wants to do translations for us will have to use that process."

• Use interpreters who are trained in health care jargon and situations:

If an institution has employees or volunteers who are multilingual and who are interested in being interpreters, then it's important to provide them with medical interpretation training, Pesquera says.

"We have a three-day course that trains people to interpret medical skills in the appropriate

setting," he says. "They can serve as a conduit between providers and patients, and they could be either volunteers or paid employees."

The training includes information on ethics and medical terminology and how to be transparent in a patient-provider relationship, he says.

One of the biggest complaints providers have of untrained interpreters is that they will develop a relationship with the patient that is independent of the provider, Pesquera says.

"Say we're both Spanish speakers and both from Puerto Rico, then all of a sudden we develop a great relationship in the exam room, and I tell you what my mom did for a cold when I was little, and I forget the doctor is there," Pesquera explains.

"Then we talk again and I'm basically taking history as an untrained physician, and I develop a relationship with you when I have no right to do that," he adds.

So the medical interpreter training teaches interpreters such details as where to stand to minimize interference with the provider-patient relationship, Pesquera says.

"We teach them to look at the floor so they don't have eye contact with the provider or the patient," he adds. "If there was a curtain in the room, we'd have them stand behind that."

When there isn't a curtain, the interpreter should stand in a way that suggests there is a curtain between him or her and the patient.

The goal is to help the provider improve his or her relationship with the patient, and the interpreter can assist by not interfering and by giving the provider information about any hot button cultural issues that arise, Pesquera says.

For instance, if the patient is a teenage girl who sees the doctor with her mother, and there is an issue involving birth control pills, then the interpreter might let the provider know that it would be wise to ask the patient's mother to leave the room so that the girl can speak freely, Pesquera says.

Interpreters who already work in the institution as an employee could be paid a differential for taking on this extra role, but they must know the medical terminology and be fluent in both English and the second language, he notes.

When there are not any local interpreters available, an institution could use a qualified medical interpretation service and have interpreters work via telephone calls. ■

What to do when the wrong end points are selected

Expert offers advice

It's not uncommon in research for the clinical trial to end without the expected positive outcomes, but with some positive results that were not an anticipated end point.

When this happens, what should sponsors and investigators do, especially when the findings suggest the study product is more effective than the study's end points show?

This question recently arose with a cancer vaccine study, says **Philip M. Arlen**, MD, director of Clinical Research Group at the National Cancer Institute's Laboratory of Tumor Immunology and Biology in Bethesda, MD.

Cancer vaccine trials use tumor shrinkage as study end points, Arlen says.

"We try to help people live longer, and the ultimate goal is survival," Arlen says. "The shrinkage of the tumor is a surrogate [end point]."

The theory is that if the treatment results in the tumor shrinking, then that will lead to the patient surviving longer with cancer, he explains.

"But what we're finding with cancer vaccines is that patients with the more advanced disease who are given the vaccine might not have actual tumor shrinkage," Arlen says.

Instead, investigators were surprised to find that patients were living longer after being given the vaccine, but this positive outcome was not picked up with the surrogate end point of tumor shrinkage, he adds.

In other words, the tumor response was different from the patient response.[1]

"Traditionally in cancer treatment we have been using drugs that are cytotoxic," Arlen says. "These chemotherapy drugs basically result in tumor shrinkage."

The drugs were very toxic to tumor cells, but also were toxic to other human cells, resulting in the side effects of gastrointestinal problems, including vomiting and diarrhea, Arlen says.

"But you don't see these side effects with the vaccine," he notes.

Arlen and other investigators looked at five different prostate cancer clinical studies that were conducted at different stages of the disease, including some phase II studies. The data suggest that survival may be changed with the vaccines.

"We're seeing a 20 to 30 percent prolongation of survival," Arlen says. "So if you expect an 18-month survival, then you'd have six months longer survival on average per cohort."

Investigators theorized that this phenomena was due to cancer vaccines initiating a dynamic immune process that was exploited in later therapies and that both radiation and some chemotherapy agents alter the tumor cells' phenotype, which makes them more susceptible to T-cell mediated killing.[1]

"When patients go from one therapy to another type of therapy, it's possible they will respond better to the second therapy because of the dynamic vaccine," Arlen explains. "And the patient may have a better response to the next therapy after the vaccine, and this could translate into survival."

The results showing the vaccine's positive impact on survival suggest that it would be worth the time and cost to enroll patients in a larger study that looks at survival end point, Arlen says.

Researchers are studying whether the cancer vaccines may be dynamic, so that even when you stop it there may be activity for years, Arlen says.

The vaccines don't act like drugs, but may be training the immune system to attack cancer, he notes.

"Maybe what we should be looking at is there isn't one primary end point," Arlen suggests. "Maybe there should be two end points built into the study."

One end point would show progression, and the other would show overall survival, he adds.

"Obviously, the progression end point is the one you'll reach much sooner," Arlen says. "And if you see that it is a surrogate to seeing overall survival, then you possibly could get approval for commercial use based on the surrogate."

But even when the progression end point doesn't show positive outcomes, the survival outcome, which is the one that is more important, may be reached, he says.

A chief problem with designing clinical trial studies this way has to do with the statistics, Arlen says.

"The current dogma is that there should be one end point to build the statistics and number of patients on," he says. "The second issue is when do you pick the second end point?"

For instance, an end point of survival requires a much longer time period to obtain, Arlen says.

"Because of the time frame, it requires a larger number of patients to be put on the study," he says. "The larger the group, the longer it takes to accrue patients and complete the study."

Often investigators and sponsors want answers quickly, so they select end points that may result in answers sooner, Arlen says.

The cancer vaccine trials' experience with having examined the wrong end points is not that unusual, and investigators should keep the phenomenon in mind when starting clinical trials, Arlen notes.

"Often times with [traditional] drugs, you will give it once, and then it's out of the system, so the benefit is only during the time you've given it," Arlen says.

CE/CME Objectives / Instructions

The CE/CME objectives for *Clinical Trials Administrator* are to help physicians and nurses be able to:

- **review** pertinent regulatory mandates;
- **develop** practical clinical trial oversight strategies;
- **review** best practices shared by facilities that successfully conduct clinical trials.

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

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

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

COMING IN FUTURE MONTHS

- ■ Optimize enrollment processes
- ■ Here are chief causes of noncompliance
- ■ Improve clinical trial completion timeline
- ■ Manage the placebo effect following this advice

"But with the vaccine and new therapies, you may see benefits continue well past the actual time the person is receiving the therapy," he adds.

Molecular-targeting therapies change the biology of the tumor. These therapies may have benefits from combining with another therapy or giving a more conventional or traditional therapy afterward. When this happens, investigators might see continued benefits from the first therapy, Arlen explains.

Investigators who study cancer might consider using survival time as an end point, but so should investigators studying infectious diseases such as hepatitis C and HIV, Arlen says.

"People are living longer with these diseases, although we may not be curing them," he says.

Survival as an end point should definitely be considered.

"The statistics could be arranged to incorporate the end points and still keep things relatively simple," Arlen says. "It may be complex with larger numbers of patients, but I think that's something that could be worked out." ■

Reference:

1. Schlom J, et al. Cancer vaccines: moving beyond current paradigms. *Clin Can Res*. 2007;13(13):3776-3782.

CE/CME *questions*

9. Under the Lean/Six Sigma process of improving clinical research, which of the following questions should both sponsors and sites ask themselves?
A. How do you get patient materials to sites faster?
B. How long will it take to schedule the first participant visit?
C. How can the organization sustain the delivery of its strategy?
D. All of the above

10. In a study that looked at patient adherence, investigators found that what percentage of college-educated patients who had glaucoma would take their eye drop therapy as prescribed?
A. 25 percent
B. 31 percent
C. 68 percent
D. 82 percent

11. Which of the following is one of the chief complaints providers have about interpreters who meet the patient with them in the exam room?
A. The interpreters take too long in interpreting what's said.
B. The interpreter infringes on the provider-patient relationship by becoming too familiar with the patient.
C. The interpreter misunderstands common medical terms.
D. None of the above

12. A study of recent cancer vaccine trials showed which of the following patterns?
A. Vaccine trials proved the therapy shrunk tumors at twice the rate of conventional therapy.
B. Vaccine trials tended to have no positive outcomes with regard to the tumor shrinkage end point, but did tend to result in patients having longer survival times, indicating that the wrong end points were studied.
C. Vaccine trials looked at too many end points and did not come up with conclusive outcomes.
D. All of the above.

Answers: 9. (d); 10. (a); 11. (b); 12. (b)