

Clinical Operations: Bringing All of the Pieces Together

AFTER DECADES OF RIDING WAVE AFTER WAVE OF INNOVATIVE NEW THERAPIES, pharmaceutical developers find themselves staring down a host of significant patent expirations, with the next generation of novel therapies not quite ready to make their market debut.

According to the Outlook 2008 report from Tufts Center for the Study of Drug Development (CSDD), the most successful drug developers in the coming years will be those who radically change their entire approach to business — from R&D to project management to manufacturing to marketing.

by
Carolyn Gretton

A recent Tufts CSDD study cites research showing that the cost to develop a new biopharmaceutical is now more than \$1 billion. Accordingly, clinical organizations are under growing pressure to reduce research and development costs while accelerating development timelines. Clinical operations executives in particular are being called upon to manage drug development functions more efficiently and effectively and to save money while doing so. They are rising to the challenge by improving their collaborations with CROs and investigative sites and employing technologies to streamline and optimize the collection and dissemination of clinical data, making it easier for R&D executives to quickly decide which candidates warrant continued investment and which need to be left behind.

TECHNOLOGY BENEFITS

According to Tufts CSDD, the near-term ability of drug developers to survive and thrive in the current environment will flow largely from their ability to evolve their management and information systems to improve access to new development platforms and tools. Clinical operations leaders have adopted a number of best practices and cutting-edge tools to manage the overall complexities and costs associated with clinical trials.

Among the most widespread technologies are electronic data capture (EDC) systems, which according to René Belder, M.D., senior VP, clinical and regulatory affairs at PharmacoPeia, have significantly improved companies' ability to manage clinical-trial programs.

"Remote data entry has affected the way trials are conducted by providing access to data the moment the informa-

tion reaches computers," Dr. Belder says. "It makes it easier for physicians to monitor the study and allows for earlier detection of potential safety signals."

Another tool being employed by the industry is the clinical trial management system (CTMS).

"Having an effective clinical trial management system is key to facilitating the planning and tracking of study deliverables within the desired time and cost constraints," says Maria Smith, global head, clinical operations affiliates, at Roche. "EDC is also critical to facilitate the collection and review of clinical-study data in a timely manner. To drive compliance and quality, we launched a quality risk management project that combines FMEA (failure modes and effects analysis) principles with data mining of quality relevant data elements and as such, this allows us to monitor in real time the performance and compliance of all entities involved in a clinical trial — sites, CROs, internal processes, and so on."

While many companies are banking on technologies to improve their clinical-trial processes, they may not be getting the most out of their systems because of some common mistakes that may occur during the implementation of complicated and highly customizable systems, which can lead to delayed rollout or systems that simply "die" before they are enacted. To ensure the successful adoption of a CTMS, experts at Campbell Alliance say organizations should be aware of the most common errors associated with implementation. (For more information on the most common errors and methods to overcome implementation miscues, please turn to page 22.)

According to recent study results cited by Wolfgang Renz, M.D., Ph.D., president of Samaritan Therapeutics, the

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number of pharmaceutical and biotechnology companies using EDC in clinical trials is projected to reach 48% this year, up sharply from 7% in 2005, constituting more than a five-fold increase in only a three year time span. Another 30% of pharmaceutical and biotechnology companies will employ EDC in 50% to 90% of their trials in the next year, Dr. Renz says.

"Pharmaceutical companies are increasingly making EDC-based trials a standard practice, and they are asking CROs to work with them in introducing technologies that will add efficiencies and greater standards of quality to clinical trials," Dr. Renz adds.

Greater regulatory emphasis on proving safety and efficacy has led to growing standardization and automation of all aspects of clinical trials. Dr. Belder says this standardization has made it easier for regulatory agencies, such as the U.S. Food and Drug Administration, to more quickly accept and organize clinical data.

"Standardization ultimately will probably make it easier for companies that in-license compounds for which there is already a database available to quickly take the product over

and continue development with no lag time from the time it took to complete the acquisition," Dr. Belder adds.

According to a PhRMA-sponsored Gartner study, more than half of the value of implementing standardized data and processes occurs during the study start-up stage, which can reduce time for these activities by 70% to 90%. Medidata Solutions experts believe that in recognition of these benefits, many pharmaceutical companies are looking for tools to enable structured data creation at the study-design stage, which has led to the emergence of the e-protocol. The basic premise behind the e-protocol is that the immense amount of work already performed at the study design and protocol development phases can be leveraged throughout the clinical process, rather than being manually copied and reinterpreted throughout the process. (To learn more about the e-protocol process, please turn to page 24.)

Pharma was initially slow to adopt electronic tools for clinical-trial management, in part because of the heavily regulated nature of the industry, Dr. Belder says.

"Pharma's hurdles to incorporate newer technologies are more difficult because of the large amount of validation



Maria Smith

Roche

THOUGHT LEADERS

■ **RENÉ BELDER, M.D.** Senior VP, Clinical and Regulatory Affairs, Pharmacoepia Inc., Cranbury, N.J.; Pharmacoepia is a development-stage biopharmaceutical company dedicated to discovering and developing novel small-molecule therapeutics to address significant medical needs. For more information, visit pharmacoepia.com.

■ **KAMRAN HOSSEINI, M.D., PH.D.** VP, Clinical Affairs and Chief Medical Officer, InSite Vision Inc., Alameda, Calif.; InSite Vision is an ophthalmic company focused on therapies that treat ocular infections, glaucoma, and ocular diseases. For more information, visit insitevision.com.

■ **MARK J. PYKETT, V.M.D., PH.D., MBA.** President and Chief Operating Officer, Alseres Pharmaceuticals Inc., Hopkinton, Mass.; Alseres Pharmaceuticals is a biotechnology company engaged in the development of biopharmaceutical products for the treatment of traumatic injuries and degenerative diseases. For more information, visit alseres.com.

■ **WOLFGANG RENZ, M.D., PH.D.** President, Samaritan Therapeutics, Montreal; Samaritan Therapeutics is a Canadian-controlled private biotechnology company focused on developing innovative drugs to treat Alzheimer's disease, cancer, heart disease, and infectious diseases; Samaritan Therapeutics is minority-owned by Las Vegas-based Samaritan Pharmaceuticals Inc. For more information, visit samaritanpharma.com.

■ **STEPHEN M. SIMES.** President and CEO, BioSante Pharmaceuticals Inc., Lincolnshire, Ill.; BioSante Pharmaceuticals is a specialty pharmaceutical company focused on developing innovative testosterone and estrogen products for female sexual health, menopause, contraception, and male hypogonadism. For more information, visit biosantepharma.com.

■ **MARIA SMITH.** Global Head, Clinical Operations Affiliates, Roche, Nutley, N.J.; Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. For more information, visit rocheusa.com.

■ **SUSIE TRUONG.** Director of Finance and Administration, Cequent Pharmaceuticals, Cambridge, Mass.; Cequent Pharmaceuticals is an early-stage biopharmaceutical company that is pioneering the development of novel therapeutics to prevent and treat a wide range of human diseases — from inflammatory diseases to cancer. For more information, visit cequentpharma.com.

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Dr. Kamran Hosseini

InSite Vision

Accelerating the clinical development critical path can be achieved by developing appropriate contracts and expediting subject enrollment strategies, which may also contribute to healthy budget control. **And employing strategies to oversee misconduct and fraud is a must to protect patient safety and prevent possible legal and regulatory consequences.**

that needs to occur," he says. "To a certain extent, the airline industry is undergoing the same challenges; flight control centers are still working with equipment that's decades old. There are a lot of good, newer technologies available, but they haven't been validated; this is a huge undertaking.

"But the pharmaceutical industry is getting there, and that's good," Dr. Belder continues. "When I first came to the United States, Bristol-Myers Squibb had filed a paper-based NDA for pravastatin, and it took a whole truck to get all the paper to the FDA, not to mention the amount of time it took regulators to sift through all the data. Now the process is much more rapid; if a company has a team prepared to put everything together the minute its last study is complete, the NDA can be filed very quickly. That wouldn't have been possible a decade ago. So there definitely have been enormous productivity gains in this regard."

Thought leaders at PHT Corp. agree that one of the key benefits of e-source technologies is the ability to shorten the time to database lock and data analysis. Technologies such as

ePRO eliminate many of the bottlenecks associated with collecting questionnaire data on paper, such as double data entry, queries, and other costly delays. Additionally, industry research indicates that 50% to 60% of trials capture health-related quality of life (HRQL) and other questionnaire data. This figure is expected to rise significantly, considering the FDA's PRO Draft Guidance and its emphasis on involving the patient perspective. (To learn more about how ePRO can be used to improve the trial process, please turn to page 26.)

Standardized technical, legal, and financial strategies are also crucial to good clinical-trial management practices, says Kamran Hosseini, M.D., Ph.D., VP, clinical affairs and chief medical officer, at InSite Vision.

"Optimizing mission success is dependent on timely recognition and classification of risks related to technical, legal, and financial domains," Dr. Hosseini explains. "Accelerating the clinical development critical path can be achieved by developing appropriate contracts and expediting subject

A Typical [adjective] Article About the FDA

EDITOR'S NOTE: PETER J. PITTS, A FORMER FDA ASSOCIATE COMMISSIONER AND PRESIDENT OF THE CENTER FOR MEDICINE IN THE PUBLIC INTEREST, POKES SOME FUN AT THE ARTICLES BASHING THE FDA BY TAKING A PAGE OUT OF THE CLASSIC "MAD LIBS" PUBLICATION. MR. PITTS CAN BE REACHED WITH COMMENTS AT PETER.PITTS@CMPI.ORG.

By Peter Pitts

[BIG CITY], [date] – Today [adjective] Citizens for [superlative adjective] Health released a [adjective] meta-analysis that [adverb] concludes the FDA "is in the [noun] of [adjective] Pharma."

"Our research of [number] concerned [plural noun] points [adverb] to an agency that has once again [verb past tense] the American public. It's a [adjective] indication that the FDA places [noun] over [noun] and cannot be trusted to [verb] or [verb] – and certainly not [verb] in the public interest," said the author's report Dr. Egor [type of animal].

The study showed that most new drugs for a wide variety of chronic [type of disease] are ineffective and also [adjective]. In the case of [brand-name drug] it was shown that [plural noun] were more likely to [verb] from [human organ] attacks than patients on older and [adjective] medicines.

"I find this new report both [adjective] and [adjective] — but [adverb] not [adjective]," commented Congressman



Peter Pitts
President, Center for Medicine in the Public Interest and Former Associate Commissioner, FDA

Bartholomew [type of insect]-man. "And I intend to hold televised [plural noun] on the matter."

"This is just another [adjective] example of the FDA's lack of [adjective] [noun]," added Dr. [name of automobile company] Buttersworth. If I were the FDA Commissioner this [adjective] circumstance would never have occurred."

In an embargoed editorial in the New [name of country] Journal of Medicine, Dr. Ethel [type of cake] opined that the [adjective] problem "is caused by the Prescription [noun] User-Fee Act and made even [adjective] by the agency's continued [verb] of direct-to-[noun] advertising." The editorial also points to the need for [adjective] importation of prescription [plural noun] from [name of country].

Supporting this notion, the [any acronym] added that in addition to being [adjective], high [plural noun] for brand drugs are a result of the [type of shrub] Administration's [adjective] program known as Part [letter] and called for [name of movie studio] care.

The FDA had [adjective] comment.

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Dr. Beat Widler

Roche

If we want to be serious about personalized healthcare, then a one-size-fits-all approach to clinical development can no longer be the path to follow.

enrollment strategies, which may also contribute to healthy budget control. And employing strategies to oversee misconduct and fraud is a must for companies to protect patient safety and prevent possible legal and regulatory consequences."

While many developers outsource some or all of their clinical-trial management processes, some believe it's best to manage those functions in-house.

"Obviously computers are key, with the appropriate software to track all aspects of recruitment, randomization, and data collections, but our people are still the critical technology," says Stephen Simes, president and CEO of BioSante Pharmaceuticals. "We believe our best practices in clinical trials are to control the process in-house: we write the protocols, submit to the FDA, and negotiate directly with the FDA. And once the protocols are finalized we contract directly with investigators and monitor the trials, so we can thereby better control budgets and timeline."

In terms of protocol development, according to experts at Ateb, the genesis of each clinical project is preprotocol feasibility. By employing pharmacy outreach services, the study team can complete a thorough preprotocol analysis of the patient profile, indication prevalence, and population prevalence. This forerunner activity occurs before the protocol submission. (To learn how preprotocol development can help sustain study design at the inception to determine overarching success of the study, please turn to page 30.)

CLINICAL FLEXIBILITY

In other best practices, clinical developers are employing more adaptive clinical-trial designs that take advantage of optimizing study sample sizes, according to Mark Pykett, V.M.D., Ph.D., MBA, president and chief operating officer of Aleres Pharmaceuticals.

"There is increasing emphasis on the use of efficient clinical-trial designs and sophisticated statistical analysis plans," Dr. Pykett says. "The advent of Bayesian statistics to drive adaptive trial designs facilitates the streamlining of subject sample sizes, earlier completion of studies, and the sparing of resources. Adaptive designs also allow for flexibility in dose ranges and less guesswork in picking appropriate protocol parameters, without sacrificing statistical rigor or power in support of demonstrating a drug's effectiveness and safety."

According to Beat Widler, Ph.D., global head, quality assurance at Roche, a better understanding of the disease biology, the rapid gain in knowledge of biomarkers and their application to the clinical day-to-day reality, plus the more widespread introduction of novel statistical techniques, are changing the approach to early clinical investigation.

"This approach will be critical in identifying dead-ends in clinical development early and to optimally position successful new drug candidates," Dr. Widler says. "If we want to be serious about personalized healthcare, then a one-size-fits-all

approach to clinical development can no longer be the path to follow."

"Adaptive clinical trials will undoubtedly have a place for certain indications and therapies," Dr. Hosseini says. "They require different methodologies and a real-time multidisciplinary approach not yet fully and proficiently adapted by many pharmaceutical companies and their vendors. This expertise needs to be developed to effectively gauge the utility of such an approach per indication, or else there is the potential that interim revisions to the study design could have a negative impact on the clinical trial."

In an effort to more quickly identify viable product candidates, more companies are employing the exploratory IND (eIND) as an option for streamlining the early-phase development process.

"In certain cases, exploratory INDs are well-suited for entry-level studies because they allow for first-in-man evaluations that are based on less nonclinical pharmacology, pharmacokinetic, and toxicity data," Dr. Pykett says. "This means that a significant amount of time and cost can be deferred until some key parameter of the agent has been demonstrated in the baseline eIND study. If the parameter is not verified through the eIND, resources that would have otherwise been expended can be spared. Of course, the tradeoff is that because lower doses and/or exposures are typically explored in an eIND, less information will be gathered than if a full IND had been pursued."

Dr. Widler hopes that the exploratory IND process will foster a dialogue between the FDA and sponsors and thus build the trust basis, allowing new models for development and techniques to be explored.

"Any change in the regulatory framework that supports the introduction of novel approaches to development is welcome," he says.

Dr. Hosseini notes that the eIND is especially useful in efficiently and rapidly identifying promising drug candidates in therapeutic categories such as cancer, where the ratio of failed drug candidates to successfully commercialized products is high.

"The potential cost savings are enormous, and this will free up more funding for additional research," he says. "Exposing patients to very low doses of drugs will enable pharmaceutical company sponsors to collect valuable data for a meaningful trial while the safety of these patients is much less likely to be jeopardized."

When it comes to protecting the safety of patients in clinical studies, there is a growing movement to develop guidelines for QT assessment in oncology agents, biologics, or large molecules. The agency is requiring data for these compounds with an eye on whether these trials will be needed in the future. Experts at Biomedical Systems are recommending that the sponsors include as many elements for the thorough QT (TQT) paradigm as possible as part of intensive QT trials. (To learn more about the ICH E14, which gives guidance

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regarding the conduct of so-called thorough QT trials, please turn to page 38.)

THE PATIENT EQUATION

Patient recruitment and retention are perennial problems for investigators and are major causes of delays in studies.

Mr. Simes recommends using companies that specialize in study recruitment through news releases, advertising, and community outreach to attract patients that are well-suited to the trial in question and thus may be less likely to drop out.

"The right recruiter can effectively organize a campaign to realize timely recruitment," Dr. Hosseini says.

But, according to thought leaders at The Patient Recruiting Agency, evaluating and allocating cost-efficient and cost-effective advertising budgets for a patient recruiting campaign are issues that rarely receive the attention they deserve. (To learn why a well-planned budget is absolutely integral to the success of any recruiting campaign, please turn to page 36.)

"Retention is highly dependent on the patients' relevant awareness and education and ultimately the sense of self-responsibility that can be achieved through positive and respectful interaction with them," Dr. Hosseini says.

"Simplifying the protocol design can make it easier for patients, investigators, study monitors, and contractors to fulfill all of their obligations toward maximum retention of patients in the database," Dr. Pykett adds. "Also, limiting the duration of follow up and the number of follow-up visits, if at all possible, can lessen the time-dependent attrition of patients in a study."

Ms. Smith says companies need to consider the patient's perspective when designing clinical trials.

"It's important that we clearly convey what the benefits and risks of the trial are, what the experimental treatments are, and the rationale for the frequency of visits and assessments that will be performed, and that we partner with sites to provide information that is of benefit to patients," she says.

Dr. Renz notes that it's essential to identify the best geographical regions and sites with proven recruitment records and protocol compliance. Consulting key opinion leaders in all regions involved substantially helps in pinpointing the best routes to take when introducing a new clinical trial for a specific therapeutic indication.

Experts at Inclinix agree that it's vitally important to question whether the needed patients are available at the investigator sites. Answering this question incorrectly means that the clinical trial will fall short of its goal, and most trials run late due to patient enrollment issues. (Please turn to page

34 to read a case study that illustrates how early scrutiny allowed the use of direct-to-patient advertising to solve an enrollment shortfall, before it occurred.)

CROS AND OUTSOURCING

According to Tufts CSDD, more difficult protocols and lower compensation could inhibit study efficiency. The burden on investigative site personnel to execute study protocols increased 10.5% annually between 2000 and 2005, as the number and frequency of procedures per protocol increased. During this same period, site compensation per procedure declined by almost 2% in nominal dollars.

Drug sponsors are expected to employ new site selection and management practices and electronic clinical-trial technology solutions to improve study conduct inefficiencies. While global clinical grant spending continues to rise — exceeding \$8 billion in 2007, according to Tufts CSDD — half of all sites continue to underperform or fail to enroll patients into trials. Therefore, sponsors are likely to focus more attention on simplifying and streamlining protocols to reduce conduct delays and improve investigative site adherence and performance.

To that end, demand for contract research organization (CRO) services is projected to increase by 16% annually over the next three years as sponsors seek assistance in managing large, complex global projects without increasing their internal headcount, the Tufts CSDD study says.

Dr. Pykett notes that specialized contract research organizations can provide key expertise the company doesn't have internally, and deliver services on a variable cost basis that can limit carrying costs.

"A combination of contractors can often provide knowledge depth and efficiency the organization could not otherwise achieve," he says.

Roche's Ms. Smith agrees that the optimal approach is to have several preferred partners to optimize the working relationship.

"And, if needed, we consider a niche CRO when a specific expertise is required," she adds.

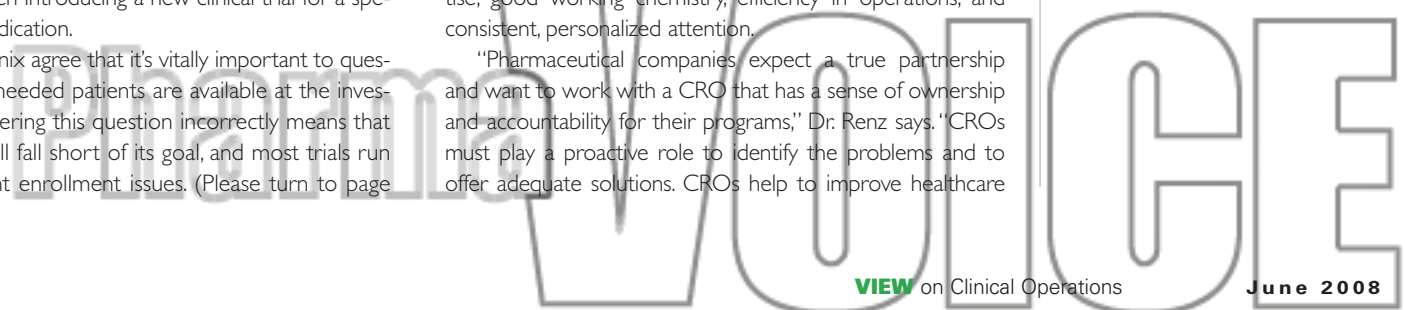
Some characteristics clinical operations executives cite as crucial for a good CRO partner include therapeutic expertise, good working chemistry, efficiency in operations, and consistent, personalized attention.

"Pharmaceutical companies expect a true partnership and want to work with a CRO that has a sense of ownership and accountability for their programs," Dr. Renz says. "CROs must play a proactive role to identify the problems and to offer adequate solutions. CROs help to improve healthcare



Dr. Mark Pykett

Alseres Pharmaceuticals



Remote data entry has affected the way trials are conducted by providing access to data the moment the information hits the computers;

this makes it easier for physicians to monitor the study and allows for earlier detection of potential safety signals.



Dr. René Belder

Pharmacopeia

worldwide by providing a broad range of professional services, information, and partnering solutions to the pharmaceutical, biotechnology, and healthcare industries. The CRO does what the sponsor needs and the way the sponsor expects at an optimal cost."

"There is no substitute for a track record in the specific area of expertise for which the CRO is being hired," Dr. Pykett says. "Even if cost differences support a less-practiced partner, our experience would suggest that the price for getting a partner along the learning curve can consume their economic advantage, and the risk of failure remains higher during the process."

Dr. Belder says Pharmacopeia, which has a cardiovascular drug candidate in Phase II trials, selected one of its CRO partners based on its technical expertise in conducting ambulatory blood-pressure measurements.

"The CRO had a lot of experience with these types of measurements, and the investigators associated with the CRO were well-known in the field," he says.

Developers often must decide whether to go with a single CRO or to select multiple CRO partners based on their various areas of expertise.

"Given the expertise often required in multiple, disparate areas of drug development, we find it preferable to

What's in Your Supply Closet?

SUSIE TRUONG, DIRECTOR OF FINANCE AND ADMINISTRATION AT CEQUENT PHARMACEUTICALS, TALKS ABOUT HOW SHE MOVED CEQUENT TO A SAAS PROCUREMENT MODEL TO HELP THE BIOPHARMACEUTICAL COMPANY FOCUS ON MORE IMPORTANT TASKS.

Many smaller start-up companies in the biotechnology sector face the challenge of managing supplies and consumables amid deadlines and milestones. In addition to the limited manpower that is devoted to purchasing and receiving, biotech start-ups must manage costs right out of the gate. It is important for companies of all sizes to have accurate recordkeeping, appropriate cost controls, and policies in place for purchasing goods and services used in R&D.

The problem, of course, is that at some point the pursuit of scientific research and management chores collide. If the company doesn't take steps to ensure operational efficiency, it will waste time and money on nonessentials that do nothing to advance the critical research it is conducting. The company may burn through funds and have nothing — or at least not enough — to show for it.

At Cequent Pharmaceuticals, progress is measured by several benchmarks. In addition to meeting our goals, we must also ask: does the company maximize its efficiencies and can we do more to streamline spending when revenue is not yet on the horizon?

Cequent orders numerous items used in drug discovery from more than 150 different suppliers, and we had traditionally managed all those orders through a time-consuming, paper-based system consisting of handwritten Post-it notes, e-mails, and scraps of paper.

After two months of increasing purchasing activity and spending, we wanted to evaluate our purchasing policy to take advantage of cost savings wherever possible.

Time is a currency that is often more valuable than money for biotech businesses. Even if generously backed by venture capital, companies must show investors that milestones are being met and progress is being made. There is a delicate balance between managing costs and accelerating progress. When I saw we were falling behind on inventory management, I knew we needed to take a more sophisticated approach to procuring supplies to keep our entire business on track.

But there was a catch. When we researched e-procurement solutions, some vendors told us we were too small for them to even consider our business. Additionally, most commonly used enterprise software applications seemed to

add more complexity to our business processes rather than simplifying them. The majority of e-procurement implementations fail or are abandoned because employees find it easier not to use them, despite the time and expense involved in implementation and training.

At Cequent, most workers were so engaged in their research they had little interest in learning a new software program related to ordering supplies.

Ultimately we discovered another approach, an e-procurement software delivered under a SaaS (software as a service) model.

SaaS is hosted as a service across the Internet, eliminating the need for companies to install software or provide ongoing maintenance. The SaaS model also eliminates a lot of the up-front investment and time requirements associated with buying and installing enterprise software, while also providing employees with more ongoing support.

The e-procurement software is designed to simplify purchasing for small and medium-sized businesses and we were able to get the software up and running swiftly so that we could better monitor orders and spending. And since SaaS solutions incorporate user-friendly Web 2.0 capabilities, we had little trouble getting employees to adopt it. It quickly became apparent how this software simplified their lives — and mine.

With a new e-procurement solution, Cequent moved quickly from not knowing what was in the supply closet to being able to track which items employees were ordering, the prices they were paying, and the dates the shipments were received.

Within three short months, the software had paid for itself. We were able to track trends in ordering and bundle orders to save on shipping expenses and handling fees. The SaaS provider we engaged was able to use the data to negotiate more favorable pricing with our top 10 vendors. Additionally, we gained the ability to approve purchases via our e-mail system to create an audit trail that appeased our auditors.

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Dr. Wolfgang Renz

Samaritan Therapeutics

Pharma companies are increasingly making EDC-based trials a standard practice, and they are asking CROs to work with them to introduce technologies that will add efficiencies to the clinical trials.

use multiple CROs to access the specific organizational knowledge capital required for the best outcome," says Dr. Pykett, whose company, Alseres, is researching a number of drug candidates across a broad spectrum of traumatic injuries and neurodegenerative conditions.

"Using a series of CROs can also mitigate certain risks associated with a single contractor and can in some cases lower expenditures as we access different cost structures," he continues. "However, simultaneously this approach can increase the internal requirements to actively manage the CROs and may lead to additional complexity if the project requires CRO integration."

"Certain CROs have developed expertise and experience for a group of indications over the years," Dr. Hosseini says. "Obviously, working with these CROs for a certain indication can significantly increase the likelihood of seamless interactions. But we need to consider the overall proficiency of a CRO to select a final partner."

Roche has established partnerships with a select number of CROs to facilitate a working relationship.

"Some expected outcomes include enhanced efficiency, flexibility, and decreased development time as we work seamlessly with the same companies and their people over time," Ms. Smith says.

Other developers believe companies, especially smaller organizations, should find one CRO that meets all their development needs.

"Pharmaceutical companies should seek a single full-service CRO partner that can handle a full drug-development

program," Dr. Renz says. "That way, fewer in-house employees are needed, while efficiently coordinating, managing, and supervising various project activities within expected timelines and especially, within budget."

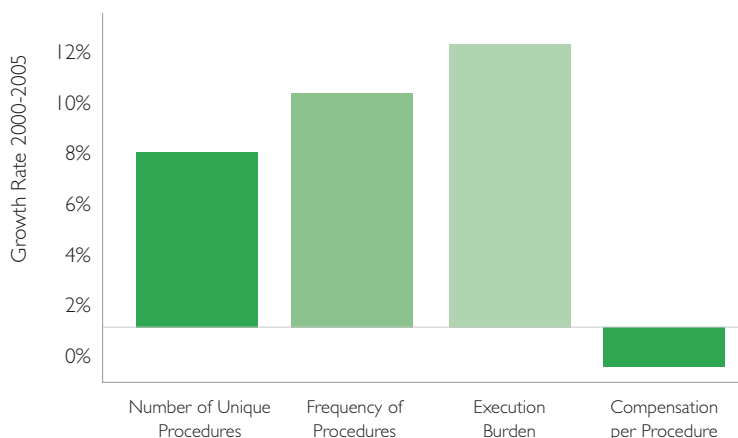
Thought leaders at inVentiv Clinical Solutions contend that biopharmaceutical companies should explore alternatives to the traditional paradigm of full-service clinical trial outsourcing to maintain appropriate levels of control that lower their overall drug development costs. As such, there is a growing trend toward flexible, integrated outsourcing models that allow the proper blend of tactics for current development needs that can be adapted quickly to meet the changing needs of the organization and the industry. (To learn more about flexible and adaptable outsourcing models, please turn to page 32.)

GROWING GLOBALIZATION

Pharmaceutical companies are conducting more and more clinical trials in countries other than the United States. For example, China and India have become increasingly attractive to drug developers because of reduced expenses and easy access to large populations of previously untreated patients available for clinical studies. According to the Tufts study, within the next three years, up to 65% of FDA-regulated clinical trials for the top pharmaceutical companies will be conducted outside the United States, up from 43% at present.

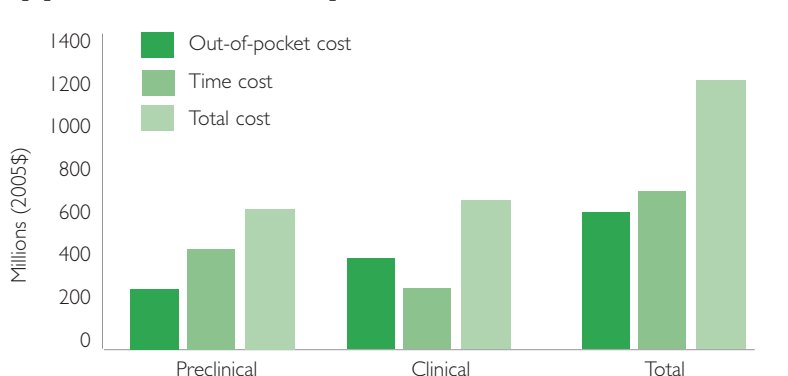
Most clinical operations executives agree that the trend toward globalization will continue.

Investigative Site Protocol Design Changes



The burden on investigative site personnel to execute study protocols increased 10.5% annually between 2000 and 2005 as the number and frequency of procedures per protocol increased. During this same period, site compensation per procedure declined by nearly 2% in nominal dollars. Source: Tufts Center for the Study of Drug Development Outlook 2008. For more information, visit csdd.tufts.edu.

Preapproval R&D Costs Per Approved New Biopharmaceutical*



*Total biopharmaceutical R&D costs include the cost of molecules that fail in testing and the time cost of investing in development years before any potential returns can be earned. Time costs account for more than half of the total cost per approved new biopharmaceutical of \$1.2 billion for recombinant proteins and monoclonal antibodies that entered the clinical testing pipeline from 1990 to 2003.

Source: Joseph A. DiMasi and Henry G. Grabowski, *Managerial and Decision Economics*, Vol. 28, issue 4-5, pgs. 469-479 (2007). Reprinted in Tufts Center for the Study of Drug Development Outlook 2008. For more information, visit csdd.tufts.edu.

Patient recruitment and retention are perennial problems for clinical investigators and are major causes of delays in clinical trials.

"If companies want to run programs efficiently and to enroll patients quickly, they need to be conducting global development programs," Dr. Belder says. "This global trend is not going to diminish."

Dr. Pykett says in the drug-development world globalization is a necessity, given the global scale on which drug commercialization is ultimately sought.

But globalized trials carry risks as well as benefits. Negotiations with local agencies and companies can prove costly and time-consuming, requiring companies to seek clinical and regulatory perspectives that take into account the intricacies of the region.

"Sponsors need to better understand and overcome challenges such as the language barrier and cultural diversities to anticipate patient enrollment and compliance throughout the studies," Dr. Hosseini says. "Additional and evolving regulatory and safety aspects for certain types of studies in some parts of the globe also call for extra vigilance."

According to experts at MediciGlobal, there's a new twist on globalization, called "glocalisation," which is a combination of thinking globally and acting locally. And this is changing how patient recruitment and retention literature needs to be developed. (To learn how technology is improving global processes, please turn to page 28.)

Ms. Smith believes that the competition for clinical-trial sites continues to increase but the number of new investigators is not keeping pace.

"Investigators in emerging economies are eager to provide their patients with opportunities for enhanced medical care," she says.

"Labor and travel efficiencies are also important to drug development and commercialization in other countries," Dr. Pykett adds. "And territory-specific approaches to sales and marketing are important to successful regional commercialization."

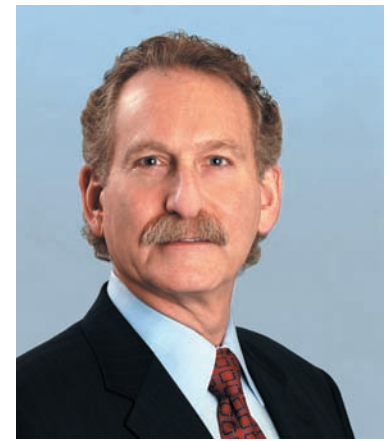
LEADING THE TEAM

Because of the complexity and continually changing nature of clinical-study management, communication and planning skills were two of the attributes most frequently cited as critical to becoming a strong leader in the clinical operations setting.

"Good planning is the key for any great operations executive," Dr. Renz says. "Also, clinical operations teams should work to develop strategic action plans focusing on high-value/high-return activities, create metrics for key clinical activities, implement efficient study management procedures, and ensure clear communications between team members to clarify deliverables and accountabilities, while meeting established timelines and the expected standards of quality."

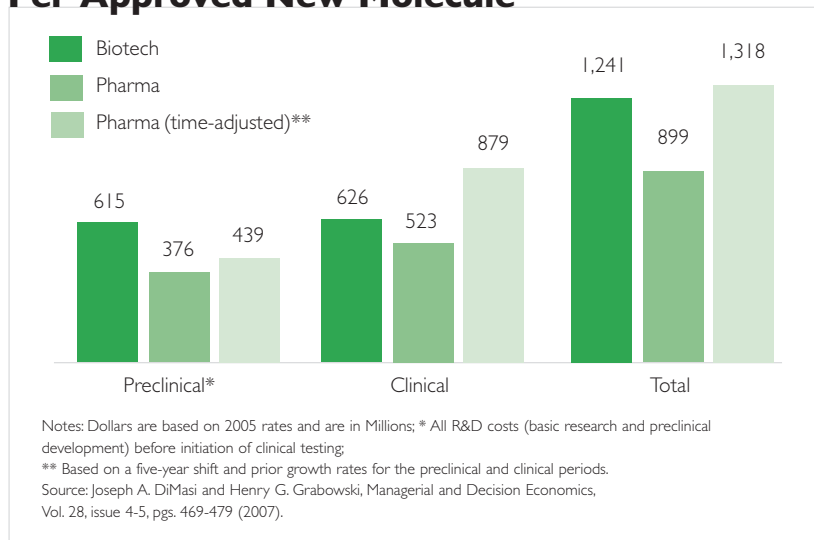
At Roche, clinical operations staffs are located throughout the world. As such, the company has developed RACI (responsible, accountable, consulted, informed) charts that clearly define who is accountable and responsible for certain activities to avoid duplication of effort and ensure a more effective allocation of resources.

When it comes to finding great clinical operations executives, Ms. Smith says Roche looks for people who have had real-life experiences in various roles.

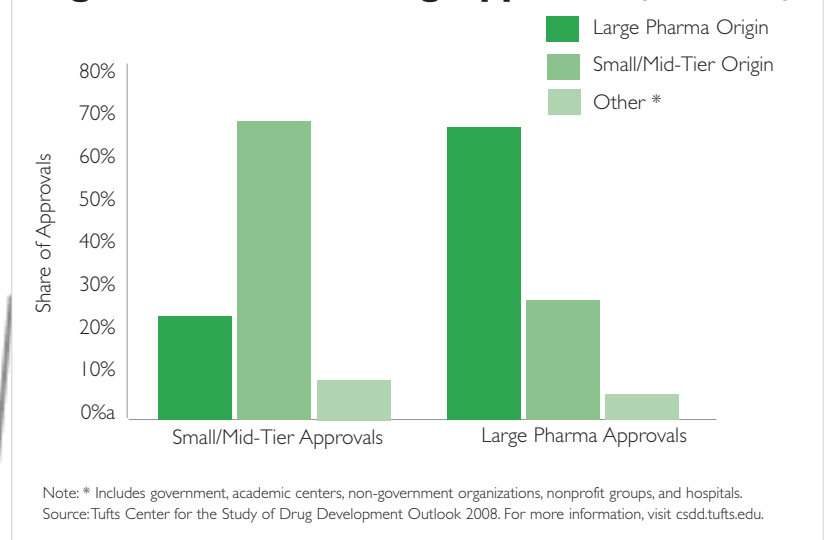


Stephen Simes
BioSante Pharmaceuticals

The Cost of Biopharmaceutical R&D — Pre-approval Capitalized Cost Per Approved New Molecule



Origin of New U.S. Drug Approvals (2000-2006)



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"For example, former monitors are more sensitive to the issues and challenges this role faces," she says. "We also recognize that there needs to be a balance between standardization and the need to be flexible to meet the demands of clinical research across the different disease areas and phases of development."

Executives also need to have extensive clinical knowledge and experience to succeed, Dr. Pykett says.

"Leaders have to have an eye toward the big picture, the ability to see through to the key efficacy outcome measures, and how the study will support the ideal drug label and target product profile; skill at wringing out clinical development risk; an ability to identify trial designs that minimize cost and time without raising risk or sacrificing the drug's market potential; and in-depth knowledge of the clinical landscape in an effort to align the drug with optimal indication positioning," he adds.

"At the end of the day, it's all about successful translation

of biological knowledge into medical practice through clinical trials," Dr. Hosseini agrees. "A great clinical operations executive stays abreast of the modern discovery findings and pre-clinical models, bridging the lab science with the clinical and regulatory domain. I'd compare a good clinical executive to a great music conductor who in this case helps groups of multidisciplinary scientists to interpret and perform pieces of drug development."

Still, Dr. Belder asserts that a top clinical executive must excel at team leadership above all.

"It goes without saying that the person needs to have a good understanding of what drug development is and which pieces need to be taken care of in a drug-development program," he says. "In a large organization, this person has to be able to hire the right people for the various tasks. He or she has to be able to communicate the vision and then be able to manage the team members effectively so that they can exe-

Insights From the Insiders

PHARMAVOICE ASKED EXPERTS IN THE CLINICAL ARENA TO IDENTIFY THE CURRENT BEST PRACTICES BEING EMPLOYED TO MANAGE THE OVERALL COMPLEXITIES AND COSTS ASSOCIATED WITH CLINICAL TRIALS.



Kathleen Drennan
Managing Director
Iris Global Clinical Trial Solutions

For more information, please turn to page 20.

Execution Before Trial Initiation

From our perspective, best practices occur when a very clearly executed strategy and tactical plan is developed before the study has even begun and when relevant market research and feasibility studies are incorporated. Unfortunately, this is a rare occurrence.

In this industry, very few study sponsors implement best practices for managing overall complexities and costs. Each study sponsor has a different approach or set of guidelines to budgeting, contract negotiations, invoicing, and cost management.

Unfortunately, there are companies that will only pay for what they perceive as essential to the trial. But these approaches to budgeting do not often coincide with what is truly needed or essential to move the trial forward and complete it on time.

Additionally, multiple suppliers are often used for a single trial, which complicates things even more. Managing the complex relationships and communications can cause redundancies, increased inefficiencies, and increased costs. Clearly with more than 80% of trials either being delayed or moving into rescue mode, the complexities (i.e., patient recruitment, site selection, and performance) are not being managed well with best practices.



Bill Gwinn
VP, New Product Development
Inclinix Inc.

For more information, please turn to page 34.

Planning and Preparation

From my perspective at a contract research organization, best practices begin with use of research and metrics for strategic planning and preparation. Much of the traditional planning in the industry is about logistics after patients enroll in the trial. Because getting patients enrolled is the most likely source of delay, planning must begin before patient recruitment and site selection.

Finding the best sites includes ranking areas according to disease prevalence. You can "fish where the fish are" to find patients. These same research

databases are the foundation of advertising tools and techniques for outreach campaigns. There is statistical modeling to predict enrollment.

After the trial begins, best practices start with centralized site management tools to understand site status. The foundation of good cost control is being able to predict the obstacles. Nobody can do that flying blind. At minimum, there are online tools for tracking patient status in real time. For a more comprehensive picture, best practices are evolving toward clinical trial management systems integrated with electronic data capture of patient information. The creators of the best systems have mined historical data to create norms for comparison with each trial's interim results.



S. Yin Ho, M.D., MBA
VP, Product Strategy
Medidata Solutions Worldwide

For more information, please turn to page 24.

Think Optimal Practices, Not Necessarily "Best" Practices

"Best practices" are usually defined as current processes that work effectively to solve a particular problem. But what happens when best practices fall short of optimal practices? For example, management of clinical trials has been suboptimal, even if effective, when sponsors fail to recognize that protocol design complexity affects trial execution risk and resulting costs.

Too often trials are designed with ideal patients and measurements in mind, or are a consolidation of multiple trials measuring similar, but subtly different effects. In either case, the need to "reality test" the protocol and its effects on sites and patients is the key to driving down execution risk.

Three practices that can be applied more consistently are: 1) testing the protocol design among practicing community physicians, rather than only academic thought leaders or physicians away from patient care for more than a few years; 2) confirming that the disease epidemiology matches the recruitment plan rationale (e.g., the face of HIV in the United States is increasingly that of African-American heterosexual women in more rural communities, thus sites should be selected from where they live); and 3) making sure sponsor processes are predictable and reliable enough to fully support the sites (e.g. ensuring drug shipments will be ready at the time of investigator meetings).

Pressure-testing protocols and execution plans against real-world logistical realities is a best practice that will enable firms to anticipate and address downstream execution risks and subsequent costs, which will in turn generate optimal results.

cute. A good operations executive hires the people who see more efficient ways of doing things, who will continuously look for even better methods, and who are adaptive to solving problems and issues through the development process."

MOVING FORWARD

In the near term, most experts agree that the clinical development process will continue to evolve, albeit at a more measured pace than in the past few years.

Thought leaders at Iris Global Clinical Trial Solutions say there has never been a better time for change in the way the industry approaches the completion of clinical trials: it's time to go beyond the protocol and embrace a newer way of thinking and planning for a trial. They believe the answer lies in adopting an intelligent trial approach, which takes into account the requirements of the study sponsor in validating its science; the needs of the physician in providing options to patients; and the desire of patients for better treatments or cures, whereby the whole system of values are analyzed rather than simply its individual components. (For more information about intelligent trials, please turn to page 20.)

"Clinical trials will undeniably be more complicated as medical science combats more complicated diseases," Dr. Renz says. "Technology will play a more complex and strategic role in facilitating the execution and management of these large, complex studies. We must also take into account that there are new geographic regions involved in clinical trials, such as Latin America, India, and China."

The existing consolidation trend among pharmaceutical companies will likely filter down to clinical services vendors, Dr. Renz adds.

"In five years, I believe there will be fewer vendors, and most likely those vendors will offer a full range of services, from project management to data management, monitoring, and writing reports," he says.

Dr. Pykett predicts a continuing focus on innovation and platform development from smaller organizations, as well as deals between large pharma and smaller drug developers to fill pipelines.

"There will be continuing emphasis on developing effective drugs that do not meet traditional blockbuster parameters, as pharma builds out increasingly specialized franchises in smaller market segments," he adds.

"The productivity with respect to coming up with new molecules has probably lagged a little bit in recent years," Dr. Belder says. "All the low-hanging fruit have been plucked, and targets have become harder to identify. We understand a lot more about biology and molecular mechanisms, but the knowledge base on how to interfere with these systems hasn't caught up. It's getting there, but it takes awhile before truly novel therapies come out of that process. The whole genetic revolution of the past decade still has to result in novel therapies, and this is taking longer than people had hoped."

PHARMALINX LLC, publisher of the VIEW, welcomes comments about this article. E-mail us at feedback@pharmalinx.com.

Insights From the Insiders

PHARMAVOICE ALSO ASKED OUR THOUGHT LEADERS TO DISCUSS THE TECHNOLOGIES THEY THINK ARE MOST USEFUL IN HELPING TO MANAGE THE COSTS AND INTRICACIES OF MODERN CLINICAL OPERATIONS.



Katherine Luca Nicholson
Client Advocate
Biomedical Systems

For more information, please turn to page 38.

Real-Time Access is Mission Critical

From a core diagnostic lab perspective, giving pharmaceutical sponsors the ability to view their data in real time has become a critical component in modern clinical operations. By using secure Web-based access to a database portal, sponsors can get an immediate overview of the number of diagnostic tests performed, PDFs of the tracings, alert notifications, queries, and other pieces of essential information, which enable them to make more informed decisions on how the trial is being managed. Delays lead to higher costs and lost revenue. Improving the access to critical trial information can help sponsors manage their trials in a more efficient and cost-effective manner.



Elizabeth Moench
President and CEO
MediciGlobal

For more information, please turn to page 28.

Going Global

Regulators are demanding more patients, more data, more countries, and more complexity. As a result technologies aimed at cutting costs and time are essential, but technologies that allow for increased customization as well as those that bring

another dimension. For patient recruitment and retention, technologies that speedily and cost-effectively tailor materials to meet the needs of different ethnicities and cultures permit modern clinical trials to operate on a global basis — thinking globally and acting locally. Furthermore, online systems that allow materials to be developed centrally, then locally adapted and approved online for content and translation in an instantly designed format, are delivering huge savings in time and costs, especially when materials are in IRB-ready format for review submission. These technologies are reducing the time delays and costs of intricate processes, while delivering truly global patient recruitment and retention materials.



Sheila Rocchio
VP, Marketing
PHT Corp.

For more information, please turn to page 26.

Safety and Efficiency

E-clinical technologies such as ePRO and EDC are helping sponsors manage clinical operations costs by making trials safer and more efficient. Protocols are getting more complicated; access to patients is extremely competitive, and sponsors are under pressure to deliver more therapies in a tougher regulatory environment. E-clinical technologies help researchers conduct better science with fewer resources. In particular, ePRO enables sponsors to capture reliable data directly from patients anywhere in the world and to monitor their safety throughout the course of the trial between visits. Real-time access to data allows investigators to manage compliance, enrollment, and safety while focusing less time on logistics and more time on caring for patients.

