Carolyn Gretton

A Changing RHYTHM

The ongoing drumbeat of healthcare reform is reverberating throughout the clinical development process, including the earlier stages once unaffected by concerns such as reimbursement and cost-benefit ratio.

According to Barbara Wirostko, M.D., chief medical officer for Altheos, the question of whether a product candidate will be reimbursed by government and third-party payers is now surfacing in the earliest stages of discovery.

"Because there are now issues around who is going to reimburse and who is going to pay for novel, expensive new medications, there's hesitancy on the R&D side to actually take risks and commit resources to a program unless there's some assurance or insight into whether the emerging product will get reimbursed," Dr. Wirostko says. "Companies need to have a solid commercial plan in place from the start, or they will be limited in their ability to run those early feasibility studies. And that commercial plan implies answering the question, 'is this reimbursable, by whom, and in what global region?'"

Some experts see the pricing pressures of the current healthcare environment as an opportunity for life-sciences companies to continue refining and improving R&D efficiency.

"It's a poorly kept secret that productivity in R&D is not where we would hope it to be," says Douglas Williams, Ph.D., executive VP, research and development at Biogen Idec. "And I think the overall concepts of healthcare reform and pricing pressures, however you want to define them, just shifts the burden back to companies needing to be that much more innovative. For example, being able to more effectively identify patients who are likely to respond or have a more robust response to an experimental agent will become important. These types of value propositions for patients are metrics that the healthcare system will always embrace."

FAST FACT

- AstraZeneca expects to trim $1 billion from its R&D budget by 2014.
- Pfizer plans to cut its R&D budget by almost $3 billion to $8.5 billion by 2011.

Source: Industrial Info Resources

CHRIS GARABEDIAN
AVI BioPharma

"Continued improvements in EDC and other clinical data management technologies will expand a company's ability to capture specific, relevant information for clinical studies, and result in faster, sophisticated data analysis."

Lineene Krasnow, executive VP, product and marketing, Medidata Solutions Worldwide, adds that protocol complexity is also taking a toll on clinical study speed and efficiency.

"Increasingly, complicated protocols are prolonging trials, increasing expenses, and burdening sites and subjects," she says. "Some sponsors are turning to global studies and restructured site relationships and management, but these responses only address symptoms, not the underlying causes. New approaches that help to justify up front the need for a particular study design are now available through tools that leverage structured data in combination with industry benchmarks, operational metrics, and the ability to integrate with downstream systems, helping to optimize the trial from beginning to end." (See the thought piece, "Bringing Process Efficiency to Clinical Trial Randomization.")

Dave Fishman, president of Snowfish, says determining the appropriate direction and maintaining focus is a key challenge when it comes to developing a research and development strategy.

"Often R&D decisions are based upon a variety of factors, including the availability of a new molecular entity, perceived competitive threat, and opinion of outside scientific/clinical experts without the proper assessment of the feasibility and value of the endeavor," he says. "This approach risks the development of a product without market potential or without a realistic development path. To address this challenge, a clinical data gap analysis can be designed to identify new opportunities and compounds." (See the thought piece "Clinical Data Gap Analysis Uncovering Hidden Opportunities.")

Designed to Adapt

Adaptive trial design is one key component being used to drive efficiency in clinical processes and can lead to significant time savings when implemented successfully. However, high-level executive support for and wider acceptance of flexible trial design are needed to drive better usage of adaptive clinical trials, according to a recent study by Cutting Edge Information.

Results of the study suggest that development teams have generally used adaptive design in limited ways, with many only using the strategy in early-stage trials.

"Adaptive design isn't a new concept, but there is a stronger demand to explore alterna-

"The future belongs to those companies that 'embrace the deconstruction of large R&D organizations', sorting their internal configurations and capturing and externalizing the value locked within."

tive trial design now," observes Adam Bianchi, chief operating officer of Cutting Edge Information. "Rising clinical costs in R&D mean that every team needs to operate faster. That, coupled with advancing technology, has supported better usage of adaptive trials."

According to data from the study, Clinical Operations: Per-Patient Trial Costs, Staffing and Adaptive Design, adaptive design can save time by enabling project teams to make faster decisions about treatments and make adjustments to a trial in progress. Almost 60% of executives surveyed said adaptive design shortened trial duration, while 13% said it lengthened trials and about a quarter said adaptive design did not impact trial length. The study shows an average of three months saved, with one company saving a year to completion.

"Teams can determine or even improve the likelihood for approval, potentially bringing a drug to market faster or terminating a trial that will not meet its endpoints," Mr. Bianchi says. "Even when development ends in a no-go decision, teams save time and money."

Bill Gwinn, VP, clinical informatics solutions at QualityMetric, says the pharmaceutical industry has invested heavily in cutting-edge technologies for use in preclinical research to detect potential drug failures early.

"These technologies have identified numerous new drug targets," he says. "In the clinical trials that follow, the biggest game changer is adaptive designs. Adaptive designs use accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial." (See the thought piece, "Metrics for Faster Clinical Trials.")

Before assuming his current role as chief medical officer of Flexion Therapeutics, Neil Bodick, M.D., Ph.D., was the founder of Chorus, Lilly's early-phase development accelerator, where he served as chief medical officer and chief operating officer and was responsible for the development of information systems distributing the work of development through a global network of suppliers.

"In our experience at Flexion Therapeutics, and before that at Chorus, the most important improvements have come in the form of adaptive trial design, for example in the employment of Bayesian adaptive allocation — an interpretation of probability that enables reasoning with uncertain statements — for dose finding, which in our experience has reduced sample size by 30% to 40%," Dr. Bodick says. "In this context, technical enhancement of operations is important in supporting real-time aggregation of and visibility into trial data."

Some experts believe adaptive design is best employed in select therapeutic areas that have a high morbidity rate or low patient populations.

"The therapeutic area is going to dictate whether or not adaptive trial design will work," Dr. Wirostko observes. "For orphan diseases, this approach will most likely work, especially in rare diseases where patient recruitment is a lengthy and difficult process because there's such a low incidence or prevalence of the disease."

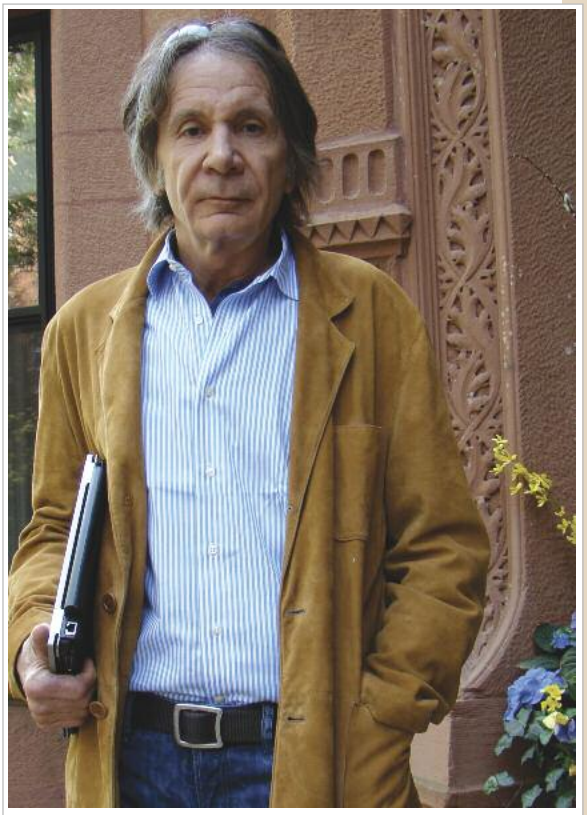
Platforms for Efficiency

E-clinical platforms, including technologies such as electronic data capture (EDC) and clinical trial management software (CTMS) have proven invaluable in streamlining the clinical development process. Thought leaders say these solutions have helped expand a company's ability to capture relevant information quickly and accurately, resulting in improved data quality, increased patient safety, and considerable time and cost savings.

According to experts at Veeva, while content management technology vendors have continued to tack on new functions and increase capacity, the platforms themselves have not fundamentally changed. In stark contrast, the life-sciences industry has undergone dramatic change in the last 20 years, including a greater focus on emerging markets, global operations, and strategic and tactical partnerships. These changes are calling into question traditional methods and tools for regulated content management. (See the thought piece, "Industry Experts Challenge the Status Quo on Content Management.")

Chris Garabedian, president and CEO of AVI BioPharma, believes continued improvements in EDC and other clinical data management technologies will expand a company's ability to capture specific, relevant information for clinical studies, resulting in faster, sophisticated data analysis.

"We should leverage these technologies to obtain additional value by applying them to power and build broad-based disease and treatment registries across multiple sites, potentially worldwide," Mr. Garabedian adds.



DR. NEIL BODICK, *Flexion Therapeutics*

Ron Waife, president of Waife & Associates, says e-clinical technologies have enormous potential, but the cliché that technology is only a tool is no less true just because it is a cliché.

"The great impact of e-clinical at the moment is the distraction it is causing — or providing — development organizations so that fundamental process inefficiencies are being ignored or avoided," he says. "The incremental impact of next-generation e-clinical technologies on those companies that are already using basic modern software platforms — EDC, CTMS, ePRO, eTMF, etc. — is likely to be very modest. The biggest technology game changers in the three-to-five year window are potential new foundational platforms, perhaps based on social networking principles, and the handheld, wireless cloud-enabled hardware of the future. Historically, however, such technology revolutions have taken many years to work through biopharma R&D on a practical operational level." (See the thought piece, "Managing Outsourced Development: Designing a Performing Process.")

"As EMRs gain wider use, they may allow regulatory agencies more complete and timely access to postmarket safety data, which could allow for earlier drug approval and more reliable postmarket safety monitoring," observes Tim Rodell, president and CEO of GlobeImmune.

However, Mr. Rodell adds, since information technology tools are only as good as the

VIEWPOINTS

Budgetary Constraints

The biggest challenge to developing an R&D strategy is the shorter and more immediate timelines sponsors are faced with due to funding challenges and budget constraints. This demands flexibility from service providers, efficiencies in study management, and the ability to execute rapid study startups at the site level and in the CRO. Also, open and honest study assessments up front allow sponsors to better manage their overall R&D budgets, timelines, and strategies.

LEE BARSKY
VP, CRO Services, *Accelovance*

Interactive Technology to the Rescue

The ongoing convergence of modern telecommunications and computer sciences presents significant opportunities to drive efficiencies in R&D, particularly in managing sites and patients. In this regard, interactive technologies, such as IVR/IWR systems and complementary technologies (e.g., email and SMS), best address the current pain points relating to recruiting, randomizing, retaining, and keeping patients compliant during clinical trials. Such global technologies are widely adopted and user-friendly, hence best suited to improve site and patient management.

JOSEPH BEDFORD, PH.D.
Director of Marketing, *Almac*

Digitizing Data

The march toward fully digitized clinical trials will be accompanied by increasing privacy and compliance concerns around the use of data from electronic sources. Recent guidance (currently in draft) promises to have significant implications for all clinical research professionals. This guidance affects when data can be reviewed and places additional administrative requirements on clinical sites. Vendors will be expected to reduce transcription requirements and eliminate redundancies, while ensuring that health information is secured and protected. I see no shortage of challenges over the next five years.

JONATHAN ANDRUS
VP, Data Management and Quality, *BioClinica Inc.*

A New R&D Model

The landscape is moving the development of new products from the large R&D model to small, nimble R&D-stage companies. The challenge will be understanding who will be driving innovation next once the shedding of large R&D IP is exhausted. For service providers, the ability to understand this process and know how to work with these companies to achieve their objectives with the same level of experience and efficiency will be integral to future success.

JEANMARIE MARKHAM
CEO, *Clinlogix*

Midsize Pharma to Lead R&D Charge

Medium-size pharmaceutical and biotech companies will be conducting more R&D than large pharmaceutical companies. Large pharmaceutical companies are spending more of their money on less risky development projects, such as Phase IV trials for their marketed products. Smaller companies are willing to take risks on small- to medium-size product projects. Large pharma companies are stockpiling their cash to buy companies or products once they're developed. The FDA and the pharma industry, as a whole, move slowly. Not much will change in five years.

JOHN M. HUDAK
President and Founder, *Criterium Inc.*

CDISC the Way Forward

Over the past decade, the development and uptake of CDISC standards have resulted in the introduction of various new technologies, among them CDISC-based study design tools and metadata repositories. The value of such technologies lies in their facilitation of the vendor-neutral reuse of content across the end-to-end clinical trial. CDISC study design tools have been proven to deliver a 68% reduction in study specification time and, by generating proprietary EDC build metadata from CDISC Database Metadata (ODM), companies have seen a reduction of 40% to 60% in database build times. In metadata management, and as proven in a sample of 35 studies, about 80% of CDISC EDC and database metadata can be reused. While the vendor-neutral nature of the CDISC standards has enabled the development of database design tools, such tools can also be used as universal EDC design tools. In summary, it is my belief that tools that use CDISC standards will become the biggest game changers in terms of reducing cost and time across the end to end clinical trial process.

MARK WHEELDON
CEO, *Formedix Inc.*

Data Respositories Replacing Ad Hoc Systems

Health Industry Insights estimate 80% of Phase III trials and 50% of all trials use some form of EDC. A clear information strategy that is transparent provides opportunities for better informed science, patient information, and quality. As such, data warehouses that serve as the repository of data from multiple sources provide a single aggregated location for all study data, no matter what the data capture tool, allowing real-time access to safety data as well as CRO and study performance data, replacing the previous reliance on ad hoc programmed output. Site performance

data are a critical marker indicating the need for increased enrollment efforts, potentially identifying issues with protocol compliance or in some cases the need to switch sites altogether. Review of safety data will increasingly reflect modern medical practice where the electronic medical record has replaced the paper system. As more trials use imaging as an endpoint, centralized imaging, either for data aggregation or for a central read, or both, will become a "must-have." We think the data repository will be the biggest game changer because of the downstream ancillary tools that can be plugged in and the real-time access to analytics that are produced.

ALAN MORGAN
President, *ICON*

Better Data, Sooner

Data monitoring technologies are driving efficiency by providing access to better data sooner as well as detecting inaccurate, incomplete, or fraudulent data more quickly. This is driving the trend toward more adaptive trials, allowing trial design to be modified in prespecified ways in response to real results. Patient recruitment also is becoming increasingly data-driven with recruitment simulation models that mine historical data, take into account previous results, and account for numerous other variables to generate timeline probabilities. Providing opportunities to refocus trials and better plan for recruitment are certainly game changers.

JAMIE MACDONALD
Senior VP and Chief Operating Officer
Kendle

Technology Standards

Over the past decade technology has brought significant advances to clinical development, nudging work processes but generally maintaining existing functional and organizational pathways. These systems' unique functionality, legacy investments, and existing utilization mean enterprises will not readily abandon them. Applications that embrace standards allowing easy interoperability are imperative for the next stage in evolution toward re-engineered, more efficient processes. In addition, this interoperability is necessary for the metrics-based insights that will allow development to continue to evolve.

LINEENE KRASNOW
Executive VP, Product and Marketing, *Medidata Solutions Worldwide*

Taking a Targeted Approach

The one-size-fits-all approach to drug development is no longer in favor. A more targeted, innovative approach to developing treatments for small groups of patients with more complicated diseases such as cancer, rheumatoid arthritis, and immune disorders is gaining popularity. Statistical databases such as insurance claims are becoming essential to find patients during clinical trials.

BILL GWINN
VP, Clinical Informatics Solutions
QualityMetric

Safety First

The biggest impact over the next several years will continue to be integrating in real time the safety-related events than can clearly impact both approval and potentially commercialization. Accordingly, companies must develop safety-related mitigation strategies during the clinical phase.

CHARLES SALDARINI
CEO, *Sentrx*

Consolidation on All Levels

Over the coming year we expect to see ongoing consolidation of efforts through numerous acquisitions, including intra-pharmaceutical as well as purchases of biotechs by big pharmaceutical companies. In addition, pharma companies are narrowing the focus of their research. Another significant trend is the emphasis in building relationships between industry and academics. While this has always been important, companies are further identifying and defining the various research centers as a means to enhance their pipeline capabilities.

DAVID FISHMAN
President, *Snowfish*

To the Cloud

Cloud-based, regulated content management will allow better, faster, and less expensive collaboration across the R&D value chain. Life-sciences organizations have moved away from a set of siloed business processes to those that are highly collaborative, highly dispersed, and global in nature. They must now manage interactions with a broad spectrum of affiliates, vendors, and partners around the world as efficiently as they do with those down the hall. The only way to do this effectively is in the cloud.

ERIC BEZAR
VP, Products and Technology, *Veeva Vault*

Building Success Relationships

The coming year in R&D will be most impacted by sorting through the proper role of third-party service providers and how biopharma sponsors can best build logical and successful relationships. The relationships today are very young on the maturity scale, with a lot of experimentation in governance, planning, staffing, and funding. Biopharma sponsors need to take more responsibility in defining these relationships and testing their answers, much as sponsors have done previously with discovery techniques and enabling software.

RONALD S. WAIFE
President, *Waife & Associates Inc.*

DR. DOUGLAS WILLIAMS,
Biogen Idec

individuals running them, trial design and conduct should remain clinicians' chief focus.

Thomas Lawler, senior director, clinical project management with AstraZeneca, predicts the real game changer will be when technology is leveraged across the entire clinical-trial value chain, rather than being employed for one-off solutions.

"An end-to-end integrated solution that changes the way we interact with patients, investigators, and data will in my view result in a true change in operational efficiency and effectiveness," Mr. Lawler explains. "This type of redesign and application of technology, coupled with advancements in standardization of electronic medical files, could completely change the way clinical studies are conducted."

One potential obstacle to adoption of e-clinical solutions is the recent draft guidance on electronic source documentation released by the FDA, says Jonathan Andrus, VP, data and study operations, BioClinica.

"This guidance for sites is significant and the implications for CRAs, data managers, and technology vendors could be potential show stoppers," he says. (See the thought piece, "Understanding the Finer Points of the Electronic Source Documentation Draft Guidance.")

Perfecting Partnerships

In the current climate of aging product lines and heightened financial pressures, successful, robust partnerships between large companies and smaller startups, as well as companies and contract research organizations (CROs), play an increasingly critical role within pharma R&D organizations.

Jamie Macdonald, senior VP and chief operating officer at Kendle, says within five years, there will be an emergence of "virtual" biopharma companies that are focused exclusively on their own core competencies and advantages, while outsourcing the rest of the clinical development process to their strategic partners.

"This will drive efficiencies in the process and help control the skyrocketing cost of clinical development," he says. "In the shorter term, there will be continued consolidation of vendors and the continued move to more efficient strategic partnerships." (See the thought piece, "Partnering with CROs: Achieving Operational Excellence.")

Mr. Rodell cites alignment of interests, so that joint development programs satisfy the needs of both partners as a crucial element to a healthy partnership. Partners should have clearly defined roles on both sides and clear communication channels and decision-making processes, he adds.

"One of the major trends in R&D over the next few years will be the use of new technology and tools to stratify patients in a prospective manner as they're entered into clinical trials."

"These dynamics cannot be legislated in alliance agreements," Mr. Rodell says. "They require experienced and empowered alliance managers and direct communication between scientists and development personnel."

"Process improvements are scalable and should provide a benefit of more efficient testing of new drugs and cost-savings," says Katherine Bowdish, president of Anaphore.

Other requirements, Ms. Bowdish says, are a robust foundation geared to the strategic interests of both sides and an operational architecture that works for both parties.

"This includes taking advantage of each other's strengths, working at the same pace, developing a work plan, and staying on plan as much as possible," she notes. "Both parties need to recognize that challenges will come, as they always do in any partnership. But if the robust foundation is in place, the teams can work through it from a strong vantage point."

"A successful partnership requires more than just alignment and agreement of contract terms and objectives," Mr. Garabedian says. "It is important to establish clearly defined roles and responsibilities for each partner so that there is some ownership of the deliverables. Likewise, the specific deliverables and timing should be outlined, and expectations for successful and unsuccessful outcomes should be clearly delineated up front."

In terms of CRO partnerships, Dr. Wirostko recommends doing due diligence.

"It's important to take the time to interview the CROs and match their styles to your company's, and match their capabilities to your needs," she says. "It is a process and requires an open dialogue."

Alan Morgan, president of ICON, says the relationship between pharma companies and CROs has continued to evolve from being transactional in nature, through a state of preferred provider relationship, to one of closely integrated strategic collaboration.

"While the pharma and biotech industries need to reduce their cost and cycle times and maintain a focus on quality, there has been an increased focus on looking to suppliers to help achieve these goals," he says. "This can be accomplished by program-level outsourcing to a CRO, supported by a robust governance structure to maintain the relationship. The performance of the relationship is further enhanced by the use of metrics to ensure deliverables are met. The metrics can also be used by the CRO to assist in identifying and quantifying sponsor-side process improvements that can drive down cost and cycle time further.

"The trend toward strategic relationships has already resulted in increased program level outsourcing with CRO partners, and we have seen this trend in both full service and functional service provider (FSP) models," he continues. "The pure FSP models are starting to become more hybrid, reflecting a combination of sponsor resource constraints, and the optimum transfer of responsibilities to achieve quality levels. The aggressive pricing that historically accompanied the pure FSP models is starting to adjust to reflect long-term sustainability." (See the thought piece, "Effective Use of Health Technology Assessment to Maximize Market Access: Start Early and Update Often.")

According to Mr. Lawler, one of the biggest challenges in an R&D partnership is ensuring a full understanding of each other's expectations.

"Almost every breakdown, from what I see and hear around the industry, arises from a misunderstanding in what the other partner is expecting to be delivered," he says. "In my opinion, the best way to overcome this is through up-front conversations, detailed planning, and clear articulation of the role each partner is to perform throughout the life of the agreement."

Mr. Lawler says over the short term, he foresees continued collaboration between larger pharma companies and smaller research organizations to identify product candidates, along with increased use of external providers for other development activities.

"In the next year, the restructuring of large pharma R&D in response to a lack of productivity will result in different models for large pharma companies and increased opportunities for small companies," Mr. Rodell says. "The challenging financing environment for small companies will continue to push them into alliances early and to adopt development practices that support early partnering."

Ms. Bowdish predicts that big pharma's reengineering of R&D operations could provide even greater opportunities for smaller biotechs to fill early pipeline gaps.

"As large pharma companies concentrate their efforts in a few therapeutic areas to get to greater success, it leaves room for smaller biotech companies to take on more risk against more novel targets, as well as develop new approaches to designer therapeutics," she says.

Mr. Garabedian says he's witnessed a broadening of partnering choices beyond industry, including academic institutions, patient advocacy groups, and private foundations.

"These new strategic partners realize not only the importance of funding research, but their ability to direct and translate these efforts into clinical development," Mr. Garabedian says.

Future in Translation

Dr. Williams foresees one of the major trends in R&D over the next few years as being the increasing implementation of translational medicine — the use of new technology and tools to stratify patients in a prospective manner as they're entered into clinical trials, and defining subsets of patients based on cellular, serological, or molecular stratification.

"Translational medicine will help define who is most likely to respond to a drug and who has a risk-benefit profile that would preclude them from treatment," he says.

Mr. Garabedian expects companies to continue to increase support for predictive modeling and translational research to improve understanding and clinical success.

"This presents some especially exciting opportunities for rare and neglected diseases for which biomarkers and improved understanding of genetic markers will support clinical development efforts in these areas, especially for treatment responses in smaller subsets of patients," he says.

Dr. Bodick believes the future belongs to those companies that embrace deconstructing large R&D organizations, sorting their internal configurations, and capturing and externalizing the value locked within.

"The best portfolio will not be a collection of snazzy science projects; it will be a set of efficient pathways to registration and commercialization," he says.

Although he expects the trend to outsource operations will continue for certain areas of R&D, Mr. Lawler believes larger pharma companies will continue to have opportunities to leverage their size in implementing efficiencies and effectiveness in development.

"Large companies are still in a position to rethink the way they employ their global presence and technology to deliver new drugs to market using the right mix of internal and external capabilities, while looking to technology for opportunities to rethink the way work is progressed," he says. "This approach could also lead companies to explore broader solutions. For example, in addition to new medicines, companies can use the information gathered throughout development to provide other solutions to patients, or even change the ways treatment is delivered at the doctor's office level." PV

EXPERTS

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