Science In a Tight Economy

Critical Clinical Research Factors

CRITERIUM
Full-Service Contract Research Organization

WHITE PAPER

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Introduction

Now, more than ever, all parties need to be extremely practical in their approach to clinical operations and development.

Pharmaceutical, biotechnology, and medical-device companies (Sponsors) have been intent on trimming budgets since well before the recent economic downturn. Certainly, lean contract negotiations are the true norm; no company — Sponsor or CRO — is walking around with money burning a hole in their R&D pockets.

Companies respond to the mandate to save costs by requiring CROs to provide unrealistic competitive budgets, which, in the end, are escalated once both parties realize the budget is inadequate to get the job done. Change-orders and constant budget negotiations have become the order of the day. Both Sponsors and CROs get a bad reputation for this type of short-sightedness with a tight budget. Operations can be better served by hiring staff and CROs at realistic prices.

Pharmaceutical, biotechnology, and medical-device companies will no doubt continue to look for cost-efficiencies across the board to meet the demands, even after the current financial crisis has improved, but they should evaluate the consequences of budget cuts on several critical factors of clinical development.

Critical factors to consider for clinical development in a tight economy:

- **Momentum:** Reduce the number of do-overs to speed timelines
- **Scientific Innovation:** Develop life-saving drugs are vitally important to the future of the industry
- **Technology:** Collect data in real time to conduct research as quickly and cost-effectively as possible
- **Patient Recruitment:** Minimize the complexity of protocols to allow as many qualified individuals to participate in studies
- **People:** Train, support, and incentive staff properly for best results

Development Momentum

Despite the nation's economic slowdown, America's pharmaceutical research and biotechnology companies invested a record $65.2 billion in 2008 in the research and development of new life-changing medicines and vaccines — an increase of about $2 billion from 2007.

Source: Pharmaceutical Research and Manufacturers of America (PhRMA) and Burrill & Company

Pharmaceutical, biotechnology, and medical-device companies that are committed and connected to the development of products that they believe in will reap the benefits when those products reach the market. Companies that don't invest adequate resources to their development efforts or cancel the development of products that could have become bestsellers are the ones that are going to suffer most.

Finding the Right Balance

Sponsor companies need to find the right balance between reducing costs and maintaining opportunities. By cutting back so drastically on their clinical budgets and by cutting key staff, companies actually pass up development and marketing opportunities, because they are unwilling to adequately fund projects to realize profit-making results. The irony is that even with budget and staff cuts, Sponsors still hope for the big results based on the quality of work that larger budgets supporting experienced people provide. This is a simplistic strategy that is unrealistic and, ultimately, unsustainable.

It's important to note that focusing solely on short-term strategies may result in long-term losses. A good mix can mean the difference between survival and prosperity. If the industry creates a sustained research business climate, prosperity will grow out from the center of the current economic strife, if Sponsors and CROs focus on:

A mix of short-term and long-term strategies should focus on:

- **Spending:** R&D spending must become smarter and the targets of development must be more precise.
- **Collaboration:** Sponsors and CRO must collaborate more closely and frequently during up-front discovery.
- **Strategy:** Sponsors and CROs must employ better ROI scenarios and make smarter decisions.

A Long-Term Proposition

R&D in the pharmaceutical industry is a long-term proposition. According to the Outlook 2009 report from Tufts Center for the Study of Drug Development (CSDD), despite the fact that the average time for the FDA to approve new drugs has

Development Momentum (continued)

declined to about 13 months in recent years, more lengthy clinical-trial processes has kept the overall amount of time needed for drug development and approval at about an average of 8 1/2 years.

Keeping in mind safety and regulatory parameters, companies and CROs are adopting different development strategies to reduce the time it takes bring a drug to market; Tufts notes several practical strategies in a recent report:

Practical strategies to improve development timelines:

- **Improving project management and portfolio decision making.**
- **Expanding reliance on partnerships and licensing arrangements.**
- **Increasing use of surrogate endpoints and adaptive clinical trials.**

In the long-term view, losing even a year or two during development because of under-funded and under-staffed development projects could potentially mean millions of dollars in lost revenue. Worse yet, stopping development or halting trials because of economic forces, could mean loss of patent protection for those years in which a new chemical entity (NCE) is not being studied.

Proper planning is often done in arrears and often implemented only when a project has to meet a timeline or a profit center is in danger of losing money. Taking the time up front to adequately plan and create alignment around a development strategy is not a waste of resources, particularly when there are only so many dollars allocated to projects.

Scientific Innovation

Total pharma R&D spending has been increasing by 15% per annum to a total of $70 billion in 2007, and is forecast to reach $85 billion in 2009. Similarly, biotech R&D spending reached $13 billion in 2007. Despite this increased spending, the number of new molecular entities (NME) being approved by the FDA has continued to fall, with only 18 NME approvals in 2007.

Source: Global Business Insights

The industry is on the verge of great scientific discoveries, as it has always been, in good times or bad. Progress in pharmaceutical discovery and development has been a constant backdrop to all scientific success even the tightest economies. During the 1930s — in the middle of the Great Depression — two major vaccines were developed and disseminated: one for yellow fever in 1932 and one for typhus in 1937. Today, patients remain the happy recipients of the discoveries made by the pharmaceutical companies and the captains of industry who chose to spend on innovation and clinical development, in spite of the drastic economic issues of their day.

Pursuing Scientific Success

In 2009, while the current economic crisis is not currently at the level of the Great Depression, scientific successes will continue to be pursued. President Obama, in line with his commitment to R&D, has stated it is his goal cure cancer in our lifetime.

R&D investment in the sector is an important engine for long-term economic growth:

- **R&D Spending:** It is estimated that America's pharmaceutical companies alone invested $65.2 billion in R&D in 2008.
- **New Medicines:** According to PhRMA estimates, there are a record 851 new medicines in development for cancer among the more than 2,900 other new medicines in development, including: 312 for heart disease and stroke, 150 for diabetes, 109 for HIV/AIDS, and 91 for Alzheimer's disease and dementia.
- **Direct Contribution:** The sector's direct contribution to GDP in 2006 was $88.5 billion, triple the average contribution from sectors in the rest of the economy, according to PhRMA.
- **Additional Economic Impact:** Through the ripple effect of the sector's economic impact, every dollar that biopharmaceutical companies contributed to GDP supports another $2.33 in contribution to GDP from other sectors.

There is no doubt that today's economic climate is compounding the challenges inherent to drug development, which is already fraught with risk, burdened by spiraling costs, and hampered by long timelines. Recent data show, however, that a drive toward scientific innovation remains strong — a proven sign of an innovative

Scientific Innovation (continued)

spirit that is not held prisoner to economic uncertainties. Investment in pharmaceutical research and development needs to continue; life-saving drugs are vitally important to the future of the industry and more importantly to the patients who are in need of novel therapies.

Controlling Costs Without Stifling Innovation

Since no one has really come up with a good reason that drug development should actually stop, Sponsor companies and their CRO partners need to find ways to control costs without stifling innovation. Diseases continue to exist and proliferate; the recent swine flu scare is a perfect example. Whether in a good or bad economy, there is really no question if drug development should continue — it must. Population increases and global travel movements lead to the spread of disease, faster and with greater impact, which in a sense makes the industry almost self-propelling.

New fields within the life-sciences industry will continue to emerge, such as personalized medicine, sometimes faster than it is possible to estimate their long-term impact, but they will define economic success for the country in the 21st century. According to experts at Archstone Consulting, medical innovation creates economic value. Biopharmaceutical advances support high-value jobs and help stimulate regional and national economic activity. For these reasons, industrialized nations around the world compete aggressively to attract biopharmaceutical investment and to create clusters of companies centered around the biopharmaceutical sector that will act as “innovation hubs” to drive sustained economic growth.

Technology

Industry experts estimate that 60% of all new trials (Phase I to Phase III) implemented EDC in 2008; these figures are expected to increase in 2009.

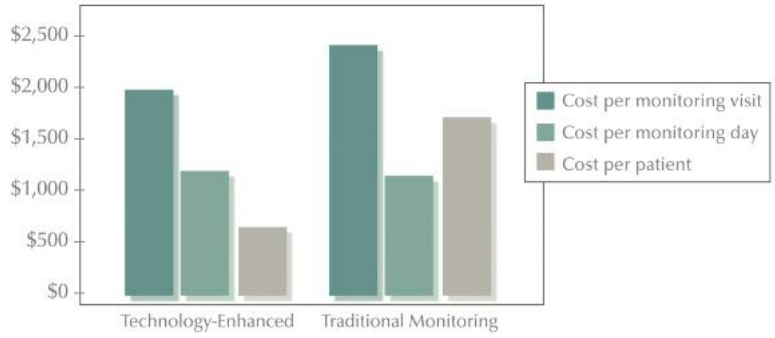
Technology is often lauded as the silver bullet when talk turns to improving efficiencies and reducing costs, but employing the hottest, most innovative technologies is a case of clever misdirection — a pencil still writes as good as a pen if the person using it knows what to say.

Technology is As Only As Good As Those Who Use the Tools

It's only by properly training clinical staff members on the appropriate use of the technology and empowering these research professionals to make decisions based on the resulting data, that organizations can actually reduce costs by speeding up the evaluation process. Technology allows for the accrual of data more quickly and that information can be disseminated downline more rapidly, or better even, in real time. All of this means that more informed decisions can be made about protocols, appropriate regions, sites, patient recruitment — just a few of the factors that when combined embody a highly complex study process.

It's not necessarily superior technology that wins the development race — it's making sure that the people working with the various tools are well trained, understand appropriate implementation, making the proper connections, communicating correctly and in a timely manner, and controlling the trial cost-effectively and efficiently. For example, real-time monitoring of data can identify potential problems before they arise, thereby reducing the cost of field monitoring per patient by as much as half when compared with traditional monitoring.

Using Technology to Streamline Process



Source: Criterium Inc.

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Technology (continued)

An Integrated Business Model

A CRO's business model should allow for maximum connectivity and integration to a vast network of staff, contractors, partners, investigative sites, and patients using a wide variety of proprietary and proven technologies, such as Smart CRFs, IVR/IWR, EDC and EDGE (Electronic Data Global Entry), and ePRO technologies, for example TeleDiary™, as well as processes developed specifically for clinical trials, such as StudyControl™.

The collection, analysis, and communication of real-time data are absolutely necessary to manage clinical trials efficiently and cost-effectively.

- **Automated Fax Scanning:** A fax form technology can convert a paper-based system at the investigative site to an automated, seamless flow of data and electronic image storage system in-house. This system is inexpensive to implement and saves monitoring costs accrued in a "traditional" practice. Among the many different applications, this technology can be implemented for case report forms, CRF corrections, fax surveys, and image management.
- **Electronic Data Capture:** Electronic Data Global Entry EDC is a state-of-the-art technology that maximizes worldwide data collection and management in real time. An EDC platform is a site-friendly system that incorporates control features not available with paper CRFs, resulting in fewer data entry errors and fewer queries to the sites. Custom HTML forms can also be developed for user-generated data; these data can then be incorporated directly into a working database. Utilizing ASP and ASP.NET technology, a CRO can provide secure online data entry capabilities for gathering clean clinical data that are stored directly into the study database where the information is managed and reviewed.
- **Interactive Voice Response:** IVR services provide real-time data tracking for patient registration, randomization, electronic patient diaries, and CTM. Remote data management using IVR combines the process of collection, correction, and database locking, as well as provides an audit trail not possible with paper patient diaries. An IVR system designed specifically for clinical trials can provide real-time data tracking for: patient registration, randomization, patient response diaries, and clinical trial management.
- **Remote Data Management:** Using IVR systems, remote data management

Technology (continued)

combines the process of collection, correction, and database locking, and provides an audit trail that is not possible with standard paper diaries. It's the perfect example of an existing technology that has proven itself to be cost-conscious in a tight economy.

- **Interactive Web Response:** Interactive Web Response (IWR) computer servers provide powerful functionality to both telephone-based and Internet-driven applications. Both interfaces connect simultaneously with the databases that direct and record study processes. Sites are able to view patient calls (date, time of call, dose time) in 24/7 real time. Sites can also view final patient diary reports and print patient confirmation of randomization.
- **Smart CRFs:** Smart Case Report Forms that can talk to each other, whether electronic or paper, are preprogrammed to be tied directly into a CTMS system and integrated with patient data from other sources (ECG, LAB, IVR/IWR) in real time from the beginning of the study.
- **Electronic Patient Diaries:** Electronic patient diary and Web-based response systems have proven to be more efficient and cost-effective than standard paper diaries. Additionally, ePRO is a superior method to paper diaries for both obtaining data and maintaining the integrity of data. Numeric data are available immediately; voiced qualitative data are compiled and available the next day. Electronic patient diaries do not require new hardware or software or maintenance by the client. Patients record their responses via a touch-tone keypad into that computer via secured toll-free numbers. All information reported in an IVR diary is available to clients and sites as it is being gathered through a secure Web Access or Virtual Private Network (VPN). Clients also have the advantage of a 24-hour help desk, with worldwide support for their studies. This technology has the advantages of real-time patient reporting, automatic data edit checks, algorithms customized per protocol, multilingual translations, and automatic study qualification reporting.

Cultivating Results

It's important to note that the fruits of technology's labors can only come to bear when staff members are well-trained and are allowed to make informed decisions based on trusted results. Efficiencies are the direct result of people, not just the technologies, that a company cultivates.

Patient Recruitment

On average, there are 23 exclusion criteria in the most recent study period, up from 21. The new count of inclusion criteria is 26, up from 10.

Source: Tufts

One of the biggest and ongoing challenges in clinical development is patient recruitment. Complex protocol designs, complicated inclusion and exclusion criteria that define the patients who qualify for the trial; global development strategies; and dwindling naïve patient pools are compounding an already cumbersome and costly, yet crucial, part of the development process.

Deconstructing the Complex

Rising numbers of protocol amendments, difficulties in patient recruitment and retention, and a high number of complaints filed against investigative sites for protocol noncompliance are driving companies — Sponsors and CROs — to find new ways to balance the scientific and operational objectives of protocol design.

Improving patient recruitment is critical to the development process.

- **70% of clinical trials run late:** According to a recent CenterWatch survey, this percentage has changed little over the years.
- **23 exclusion criteria:** the average number per study, according to Tufts, up from 21.
- **26 inclusion criteria:** the new new count, up from 10, also according to Tufts.
- **Patients must meet all of the criteria:** the increase in exclusion/inclusion criteria means that fewer patients are eligible for studies.

Broadening the Patient Field: At What Cost?

Companies are looking to conduct trials in the countries where they can enroll the largest number of patients in the shortest amount of time. Sponsors are putting pressure onto CROs to achieve this goal. CROs are then putting pressure onto the sites to enroll patients. All of this is placing a great deal of stress on all of the stakeholders, creating untenable pressure points.

Sponsors and CROs are well-advised to develop a global R&D plan, which provides the option to go where the patients are and where trials can be conducted more efficiently and less expensively. Likewise, if there are regions where research has been reduced because of tough economic times, a company might leverage the lack of competition for research resources to lower costs even more.

To develop better drugs, especially those that are for worldwide commercialization, it will become increasingly more necessary to have a huge global sample.

People

R&D spending by biopharmaceutical companies equaled roughly $65,000 per direct employee in 2006 — about eight times the published estimates of R&D spending per employee in all manufacturing industries between 2000 and 2004

Source: Archstone Consulting

People are the direct resource by which research is conducted and discoveries are made. If Sponsor Companies and their CRO partners don't employ great minds, the results won't matter. Unfortunately, staff reductions and attrition will no doubt continue, but this is the last place Sponsor companies should make cuts to reduce costs. To be successful in the future, Sponsors need to engage in meaningful partnerships with their CROs that encourage a culture of innovation and allow for maximum flexibility. With the acquisition and monitoring of real-time data, a CRO has the ability to connect with the site, communicate with the monitor, and ultimately keep trial budgets in line. Sponsors want control over their budgets, and the only way this is possible is having connections and communications between in-house experts and monitors in the field to resolve queries early on and lock the database according to the timeline.

The Emerging Role of the CDL

One of the emerging roles that allows a CRO to achieve a Sponsor's goals is that of the clinical data liaison (CDL). A CDL can facilitate the communication of data between all stakeholders involved in the clinical trial process. The CDL conducts real-time data review and facilitates centralized control of clinical studies. In-house CDLs clean and correct data before the field monitor makes his or her visit to the site. This process streamlines the CRA's on-site role, which is to troubleshoot patient enrollment and to check source documents. Technology-enhanced monitoring from a centralized location reduces the number of days to complete on-site queries, trims the number of site visits, and reduces the number of days needed in the field. Because CDLs monitor a site's data daily, they are able to identify potential problems before they arise thereby reducing the cost of field monitoring per patient by as much as half when compared with traditional monitoring.

Talent Can Be the Game Changer

CROs that support the well-being of their employees and encourage a company's growth will be the ultimate winners after this recession. How can companies make the recession work for them: keep talented staff. How? By becoming smarter with spending, and making sure that every penny spent is an investment in the future. Why? Because when the market turns the corner, the company that continues to invest in its people and processes will be positioned to hit the ground running.

People (continued)

Employees: By the Numbers

According to study conducted by Archstone Consulting and Dr. Lawton R. Burns, Director, The Wharton Center for Health Management and Economics at The Wharton School, University of Pennsylvania, analysis at the national, state, and local levels found that the life-sciences sector contributes significantly the nation's economy.

- **Domestic R&D Spending:** Bopharmaceutical companies spent about $65,000 per direct employee in 2006 — about eight times the published estimates of R&D spending per employee in all manufacturing industries between 2000 and 2004. Roughly one-quarter of the more than 686,000 direct employees of the sector were engaged in life, physical, or social sciences research in 2006. This research-intensive sector also supported 1 million indirect jobs and 1.5 million induced jobs that year.
- **Broad and Deep Economic Footprint:** The biopharmaceutical sector provides jobs in all 50 states, Washington, D.C., and Puerto Rico. States in which the national biopharmaceutical sector supported the largest number of jobs in 2006 included California, New York, New Jersey, Pennsylvania, and Illinois.
- **High-Value Jobs:** The biopharmaceutical sector directly provided 686,442 jobs in 2006 and supported an estimated 3.2 million jobs across the U.S. economy when accounting for its full ripple effect (i.e., direct, indirect, and induced jobs).
- **Average Wage:** On average, biopharmaceutical employees earned annual wages of $88,929 and paid approximately three times as much in federal (including Social Security) and state taxes as employees in the rest of the economy in 2006.
- **Job Growth:** In approximately 80% of the locations studied, direct employment in the biopharmaceutical sector grew at a faster rate than employment in the rest of the economy in that location between 1996 and 2006. From 1996 to 2006, direct employment in the national biopharmaceutical sector grew more than twice as fast as employment in the rest of the U.S. economy, with compound annual growth rates of 3.1 percent and 1.4%, respectively.
- **Macroeconomic Impact:** The biopharmaceutical sector's direct contribution to GDP in 2006, $88.5 billion, was triple the average contribution from sectors in the rest of the economy. On a per-employee basis, the sector's direct contribution to GDP was 71% more than the average contribution from sectors in the rest of the economy.

People (continued)

- **Ripple Effects:** Each direct job in the biopharmaceutical sector supported 3.7 other jobs in the United States in 2006. The ripple effect of the sector has increased since 1996, when each direct job supported 2.2 other jobs. For every dollar that biopharmaceutical companies contributed to GDP in 2006, the ripple effect of that activity supported another $2.33 in contribution to GDP from other sectors. The impact of the sector's activity has increased since 1996, when each dollar of GDP contribution from the sector supported a contribution of $1.29 from other sectors.

Conclusion

Maintaining efficient clinical operations in a tight economy is just good business.

Clinical trial operations require intelligent people; these are serious times that require serious people doing serious work. Today, clinical managers had better know the day-to-day, on-the-ground, actual activities of clinical trials so they can make faster, smarter decisions. Staff members who are in direct contact with patients and protocols need to understand how their actions affect the entire trial.

Serious Times Ahead Require Serious Work

The economy will eventually rebound, and that can happen quickly. Companies that become too lean in terms of headcount, may not be able to compete if they do not have the right people resources in place. They need properly trained clinical staff members ready to do the work. A record investment in R&D also means record levels of clinical testing of new medicines.

In the end, companies that put their best dollars into R&D, usually get to market first, and obtain not only bragging rights but more importantly, the branding rights; their competition is left behind in the race, forced to create "me-too" products or generics that will compete against each other.

CEOs need to make real investments in their internal operations that provide true value-added opportunities and clinical partnerships that provide efficient services. Sponsor companies partnering with CROs that are set up to provide full-service and a la carte functional choices enjoy greater flexibility. This means they can put more high-return dollars toward R&D, instead of spending low-return dollars on functions that a full-service and flexible CRO can provide more efficiently. CROs are poised to be the best ancillary arms for clinical research functions; they already have the existing expertise.

About Criterium

Criterium Inc. (www.criteriuminc.com) is a global, full-service, and technology-driven contract research organization that offers a unique mix of high-quality, innovative clinical research solutions for the biopharmaceutical, pharmaceutical, medical device, and CRO industries.

Using innovative technology solutions, such as Interactive Voice Response (IVR), Electronic data capture (EDC), and Electronic Patient Diaries (ePRO) to connect, communicate, and control clinical trials, Criterium's experienced and dedicated staff can handle small- to large-scale clinical research projects.

With broad therapeutic experience as well as regional and global expertise — New York, California, Florida, Canada, South Africa, The Netherlands, India, Russia, and Israel — Criterium's mission is to deliver every job to every client done right, on time, and on budget.