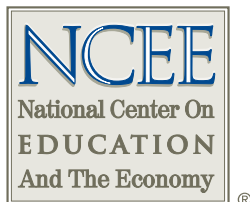


Clinical Research Industry Trends

**Peter E. Carlson
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Clinical research is the bridge between the lab and the market for new drugs, and that market is expanding rapidly. Spending in the US for prescription drugs increased by 12 percent a year during the 1990s, and has continued to increase by 8 percent a year since 2000. The Kaiser Family Foundation projects that spending will continue to increase by around 8 percent a year over the next decade.¹

The biggest factor driving the increase in spending is utilization. The average number of retail prescriptions per capita increased from 7.9 in 1994 to 12.3 in 2005.² There are a number of reasons for this increase. First, the incidence and prevalence of many chronic conditions -- such as asthma, diabetes, high cholesterol and arthritis -- has increased in recent years, in part because the population is aging but also, in some cases, because it is less healthy. There are many new drugs for these conditions, which must be taken daily over many months or years (and sometimes for life), increasing the volume of prescriptions. Second, doctors are diagnosing and treating these chronic illnesses at a higher rate than in the past, and they are using a wider variety of drugs to do so. Third, newly-approved medicines are being more heavily marketed to both doctors and consumers. Fourth, many brand name drug companies have been extending the “franchise” of their branded blockbuster drugs by spinning off new formulations or versions of them.³ And finally, the introduction of Medicare Part D drug coverage has significantly increased utilization.

¹ Kaiser Family Foundation, “Prescription Drug Trends,” June 2006.

² *ibid.*

³ National Institute for Health Care Management Research and Education Foundation, “Prescription Drug Expenditures in 2001: Another Year of Escalating Costs,” May 6, 2002.

In addition, there is an expanding market for new biologic drugs. Prior to decoding the human DNA, only about 500 disease-causing functions in cells or viruses had been found. But with the growing understanding of how DNA works, the number of potential new drugs could grow into the thousands.⁴ A decade ago, 14 biotech firms in the US marketed a total of 22 products. In 2003, 66 companies marketed 187 products, including 12 blockbusters that reap over a billion dollars a year. Today, there are 230 medicines on the market developed using biotech techniques. An estimated 50 more in late-stage clinical trials are expected to win FDA approval, and another 400 products are in the pipeline going through Phase III trials.⁵ Four out of five drugs currently in development are founded on biotech discoveries or employ biotech tools.⁶

Research and development of new drugs is also being fueled by public investment in bio-defense and stem-cell research. The federal BioShield law provides \$5.6 billion over the next 10 years to develop products critical to defending against bioterrorism. In California, voters passed an initiative to fund \$3 billion in stem cell research over the next 10 years, and Connecticut followed suit with a similar \$1 billion initiative. These public funds will spur research that is likely to spin off many new commercial applications.

Streamlining Drug Development

At the same time that the market for new drugs has been expanding, there has been increasing pressure to reduce the cost of prescription drugs. The price of prescription drugs increased an average of 8.3 percent a year over the past decade, more than triple the annual rate of inflation.⁷ Health plans have responded by excluding certain drugs from coverage, requiring generic drugs when available, and increasing co-payments. Consumers have responded by requesting cheaper drugs from their physicians, using the internet to find lower prices, using over-the-counter rather than prescription drugs, and buying in bulk and by mail-order.

One way drug companies have responded to mounting cost pressures is by trying to streamline the development process for new drugs. In the early 1990s, the industry focused on reducing delays in the FDA's approval process. Following enactment of the Prescription Drug User Fee Act (PDUFA) in 1992, the FDA

⁴ Brian O'Reilly, "There's Still Gold in Them Thar Pills," *Fortune*, July 9, 2001.

⁵ Mike Hildreth, "Resurgence Reported in U.S. Biotech Sector," Ernst & Young Video Transcript; Cynthia Webb, "Biotech: Mainstream or Pipe Dream?" *The Washington Post*, June 7, 2004.

⁶ Arthur D. Levinson, "Beyond Borders: The Global Biotechnology Report 2005," Ernst & Young, June 21, 2005.

⁷ Kaiser Family Foundation, "Prescription Drug Trends," June 2006.

significantly increased the number of staff devoted to new drug review, nearly doubling the number of FTEs between 1992 and 2003.⁸ However, due to the growing number of new drugs requiring review, of applications for new uses for existing drugs, and of appeals of “holds” put on clinical trials, the FDA workload increased substantially. As a result, after clearing its backlog of new drug applications between 1996 and 1998, the pace of FDA approvals for new drugs fell again through 2004.⁹

At the same time that delays have crept back into the approval process, public concern about patient safety has prompted more extensive clinical trials to demonstrate the safety of new products. The FDA now requires larger patient populations and more trials in each study phase to better monitor adverse effects. Some estimates suggest that clinical trials today require 2-3 times as many participants as they did 10 years ago.¹⁰ In addition, the average length of a clinical trial has increased by 21 percent since 1999.¹¹ And it will undoubtedly increase even further in the aftermath of the Vioxx recall, as drug companies are now required to track and report more extensively on Phase 4 trials (once the product has hit the market).

Outsourcing Clinical Research

This creates a real dilemma for drug companies. Under pressure to reduce drug prices, they are intensively searching for efficiencies in their product development process. Meanwhile, the number of new drugs entering clinical testing has increased by 52 percent since 2000.¹² The combination of more drugs in the pipeline and the need to test them more extensively is straining the organizational capacity of companies sponsoring those drugs. This is particularly true in biotech companies, which tend to be small and lack the internal resources to conduct clinical research on their own.

As a result, more and more drug companies are outsourcing their clinical research to contract research organizations (CROs). The Tufts Center for the Study of Drug Development estimates that drug companies have been increasing their spending

⁸ U.S. Food and Drug Administration, “White Paper on Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications,” November 10, 2005.

⁹ Tufts Center for the Study of Drug Development, “Longer Clinical Times are Extending Time to Market for New Drugs,” *Impact Report*, November/December 2005.

¹⁰ Cullen T. Vogelson, “We are the World?” *Modern Drug Discovery*, June 2001

¹¹ *ibid.*

¹² Tufts Center for the Study of Drug Development, “New Drugs Entering Clinical Testing in Top 10 Firms Jumped by 52% in 2003-2005,” *Impact Report*, May/June 2006.

on contract clinical research services by 15 percent a year since 2001. As a result, the number of CROs has grown by 65 percent since 2001.¹³ And headcount at CROs has grown by 6 percent a year since 2001, while headcount at the drug companies has remained flat.¹⁴

Studies show that CROs are able to complete drug development faster than the drug companies themselves, without sacrificing data quality. Even though clinical research conducted by CROs tend to involve larger numbers of investigative sites and study volunteers, the projects are typically completed closer to the projected completion date than when drug companies conduct the research themselves.¹⁵ This can make a huge difference financially, since taking a month off development time can generate an additional \$40 million in sales for the average drug. During the 1990s, more than half of all US clinical trials missed their deadlines by at least a month.¹⁶

As a result, there is a trend toward outsourcing full-service clinical research projects, and even entire drug development programs, to CROs. This is particularly true in the biotech sector, where outsourcing has increased dramatically.¹⁷

Moving South and Going Global

Another response to cost pressures has been to shift clinical research to lower-cost areas. During the past decade, there has been a migration of FDA-approved principal investigators from the Northeast to the South within the US. Between 1994 and 2004, the proportion of principal investigators working in the South grew by 20 percent (to nearly 40 percent of the nation's total), while the proportion working in the Northeast declined from 23 percent to 19 percent of the nation's total.¹⁸

¹³ Kenneth A. Getz, "Insights from Today's CRO Renaissance," *Applied Clinical Trials*, June 1, 2006.

¹⁴ Tufts Center for the Study of Drug Development, "CRO Contribution to Drug Development is Substantial and Growing Globally," *Impact Report*, January/February 2006.

¹⁵ Kenneth A. Getz, "Insights from Today's CRO Renaissance," *Applied Clinical Trials*, June 1, 2006.

¹⁶ Janice Cruz Rowe, Martin E. Elling, Judith G. Hazlewood, and Randa Zakhary, "A Cure for Clinical Trials," *The McKinsey Quarterly*, 2002.

¹⁷ Kristin Brooks, "CRO Industry Update: Growth, Expansion, and New Opportunities," *Contract Pharma*, May 2006.

¹⁸ Marc Kauffman, "Clinical Trials of Drugs Fewer, Study Says," *Washington Post*, May 4, 2005; Tufts Center for the Study of Drug Development, "Number of Active Investigators in FDA-Regulated Clinical Trials Drop," *Impact Report*, May/June 2005.

There has also been a significant increase in the scope of clinical research being conducted outside the US. During the 1990s, the number of foreign principal investigators seeking FDA approval increased sixteen-fold.¹⁹ By 2001, roughly 27 percent of new drug applications to the FDA included foreign test results.²⁰ And by 2004, around 21 percent of the spending on clinical trials was on studies conducted outside the US.²¹

There are several factors driving this trend. The first is cost. Companies can reduce their costs by 10-50 percent by conducting clinical trials outside the US.²² The second is the ability to find test subjects. It is much easier to find the 3,000-4,000 patients needed to complete all phases of clinical testing overseas, because the lack of insurance, the high cost of medicines, and the abundance of diseases in need of treatment make recruitment much easier.²³ The failure to find enough patients accounted for 85-90 percent of the days lost during clinical trials in the US during the 1990s.²⁴ Also, clinical researchers claim that Americans often make poor test subjects, because they already take so many medications that it's difficult to isolate the effects of the drug being studied. And finally, there is much less government bureaucracy to deal with outside the US, since many of the FDA's regulations stop at the border.²⁵

The ability to operate on a global scale is becoming a must for CROs. By 2002, one-third of US-based CROs had opened a foreign office and increased their recruitment of foreign test subjects. Industry observers expect that this trend will continue, and that mid-sized and large CROs with global operations will have a competitive advantage.²⁶

Going Paperless

In addition to outsourcing and off-shoring clinical trials, another way to cut the cost of new drug development is to adopt new technologies to manage the huge amounts of patient information involved. A typical new drug application to the

¹⁹ Sonia Shah, "Globalizing Clinical Research," *The Nation*, July 1, 2002.

²⁰ Cullen T. Vogelson, "We are the World?" *Modern Drug Discovery*, June 2001.

²¹ *Medical News Today*, "US Drug Companies Conducting More Clinical Trials Overseas to Reduce Costs, Speed Approval," May 18, 2005.

²² *ibid.*

²³ Cullen T. Vogelson, "We are the World?" *Modern Drug Discovery*, June 2001.

²⁴ Janice Cruz Rowe, Martin E. Elling, Judith G. Hazlewood, and Randa Zakhary, "A Cure for Clinical Trials," *The McKinsey Quarterly*, 2002.

²⁵ Sonia Shah, "Globalizing Clinical Research," *The Nation*, July 1, 2002.

²⁶ Kristin Brooks, "CRO Industry Update: Growth, Expansion, and New Opportunities," *Contract Pharma*, May 2006.

FDA involves hundreds of thousands of paper records, which often arrive by the truckload. In 2003, an estimated 95 percent of clinical trials relied on paper records.²⁷ But there has been a dramatic increase in the adoption of electronic records over the past several years, as electronic records have proven effective in reducing the costs of development and data management in clinical research.²⁸

This trend parallels the adoption of electronic health records by hospitals and physician practices, which holds significant promise for clinical research. In large organizations -- such as the Veterans Health Administration, Kaiser Permanente, and the Geisinger Health System -- clinical data captured in electronic health records are now being used to answer questions about the safety, effectiveness, and costs of new treatments.²⁹ Similar databases for research purposes are being built by the National Cancer Institute and the HMO Research Network, the Centers for Disease Control and Prevention, the American Medical Group Association, and the Centers for Medicaid and Medicare Services.

These computer-searchable databases, which include clinical information on tens of millions of patients, can help fill some of the gaps in the current clinical research. Most clinical trials focus on younger adults in carefully controlled circumstances. Groups like seniors, the disabled, children, minorities, and patients with multiple health problems are frequently under-represented in these trials, even though these groups account for the bulk of health care spending in the US. Information on how these groups respond to drug treatments under normal conditions could shed new light on the effectiveness of different therapies, reducing the need to track selected patients for years to get the same information.

These databases could also dramatically reduce the amount of time and effort required to recruit participants into clinical trials. Currently, tens of thousands of people need to be screened for a clinical trial to get the 4,000 or so needed to conduct the trial. That's because only a fraction turn out to be medically eligible.³⁰ Searching large databases could identify medically eligible candidates in a fraction of the time it currently takes.

²⁷ Tufts Center for the Study of Drug Development, "CROs Provide Gateway to Worldwide Clinical Trial Recruitment Efforts," *Impact Report*, July/August 2003.

²⁸ Kristin Brooks, "CRO Industry Update: Growth, Expansion, and New Opportunities," *Contract Pharma*, May 2006.

²⁹ Lynn M. Etheredge, "A Rapid-Learning Health System," *Health Affairs* Web Exclusive, January 26, 2007.

³⁰ Sonia Shah, "Body Hunting: The Outsourcing of Drug Trials," *The Globalist*, January 31, 2007.

This is particularly important when it comes to biotech drugs, which are usually targeted to specific population groups. It is enormously time consuming and expensive to identify the subpopulations for whom these drugs are targeted, using the normal screening process. But, large computer-searchable databases could accomplish this task in weeks or even days.³¹

A recent study suggests that around 24 percent of physicians currently use some form of electronic health record, with the adoption rate much higher in larger physician practices than in smaller practices. Only about 5 percent of hospitals have similar electronic record systems currently in place.³² But there is a concerted national effort to pick up the pace, given the widely held view that the adoption of information technologies is key to curbing the rapid rise of health care costs in the US.

Implications

Taken together, these trends suggest that the regions in the US that are best positioned to expand their clinical research industry are in the Southern states, and have a strong or emerging biotech sector, a large patient population and/or contract research organizations with global reach, and are ahead of the curve in adopting electronic health records and/or have the ability to tap into the large national databases that are being built.

³¹ Lynn M. Etheredge, "A Rapid-Learning Health System," *Health Affairs* Web Exclusive, January 26, 2007.

³² Ashish K. Jha, Timothy G. Ferris, Karen Donelan, Catherine DesRoches, Alexandra Shields, Sara Rosenbaum, and David Blumenthal, "How Common are Electronic Health Records in the United States? A Summary of the Evidence," *Health Affairs* Web Exclusive, October 11, 2006.