



Commercializing Clinical Trials — Risks and Benefits of the CRO Boom

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In a trend that has received surprisingly little attention, contract research organizations (CROs) have gradually taken over much of academia's traditional role in drug development over the past

decade. They've been able to do so by offering greater speed and efficiency in conducting clinical trials than academic groups can, but questions have been raised about their qualifications, ethics, accountability, and degree of independence from their pharmaceutical-industry clients.

Annual CRO-industry revenues have increased from about \$7 billion in 2001 to an estimated \$17.8 billion today; of more than 1000 CROs in operation, the four largest — Quintiles, Covance, Pharmaceutical Product Development (PPD), and Charles River Laboratories — are now billion-dollar companies, and two others — Parexel and MDS Pharma Services — are worth more than

\$500 million each (see Fig. 1).¹ This growth reflects the industry's contribution to clinical trials: a study sponsored by the large CROs and conducted by the Tufts Center for the Study of Drug Development showed that 10 of the largest firms had enrolled more than 640,000 subjects in trials in 2004. According to the clinical-trials information company Thomson CenterWatch, CROs played a substantial role in 64% of phase 1, 2, and 3 clinical studies in 2003 (for about \$7.6 billion in contracts), as compared with 28% in 1993 (for \$1.6 billion) (see Fig. 2).¹

But some recent events have raised questions about whether the commercialization of clinical

trials, in its current form, is in the best interest of science or the public. In 2005, a Bloomberg News report revealed the inadequate conditions and minimal oversight at a phase 1 and 2 clinical-trials unit housed in a converted Holiday Inn in south Florida and owned by the SFBC International CRO. With 675 beds, the site was the largest experimental-drug test center in North America. But SFBC's clinical-trials director was an unlicensed physician, and its Florida research subjects, many of them poor Hispanic immigrants lured by per-trial payments, enrolled without fully comprehending the risk of injury or death and were enticed to stay in trials in some cases by "backloading," in which the largest payments are made near the end of the trial. At an SFBC site in Montreal, a patient was allowed to remain in a trial despite having active tuberculosis; nine other trial partici-

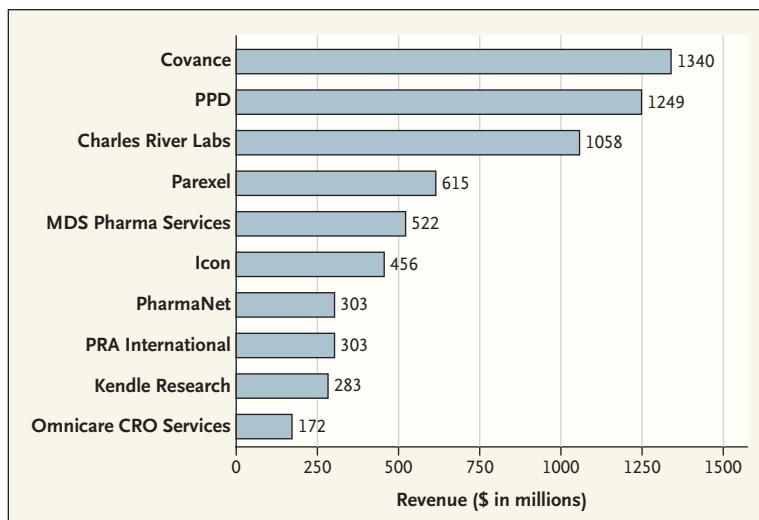


Figure 1. Total 2006 Revenues at the Top-Grossing Public CROs.

Data are from Thomson CenterWatch. Quintiles, which is privately held, reportedly has annual revenues of \$2 billion.

pants later tested positive for the disease. The company, now called PharmaNet, shut down its Florida site and settled a resulting shareholder class action lawsuit for \$28.5 million in August 2007.

In 2006, human subjects were seriously harmed during a phase 1 trial in Britain that was managed by the CRO Parexel. Eight men had signed on as healthy volunteers, but soon after the six assigned to the test drug — a monoclonal antibody developed by the German company TeGenero — had received it, their organs began to fail and they required intensive care. Inspectors for the British Medicines and Healthcare Products Regulatory Agency found that a Parexel physician involved in the study had had inadequate training and experience and that Parexel had no formal system in place for providing round-the-clock medical coverage — though the expert scientific group that investigated the case for the British Secretary of State for Health concluded that it was “highly unlikely” that these deficiencies caused the events.²

Industry observers say that such problems stem in part from outmoded norms that emphasize speed at the expense of quality and from drug regulations that were written in the 1970s, about a decade before the contract research industry emerged, and thus don't really address CROs' accountability. CROs tend to keep quiet about the problems, referring any inquiries to the professional association established 5 years ago by five of the largest CROs, the Association of Clinical Research Organizations (ACRO). When asked about recent signs of laxity, the association's director, Doug Peddicord, defends CROs in general terms, arguing that they have an incentive to perform well in order to win contracts in a highly competitive industry and are “very highly regulated.”

The nature and extent of regulators' authority over CROs, however, are uncertain, according to Rachel Behrman, director of the Office of Critical Path Programs at the Food and Drug Administration (FDA). CROs are accountable to the FDA, said Behrman,

but “it's not clear whether their accountability is through the sponsor or directly to us.” The agency is working to clarify such points. In the meantime, CROs that encounter problems with trials and want to act honorably and correct them rarely go directly to regulators, instead reporting any concerns to their drug-company clients — but they apparently don't always get an appropriate response. In the recent case of the antibiotic telithromycin (Ketek), which was linked to liver failure, the drug's manufacturer, Aventis, had contracted out a clinical trial to PPD, whose monitor discovered evidence of fraud at a study site. PPD informed Aventis, but the drug company didn't shut down the site or remove its data from the application for FDA approval of the drug. Aventis (now Sanofi-Aventis) later claimed it was unaware of the fraud, but this assertion was contradicted by the PPD monitor in congressional testimony, and the FDA found extensive fraud when it audited the site.

A case involving Bayer's anti-fibrinolytic drug aprotinin (Trasylol) suggests that drug companies expect CROs to refrain from approaching the FDA directly. A postmarketing safety study that Bayer had contracted out to i3 Drug Safety, a Boston-based division of the CRO Ingenix, showed that patients who received aprotinin were at increased risk for death, renal failure, heart failure, and stroke. Alexander Walker, an i3 researcher and a former department chair at the Harvard School of Public Health, says he expected Bayer to present his group's findings at a 2006 FDA advisory committee meeting about the safety of aprotinin. When the company didn't do so, he threatened to call the FDA himself. Its hand forced,

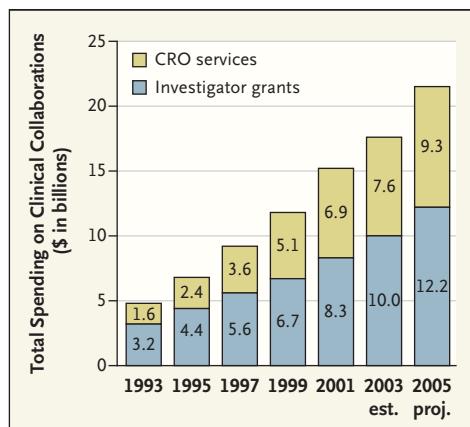


Figure 2. Total Spending on Clinical Collaborations by Member Companies of the Pharmaceutical Research and Manufacturers of America.

Data are from Thomson CenterWatch.

Bayer submitted the study results to the agency, admitted its mistake, suspended two officials, and hired outside lawyers to investigate. The lawyers' report concluded that Bayer scientists had initially opposed the i3 study owing to skepticism about its scientific value, a view that affected the company's "approach to disclosure," but that the subsequent failure to disclose the study was human error.³

Such conflicts notwithstanding, reliance on CROs remains strong. Many pharmaceutical companies have faced internal layoffs and cutbacks, and outsourcing costs them less than doing work in-house, partly because the pay scales for the two types of organizations are quite different. Yet speed is maintained: projects with greater use of CROs are finished closer to their projected completion date than those with less CRO use, according to the Tufts study. The Tufts group found that CROs were still able to turn out high-quality research, but others worry that greater speed means inferior results.

CROs meet their deadlines by

breaking the conduct of each study into discrete steps — for instance, finding investigators, enrolling a specified number of patients, and checking the case-report forms where patient-level data are recorded — and emphasizing speedy completion of each step. Philip Mirowski, an economist at the University of Notre Dame, argues that this "commodification" of research projects has begun "to kill" clinical research. Pierre Azoulay, an economist at the Massachusetts Institute of Technology's Sloan School of Management, describes CROs as "data-production sweatshops," where "everyone's very focused on the data," rather than on the totality of the knowledge required to determine whether a drug is worth pursuing further, and where "all the incentives are to do [the work] fast." Azoulay has been told by CRO and pharmaceutical-industry insiders that quality suffers from the focus on speed and on "hard deliverables."⁴

Inadequacy of the workforce may be an even greater barrier to high-quality research. CRO employees are generally younger, less skilled, less experienced, and less educated than researchers in the pharmaceutical industry or academia. This "de-skilling" of the research enterprise, as Mirowski describes it, enables CROs to spend less on compensation than do pharmaceutical firms. But the lower salaries result in turnover that can be as high as 100% during the lifespan of a single project.⁴

Aware of the differences between their employee base and that of CROs, many large pharmaceutical companies partition their portfolio into two parts, says Azoulay. They keep the more innovative work, such as testing

drugs for a new indication, in-house and outsource the "more routinized part," such as phase 3 trials of a me-too drug, "where in a sense no bright ideas are required." However, it's not always clear which study will require bright ideas. "There's a lot of innovation that happens in the clinic — it's a very open-ended process," says Azoulay. "You don't need robots doing this, you need employees who are engaged and have some element of job security." Since CRO employees must be kept "fully billable," they are shifted from project to project as the need arises and may never build up expertise on a particular project.⁴

An alternative model, the academic research organization (ARO), avoids some of the workforce qualification problems — housed within universities, AROs often use faculty members as clinical investigators. Because they must comply with university requirements, AROs are also likely to ensure that investigators have the right to publish their findings, whereas publication rights for studies conducted by CROs typically belong to the drug company. But most AROs are considered less efficient than CROs, and since they must bid against CROs to win research contracts, their researchers reportedly face considerable pressure: if they oppose a study's design, the sponsoring company can easily take the work elsewhere. Muhammad Mamdani, who recently left the pharmaceutical industry to direct an applied research center at St. Michael's Hospital in Toronto, has found that academic and commercial organizations both generally comply with the industry's requests, agreeing to conduct "very conservative" studies that leave important questions

unmasked, rather than lose a contract.

Brian Strom, editor of *Pharmacoepidemiology and Drug Safety*, tells a story that raises similar issues. Strom's journal received a report from i3 Drug Safety researchers of an observational safety study of rosiglitazone (Avandia), Glaxo-SmithKline's antidiabetic drug. Hired by GlaxoSmithKline to evaluate Avandia's cardiovascular risks, i3 had found those risks to be intermediate between those associated with sulfonylureas and metformin, but it hadn't compared Avandia with the only other marketed drug in its class, Takeda Pharmaceuticals' pioglitazone (Actos). When Strom asked the authors to add this comparison, they said they couldn't, because the cohort of patients using pioglitazone in their database was too small in the period they focused on (2000 to 2004). Yet Takeda scientists later used the same database, for the period 2003 through 2006, to show that the risk of myocardial infarction was higher with Avandia than with Actos.⁵

Greg Koski, former director of the Office for Human Research Protections in the Department of Health and Human Services and now a leader in a movement to improve clinical trials, believes that the problems with CRO research are fixable, perhaps through a requirement for certification of researchers or research sites. But it's not clear who would make such a change happen. CROs "fly under the radar," says Michelle Mello, an associate professor of health policy and law at the Harvard School of Public Health, who notes that problems with CROs are even more difficult to detect now that many of their trial sites are in Eastern Europe, Russia, India, and Asia, where costs are lower and research subjects are more plentiful but where there is also less governmental oversight of clinical-trials sites than there is in North America. Although ACRO's Peddicord asserts that the CRO's "principal roles" are protecting research participants and ensuring the integrity of research data, critics are concerned that in competing for contracts, CROs are

spending too little and working too quickly to do good clinical research. Given the steady dominance of CROs in the clinical-trials domain, the current flaws in the model will need to be remedied. This will require some shift in focus — less single-minded attention to "deliverables" and "billable hours" and greater concern with the discovery of new knowledge.

Dr. Shuchman is a national correspondent for the *Journal*.

1. State of the clinical trials industry: a sourcebook of charts and statistics. Boston: Thomson CenterWatch, 2007.
2. Expert Scientific Group on Phase One Clinical Trials. Final report: November 30, 2006. Norwich, United Kingdom: The Stationery Office, 2006.
3. Report on Trasylol for Bayer Corporation and Bayer AG by Zuckerman Spaeder LLP, August 2007. (Accessed September 13, 2007, at http://www.bayerscheringpharma.de/scripts/pages/en/press/information_on_trasylol/index.php.)
4. Azoulay P. Agents of embeddedness. NBER working paper 10142. December 2003. Cambridge, MA: National Bureau of Economic Research. (Available at <http://www.nber.org/papers/w10142>.)
5. Strom BL, Lewis JD. In clarification. *Pharmacoepidemiol Drug Saf* (in press).
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The Development of Prosthetic Heart Valves — Lessons in Form and Function

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The 2007 Lasker Award for Clinical Medical Research, granted in mid-September to Albert Starr and Alain Carpentier, recognizes their extraordinary contributions to the development of the prosthetic heart valve, which represents a milestone in the journey toward the fabrication of synthetic living tissues and organ sys-

tems. The prosthetic heart valve was built on a foundation laid down during the first half of the 20th century with the introduction of cardiac catheterization by André Cournand and Dickinson Richards, the development of innovative surgical techniques by Alfred Blalock, the invention of the heart-lung machine by John Gibbon, and

the discovery of heparin by Jay McLean and dicumarol by Karl Paul Link. In the late 1950s, as clinical practice was being linked more closely to the surgical laboratory and collaborations were established with those working in the nascent field of biomedical engineering, new intellectual and technical frameworks were cre-