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Feature

Contract Research Organisations

Truly independent research?

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*Research contracted to commercial or academic organisations might sound less biased than that done by industry. But as **Jeanne Lenzer** reports, influence is hard to avoid*

Drug and medical device companies are increasingly outsourcing clinical trials to commercial and academic contract research organisations (CROs). As well as cutting costs, this could potentially put desperately needed distance between sponsor and research product. If achieved, such distancing couldn't come at a better time: a Harris Interactive poll shows that of the top 11 industry sectors, only tobacco companies had higher negative public opinion ratings than drug companies (76% and 52% respectively).[1]

Although the literature about the biasing effects of industry sponsorship on medical research is rapidly expanding, little is known about whether studies conducted by CROs are subject to similar biases. This raises the question whether research outsourced to CROs is genuinely independent or subject to influence from corporate sponsors.

Contracted research

CROs contract with industry or public agencies to perform research activities such as recruiting participants, data collection, study design and analysis, and ghost writing. They reduce costs through economies of scale and by outsourcing to poorer nations.[2 3 4] Kevin Schulman, associate director of the academic CRO Duke Clinical Research Institute, says that research conducted by CROs is independent, partly because they are not beholden to any one client. Only by providing high quality research, can they survive in the marketplace and retain credibility. Dr Schulman says his organisation's strategy "is to have a mix of private and public sources of funding, and it's more important for us to maintain the integrity of the university than our relationship with any individual sponsor."

However, CROs face a fundamental conflict of interest—if they do not please their commercial clients, they may be less likely to get more work from them. Instances of study bias favouring the sponsor, discussed below, suggest that independence may have its limits. The appearance of independence is so highly prized that some CROs and their sponsors camouflage the commercial nature of their studies by emphasising the researchers' academic affiliations while de-emphasising or not reporting institutional and individual ties to the study sponsor. Important and highly cited clinical trials conducted by CROs have been widely reported, and perceived, as independent research conducted by academic scientists and clinicians affiliated with prestigious medical schools when in fact they are commercially sponsored.

It is hard to know just how serious or widespread these problems are, but the increasing role of CROs in research calls for scrutiny. Jerome Hoffman, professor of medicine at the University of California, Los Angeles, says, "CROs have become tremendously important players on the scene. It's hard to imagine that such organisations—even when they are housed at prestigious academic institutions—can be completely independent when they are so fundamentally dependent on industry money for their continued existence."

Case of Dr LeFever

Take the case of Gretchen LeFever, a clinical psychologist. In March 2005, Dr LeFever, then an associate professor in the department of

paediatrics at the Eastern Virginia Medical School, made headline news when school officials seized her computers and shut down her massive $750 000 (£400 000; €500 000) research project on attention deficit hyperactivity disorder (ADHD) funded by the US Centres for Disease Control and Prevention. The action came after an anonymous letter, dated 19 April 2004, was sent to the school charging Dr LeFever with scientific misconduct and violating requirements for the protection of human subjects.[5]

Just two months before the anonymous charges surfaced, Dr LeFever, writing in the *Scientific Review of Mental Health Practice*, cautioned that ADHD might be overdiagnosed, saying, "The 700% increase in psychostimulant use that occurred in the 1990s justifies concern about potential overdiagnosis and inappropriate treatment of child behaviour problems."[6]

Two months after the anonymous letter, Donald Lewis, a professor of paediatrics at the medical school, told Dr LeFever in an email dated 30 June 2004, that "repeated news media reports, fuelled by your reports, which depict our clinicians as quick-triggered, pill-pushers undermines the credibility of the Children's Hospital as well as our community partners."

Colleagues of Dr LeFever say the charges against her lacked substance; one well known ADHD researcher, William Pelham, professor of psychology, paediatrics, and psychiatry at the State University of New York, Stony Brook, dismissed the accusations as "overblown." Professor Pelham signed a petition in June 2005 with an international group of 39 psychiatrists and psychologists, telling the medical school's president that instead of threatening to fire Dr LeFever, the school "should have commended and promoted her for having the courage to be among the first to sound the alarm about these concerning trends."[5]

The heated debate swirling about Dr LeFever appeared to derive simply from philosophical differences that typify many vigorous academic debates. However, over the past decade, says Professor Pelham, attacks on those who question the escalating use of psychotropic drugs have increasingly come from proponents who have financial conflicts of interest. Professor Lewis, one of Dr LeFever's chief critics, did indeed have a financial interest in ADHD drug research. He was a part owner of Monarch, a commercial CRO that in 2005 was conducting four ADHD drug trials.[7] Professor Lewis is also a principal investigator for Monarch.

When Dr LeFever came under attack, she knew Professor Lewis as an academic, faculty member, and physician with the Children's Specialty Group, a multidisciplinary, paediatric practice that describes its doctors on its website as "faculty in the Department of Paediatrics at Eastern Virginia Medical School." However, Children's Specialty Group registered itself, quietly but legally, under what the Virginia State Corporation Commission says are "fictitious" or "assumed" names, including Monarch Medical Research and Monarch Research Associates. Fictitious names are often used for "marketing or branding purposes," according to the commission clerk's office.

Monarch has a list of sponsors that includes industry giants such as AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Hoffman-LaRoche, Novartis, Organon, Pfizer, Shire Laboratories, Wyeth-Ayerst Research, and a host of other companies.[8] According to it's 2004-5 fact book, Eastern Virginia Medical School "routed" at least a portion of its neurology research funds through Monarch. Despite Professor Lewis's commercial interest in Monarch, a PubMed search of his publications through 2005 (when his interest in Monarch first came under scrutiny) shows that he consistently listed his affiliations with the medical school or its affiliated hospital without mentioning Monarch.

Neither Professor Lewis nor the current medical school dean, Gerald Pepe, responded to written questions or to repeated requests for an interview. Dr LeFever was eventually cleared of the charge of scientific misconduct.

Rise of contract research

The dramatic increase in CROs can be tracked back to 1980 when only a handful existed. Now there are over 1000 such organisations in North America.[9] In 1993, drug companies outsourced 28% ($1.6bn) of their research money to CROs, according to CenterWatch, a Boston based publishing company that focuses on the clinical trials industry.[10] By 2003, CROs captured $7.6bn in research money and were involved in 64% of phase 1, 2, and 3 clinical trials.

CROs reduce costs partly by their ability to recruit volunteers quickly and partly by recruiting participants from impoverished regions of the world. The savings can be impressive. According to former chief executive of GlaxoSmithKline, Jean-Paul Garnier, a trial conducted in Romania costs only $3000 per participant compared with $30 000 in the United States.[4] He told *Fortune* magazine in July 2005 that a third of his company's trials were already being conducted in "low-cost countries"—a portion he hoped to ratchet up to a half within two years.[4] "Globalization," he said, "is the ultimate arbitrage for companies like GlaxoSmithKline."

The first CROs to arrive on the research scene were commercial companies like Monarch. As academics saw research money diverted away from universities into commercial organisations, they began to form their own quasi-commercial companies, known as academic research organisations. James Breitmeyer, past president of the Harvard Clinical Research Institute, an academic research organisation, urged his colleagues to "take back" their leadership role, saying, "commercially sponsored research organizations have out-distanced academic medical centres in conducting clinical trials."[11]

Are academic organisations different?

Although academic research organisations offer the imprimatur of university based research, like commercial organisations they are beholden to their industry sponsors. According to industry sources, drug companies look for CROs that can best meet "the needs of sales and marketing," especially for "commercialization studies," such as phase IIIb and IV clinical trials.[12] Lisa Bero, professor at the Schools of

Pharmacy and Medicine at the University of California, San Francisco, says that institutional conflicts can affect research outcomes. Professor Bero, who is chair of the conflicts committee at the university, says research priorities can be affected when a university gives preferential treatment or more space to a faculty member who brings in a lot of industry money.

When the research agenda is left to industry and the contract research organisations they use, the questions asked and tested may be influenced by financial, rather than public health, interests. Researchers, says Professor Bero, can, consciously or unconsciously, affect research outcomes. For one thing, she says, "you can ask a question which you know will give a favourable answer for the funder—and not ask other questions. For example, you can ask whether a drug reduces pain as measured by an unvalidated pain scale developed by the funder rather than measured by an independent, validated scale."

A study currently being conducted by the academic research organisation Cleveland Clinic Clinical Coordinating Center, known as C5, has been criticised by several experts, among them Garret FitzGerald, professor of medicine and pharmacology at the University of Pennsylvania, and Curt Furberg, a former adviser at the Food and Drug Administration. The $100m, phase IV safety study, funded by Pfizer and known as the PRECISION trial, is examining the relative cardiovascular and renal risks of celecoxib, naproxen, and ibuprofen for treatment of arthritis in people with, or at high risk of, heart disease.[13]

FitzGerald and Furberg say that testing Pfizer's drug, celecoxib, a cyclo-oxygenase 2 inhibitor known to increase cardiovascular events in the general population,[14 15] is ethically questionable—especially in people who have heart disease or are at high risk of it. Professor FitzGerald says while it is "entirely appropriate" to study the relative safety of ibuprofen and naproxen, it is not appropriate to "expose people at high cardiovascular risk to a drug that has been shown in placebo controlled trials to confer cardiovascular risk."

Steve Nissen, lead researcher on the PRECISION trial and chairman of the department of cardiovascular medicine at the Cleveland Clinic Foundation, says that the trial design is justified because "there is great uncertainty about which therapy is best." C5 has taken "extraordinary" steps, he says, to ensure that the conduct of the trial is "fully independent" from Pfizer. But that independence may have its limits. When I asked him to provide a copy of the patient consent form, Dr Nissen replied, "I don't know that I'm allowed to release that." A spokesperson for the Cleveland Clinic Foundation later called to say they "would not release the consent form."

Dr Nissen is widely admired for his integrity; he provided critical analyses and data that brought the dangers of rofecoxib (Vioxx) and rosiglitazone (Avandia) to light. To avoid personal conflicts of interest, he directs his consulting fees and honoraria to charities. And C5 has arguably gone further than many academic research organisations to reduce industry influence. However, regardless of the individual integrity of researchers or research groups, the ability of a sponsor to pick and choose which organisation will conduct a trial, raises questions about who, ultimately, is in control of the research design and the questions being asked.

Before awarding the contract to C5, Pfizer talked with the US National Institutes of Health (NIH). Dr Nissen said that NIH "wanted very badly" to do the study. Ultimately, however, Pfizer decided to take the study to C5. Although Pfizer's reasons for taking the study to C5 may be entirely legitimate (Pfizer officials declined to give a reason for the decision saying only that the choice not to conduct the trial with NIH was a "mutual decision"; NIH declined to discuss their talks with Pfizer), the ability of drug companies to pick the research organisations they want is concerning.

Jennifer Washburn, author of *University, Inc: The Corporate Corruption of Higher Education* and senior fellow with the New America Foundation, a non-profit, non-partisan public policy institute in Washington, DC, says academic research organisations are little better than commercial CROs. She said: "Academics truly felt they could perform studies in a more objective manner than the private sector. But in the process of competing for research dollars they've started looking and acting just like their commercial counterparts in order to placate their sponsors."

In another case involving the world's largest academic research organisation, Duke Clinical Research Institute, individual and institutional conflicts of interest were downplayed while the researchers' academic ties were highlighted. The institute, which boasts more than 5000 investigators in 64 countries and has carried out studies in over 545 880 people, conducted the 2004 treatment of adolescent depression study.[16] Headlines announced that researchers "at Duke" found that fluoxetine (Prozac) plus talk therapy was effective treatment for depressed adolescents. The study was heralded in news reports as a "landmark study" conducted by "independent" researchers "at Duke." *US News & World Report* declared that the study was "significant because it [was] one of the very few studies of antidepressants that were not financed by a drug manufacturer; instead, backing came from the National Institute of Mental Health."

Although the study was publicly funded (Lilly supplied the study drug and placebo free), some aspects of the trial and its reporting suggest that even publicly funded research may be affected by individual and institutional conflicts of interest when the research is conducted by a contracted research organisation. The principle investigator for the study, John March, and five of his coauthors had received funding from Eli Lilly, the manufacturer of Prozac, according to the authors' disclosures.[16] In addition, Duke Clinical Research Institute has had multiple research contracts with Eli Lilly. Neither the institute nor Lilly would reveal the value of their research contracts; Lilly said the information is "proprietary."

Whether funding from Lilly consciously or unconsciously affected the design of the fluoxetine trial can't be known. However, at least one aspect of the study design seemed to favour the drug. In two of the four treatment arms, the use of fluoxetine was not blinded—and part of the claim of fluoxetine's efficacy was based on the outcomes in the unblinded arms. In the blinded arms, participants taking fluoxetine did no better than those taking placebo on a key depression scale. In the two unblinded arms, adolescents who knew they were receiving fluoxetine

fared better than those who knew they were not receiving the drug. Since participants who know (or believe) they are receiving a drug can be expected to improve simply because of the placebo effect, the unblinded arms created a study design bias in favour of fluoxetine. Robert Temple, director of medical policy at the FDA, described the trial design in an email to me as "bizarre," adding, "It would have been perfectly simple to randomize all to [placebo or fluoxetine] and then secondarily randomize to cognitive [treatment]."

Although the total value of the Duke institute's contracts with Eli Lilly is not public, it can be assumed that losing a client is financially important. To its credit, the institute has insisted on publishing a study with a negative outcome against the wishes of one commercial sponsor. The company subsequently sued the institute, showing the commercial pressures that exist. The question is, can CROs reliably resist the biasing effects of such pressures?

Advocates of academic research organisations argue that their research is more independent and credible than that of commercial organisations because they insist on the right to have access to and retain clinical trial data. However, the right to retain data is not the same as right or willingness to release the data. Dr March and his colleagues reported the positive outcomes on the clinical global improvement scale in the fluoxetine trial but failed to report the negative outcomes on the same scale. Using a "dichotomised" scoring system, the researchers reported only scores of 1 (very much improved) or 2 (very improved) but did not report how many patients scored worse or very much worse.[16] The NIH refused my request for details of the unpublished negative outcomes through the Freedom of Information Act on the grounds that the principal investigator, not the NIH, retained the data. Both Dr March, the principle investigator, and the Duke institute declined to release the data from this "publicly funded" study.

Asking the right questions

The perception that CROs are independent is undermined by the advertising appeals they use to attract industry contracts. Quintiles Transnational, based in North Carolina and the world's largest commercial CRO, promises that it can deliver "scientifically valid" research designs that will "help customers prove the value of their products to patients, physicians, and regulators."[17] Disproving the value of a product would hardly keep clients coming back. Dick Jones, senior director of corporate communications at Quintiles, responding to a question about the seemingly biased nature of their promotional material, says that citing "this one short phrase taken out of context . . . mischaracterises our advertising." Mr Jones said, "Customers come to Quintiles because we are the largest global CRO with the experience and expertise to give customers timely, objective data for use in determining safety, efficacy and value."

CROs like Quintiles have become adept at using academic connections to advance their commercial goals. Quintiles founder and chief executive, Dennis Gillings, recently donated $50m to the University of North Carolina School of Public Health in Chapel Hill—now renamed the Gillings School of Global Public Health. In a letter dated 20 February 2007, the university chancellor, James Moeser, wrote to Mr Gillings and his wife, thanking them for the gift and affirming that the school would commit to the "alignment of faculty behind focused programs," and that their priorities would include "New methodologies to speed clinical trials innovations." Eight current or former Quintiles executives now head school programmes or sit on the school's boards and advisory councils.

Steve Wing, associate professor of epidemiology at the Gillings school, worries that the $50m gift could pit "mass drug therapy" against sound public health policies that "focus on working and living conditions that prevent disease." He says that some of the "focused programmes" supported by the gift "appear to address issues of commercial interest to a large donor who is the CEO of Quintiles Transnational." As for Quintiles' promise to "prove the value" of industry's products, Dr Wing says: "This sort of advertising tells drug companies, 'We know how to get the answer you want.'"

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