The commercialization of clinical research: who pays the piper, calls the tune?

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Clinical research has become a massive global endeavour. Clinical trials are regularly conducted in many thousands of patients across multiple countries. “Most clinical studies that bring new drugs from bench to bedside are financed by pharmaceutical companies. Many of these drug trials are rigorously designed, employing the skills of outstanding clinical researchers at leading academic institutions.”\textsuperscript{1} However, medical science is developed in a harsh commercial environment. As Backhouse, an economist working in the pharmaceutical industry, comments: “the design choices made in the planning of RCTs, such as which comparators to use, which endpoints to evaluate and which sample size to adopt, are effectively investment appraisal decisions.”\textsuperscript{2}

Contract Research Organizations (CROs), which undertake ‘for profit’ research almost exclusively for industry, are big business. In April this year, Quintiles, one of the major CROs which employs ~16 000 people worldwide and claims to be the largest employer of biostatisticians in the world, was valued at US$1.7 billion.\textsuperscript{3} A survey of researchers in academic health centres reported that 48% saw competition from CROs to be a moderate or large problem for clinical research.\textsuperscript{4}

So why does industry use commercial vendors to undertake research? There is some evidence that CROs complete trials more quickly and cheaply than academic researchers.\textsuperscript{5} Bodenheimer claims that “for each day’s delay in gaining FDA approval of a drug, the manufacturer loses, on average, US$1.3 million.”\textsuperscript{1} CROs are said to do the job for less money and with fewer hassles than academic investigators.\textsuperscript{6}

Aside from the turf war for research income, the schism between academic and ‘for profit’ research is less clear. Dennis Gillings began providing biostatistical and data management services to pharmaceutical companies in 1974, as professor of biostatistics at University of North Carolina, Chapel Hill, before founding the Quintiles Transnational Corp. Academics are also frequently involved on Trial Steering Committees and other research advisory groups even when the day to day organization and management of the trial is delivered by a CRO.

The commercialization of research has a downside. Although the standards of clinical research intended to support licensing applications to the Food and Drug Administration (FDA) and equivalent authorities in other countries are heavily regulated, there are still times when outcomes may not be in the best interests of patients. For example, in resectable pancreatic cancer, there may be a survival benefit for chemotherapy.\textsuperscript{7} An ongoing Cancer Research UK study is investigating chemotherapy and examining the role of Gemcitabine as an alternative regimen, but answering important clinical questions has to be paid for, and progress has been restricted through lack of funding to cover the Gemcitabine costs.

Scientifically, a neutral or negative trial is as valuable as a positive one, although commercially this is clearly not the case. It is well known that negative trials are often not published as quickly (if at all) as those with positive results, but commercial influences may make this more common. DeMets and Califf list a number of trials in cardiology where publication was delayed or compromised because of a lack of resources available to finalize and analyse the data after a recommendation to terminate on safety grounds on the advice of the independent Data Safety and Monitoring Committees (DSMCs).\textsuperscript{8} On one occasion listed, the trial sponsors even took legal action against the principal investigator of a trial because of the publication of results.

It is highly desirable for the findings of clinical trials to be informed by meta-analysis of previous trials as well as necessary phase I and II studies. Commercial pressures mean that, on occasions, corners may be cut. The confirmatory MOXCON trial of moxonidine in patients with heart failure was commenced before

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the dose-ranging MOXSE trial was completed. MOXCON achieved an early and negative imbalance of deaths: 46 out of 918 in the moxonidine group versus 25 out of 875 in the placebo group. The DSMC for the moxonidine trial programme recommended a change in dose of moxonidine in response to their review of the results of the MOXSE trial, but the trial sponsors elected instead to terminate the trial.

Recognizing that the commercialization of medical research is a fact of life, mechanisms can be built in to protect access to data and allow independent scrutiny. DSMCs are external independent advisory groups, responsible for the safety of patients involved in clinical trials, and may provide balance to the pressures of commercial influence. They are recommended but not required by relevant guidance for regulatory trials, although there are good arguments to support forming DSMCs in all important clinical trials. Regardless of the presence of an academic steering committee or independent DSMC, sponsors can and will remove their support for projects that do not appear in their commercial interest. Coats asks whether “the Steering Committee [is] really in charge of modern RCTs or are they really a scientific advisory board without crucial control.”

The recent initiative of editors of major clinical journals on publication ethics outlining the requirements of journals in order to ensure that the authors of an article have had a meaningful and truly independent role in the study that bears their names is welcome. However, there is a limit to the influence that medical editors may, on their own, wield. Efforts by the Cochrane Collaboration and others to ensure that the results of all randomized controlled trials (RCTs) are available for other researchers have not by-and-large persuaded the industry to open its trial records. There is perhaps a role for ethical approval to be made dependent on allowing such access after a reasonable period of time. Regulation could be strengthened, particularly in mandating the requirement for independent DSMCs in clinical trials of human subjects. Non-commercial funding sources should provide funding for clinically important but non-profit-making trials or, alternatively, industry should be regulated to do so. Ideally, trial development should create a partnership between the clinical community and industry, ensuring that the primary focus remains on patient needs and fast-tracking drugs to clinic. It is the responsibility of all those involved in clinical research to ensure that we do not stray too far from that ideal.

References