

Research integrity and pharmaceutical industry sponsorship

Trial registration, transparency and less reliance on industry trials are essential

Over the past 20 years, politicians, hospital administrators and university deans have encouraged academic researchers to increase their participation in projects sponsored by the pharmaceutical industry, and the industry's share of biomedical research has increased dramatically in that time (from 32% to 62% in the United States).¹ Increasingly, the wisdom of this development has been challenged.

The research agenda predominantly serves the interests of industry rather than those of patients. Surveys have shown that manipulation of clinical trials — whereby, if the results are published at all, the control treatment is disadvantaged by design, analysis, or interpretation²⁻⁵ — is common. Even when the results for the active and control therapies are no different, industry-sponsored trials come to a positive conclusion in favour of the sponsor's drug five times more often than do not-for-profit-sponsored trials.⁴

This sponsor bias can have serious consequences. A meta-analysis supported by Merck concluded that there was no increased risk of arterial thrombosis with the company's cyclo-oxygenase-2 (COX-2) inhibitor, rofecoxib.⁶ However, another meta-analysis, not sponsored by industry, showed an increased risk, which was apparent in publications available to the authors of the industry-sponsored meta-analysis 4 years before the drug was withdrawn because of thromboses.⁷ Such down-playing of harms in published papers has often required the collaboration, or acquiescence, of academic clinical researchers. It is likely that the widespread use of COX-2 inhibitors has caused thousands of premature deaths.

An article by Henry and colleagues in this issue of the journal (page 557) reports important breaches in research integrity in industry-sponsored research, based on the experience of medical specialists in Australia.⁸ There are several reasons why the prevalence of the problems probably represents only the tip of the iceberg.

Firstly, the authors note that their findings are limited by reliance on self-report, and only 39% responded.

Secondly, while only about 9% of respondents reported one or more episodes of potentially serious research misconduct, the authors note that this is equivalent to 21% of those who had an active research relationship with industry.

Thirdly, the authors did not consider protocol changes to be serious research misdemeanours. They need not be, but we found that at least one *primary* outcome was changed, introduced, or omitted while research was under way in 51 of 82 trials (62%).⁵ We think this is a serious problem as, with a median of 27 outcomes per trial,⁵ one would expect one outcome to become statistically significant by chance, even if the compared treatments were identical.

Finally, 2% of respondents in the paper by Henry et al reported changes to study protocols while trials were under way.⁸ Our study comparing protocols with corresponding publications showed that formal changes submitted to scientific ethics committees are not

common, but that informal changes are. We found that 86% of the respondents in a survey of triallists denied the existence of unreported outcomes, despite clear evidence to the contrary — we did not reveal to them until later that we had access to their trial protocols through the scientific ethics committees.⁵

Research misconduct and bias in intervention research could be markedly reduced if ongoing initiatives to register all trials at their inception, and ensure public access to trial protocols and all data generated by a trial, become successful. The International Committee of Medical Journal Editors have made a very positive and strong move towards this goal. They have agreed that after 1 July, 2005, its member journals, as a condition of considering a trial for publication, will require that it be registered in a public trials registry before patients enter the trial.⁹

Ethics committees would also have to play a central role to make this happen, and to ensure that commercial considerations will not be allowed to block access to the collected data, whether or not they are formally published.

It would be even better, of course, if testing drugs in patients was a public enterprise (whether or not financed by industry) with blinding during data analysis and writing of manuscripts, till everyone involved had approved them.¹⁰ This would ensure that commercial influences on trial design, analysis, manuscript preparation and publication would no longer distort our views of the value of drugs and other treatments. It would also ensure that the comparison treatment was relevant, that the outcomes were directly relevant for patients, and that the patient population was relevant (eg, elderly patients in the case of COX-2 inhibitors, who are also those most likely to develop thromboses). A case in point is the publicly sponsored ALLHAT trial, the biggest trial ever performed on hypertension, which showed that the cheapest drug available was also the best.¹¹

It is clear that governments could save money and treat patients better by investing much more in trials and academic trial centres than by relying on industry's own trials and conclusions. Who would buy a washing machine that is five or 10 times more expensive than other machines just because its manufacturer has compared it with other machines and claims that it is the best? Unfortunately, such absurdities are often seen in health care, and are allowed to happen even in the absence of any direct head-to-head comparisons.

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It would be even better if testing drugs in patients was a public enterprise...

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