Blurring the Boundaries: Research or Promotion?

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In Japan, the industry association (JPMA) developed formal guidelines for sponsors of clinical trials in 1995 after Glaxo's Japanese subsidiary, Zeria Pharmaceutical, was accused of making payments to doctors to alter trial report forms during a study of lacidipine, a calcium antagonist.[(166)] Two doctors were arrested as a result. Zeria simply received a caution against making such unacceptable payments.

When the company Boots sponsored research on bioequivalence between its product Synthroid (synthetic levothyroxine) and three competing products, it expected the results to show Synthroid to be superior. The product dominated the thyroid hormone market, with sales of US$600 million a year, and owed at least part of its dominance to claims that other products were not bioequivalent.[(167)] The results of the Boots-sponsored study, carried out by Betty Dong from the University of California at San Francisco and her associates, showed that all four products were bioequivalent. What followed was a seven-year battle by the company to discredit the authors and prevent publication. Dr Dong completed the manuscript in 1990 and sent a copy to Boots in preparation for publication. The *Journal of the American Medical Association* accepted the article in 1994 following review and planned to publish it when the author suddenly withdrew the manuscript because of threatened legal action by the manufacturer. She had signed a contract giving the company the right to veto publication of the study.

The study was finally published in 1997, in no small part because of negative media publicity. The *Wall Street Journal* published an article in 1996 publicly exposing the company's actions to prevent publication. In the meantime, Boots had reanalyzed the study results so that they reached the opposite conclusion to that of the researchers, and published them without acknowledging the original authors. They were published in a new journal, the *American Journal of Therapeutics*. One of the authors of the reanalysis, Mayor, was also an associate editor of the journal.

This "cautionary tale", as Drummond Rennie calls it in a *JAMA* editorial, may never have come to light had an investigative journalist not exposed Boots' activities. How common are delays in research contracts? A study by researchers at Carnegie Mellon University, Cohen and Goe, found that 35% of agreements signed between industry and academic researchers allowed the sponsor to delete information from publication, 53% allowed delays in publication, and 30% allowed both deletions and delays.[(168)]

Richard Horton comments in *The Lancet* that: “Funding alone is not really the concern, of course. Rather, it presents a surrogate for the potential commercial influences over how data are collected, analyzed, and interpreted.”[(169)]

Lisa Bero and Drummond Rennie looked at how the design of a drug study can introduce bias. In a review of studies published between January 1966 and April 1994, they found that, “flaws in the study design almost always favor a new drug in comparison with competing products,” and suggested that, “pharmaceutical industry funding influences drug study design and outcomes.”[(170)]

These are a few of Bero and Rennie’s recommendations to reduce bias in publication of research results:

- registries for drug trials should be set up and all drug trials registered when first started
- all data from drug studies should be published, to avoid the “positive publication bias” of only studies favouring a sponsor’s drug being published
- regulatory authorities should require publicationof all data submitted as part of the drug approval process
- authors of the reports should be the researchers not industry-supported writers
- industry funders should not be allowed to buy their way out of the peer review process by funding journals.

A 1998 study published in the *New England Journal of Medicine* reviewed 70 articles on the use of calcium-channel blockers to treat high blood pressure published in 1995 and 1996.[(171)] There are safety concerns about the use of calcium-channel blockers because of research showing a higher risk of heart attacks. All but one of the authors of articles supporting the use of calcium channel blockers (96%) had received funding from the manufacturers as compared to 67% of neutral authors and 43% of authors who criticized the safety of these products. “The association was quite a bit stronger than we expected,” said Alan Detsky, a professor at the University of Toronto who co-authored this study.[(172)]

A consensus conference on controlled clinical trials involving academic researchers and industry representatives highlighted differences in attitudes towards research independence in the two groups. The consensus conference involved 46 people from industry and 36 from academic institutions. Over three-quarters of company representatives did not agree that sponsors should be excluded from committees governing the operations of a trial, such as the trial board, data monitoring committee, coordination centre and data quality centre, in order to minimize bias. In contrast, over three-quarters of the academic researchers agreed with introducing such measures as a means of minimizing bias.[(173)]

Industry sponsorship affects not only research results but the questions researchers examine. A review of 151 comparative studies of non-steroidal anti-inflammatory drugs (NSAIDs) to treat osteoarthritis published betweem 1985 and 1991 found that 149 compared one NSAID to another; only two compared an NSAIDs to a simple analgesic.[(174)] NSAIDs are in general more expensive and subject to serious adverse effects.

Research showing NSAIDs to be more effective than analgesics in treating arthritis would give prescribers and patients a reason to prefer them in spite of the extra expense and risk. However, companies are vying for a market position in comparison to other NSAIDs, not to cheaper analgesics, and this guides their priorities for research funding.

Another review looked at the results of 56 industry sponsored studies of NSAIDS published between 1987 and 1990. In all cases the sponsor's drug was found to be either equally or more effective than the comparison drug.[(175)]

International Committee of Medical Journal Editors:

The International Committee of Medical Journal Editors representing major peer-reviewed medical journals, also known as the "Vancouver Group", have been meeting regularly in order to develop guidelines for publishing research results, such as full disclosure by authors of sources of funding.

Excerpts of Vancouver group journal editors' guidelines for sponsored research:

- Financial and material support should be acknowledged and the nature of the support specified.
- Authors should not enter into agreements that interfere with their control over the decision to publish.
- Influence of the sponsor if any on how the way the research has been carried out should be clearly stated: editors should require authors to describe the role of these sources, if any, in study design, collection, analysis, interpretation, and reporting. The type and degree of involvement of the supporting agency should be described in the methods section.
- Editors should require disclosure of whether the sponsor controlled or influenced the decision to submit the manuscript for publication.

Source: Horton R. Sponsorship, authorship, and a tale of two media. The Lancet 1997; 349;1411.

PHARMACOECONOMIC STUDIES

"A pseudo-discipline... conjured into existence by the magic of money"[(176)]

During the last five to ten years there has been an enormous growth in the number of cost-effectiveness studies of pharmaceuticals. These studies can provide a useful framework for governments and health services to make decisions about how resources will be allocated and what products they decide to reimburse. However, they appear to be biased all too often by commercial interests. In an editorial in the *Annals of Internal Medicine*, Evans

discusses the link between this boom and the growth of managed care in the US as well as cost-cutting initiatives by public health financers: “Control over decisions on drug purchasing is allegedly shifting to the health care plan managers who must actually pay for the drugs. Marketing systems aimed by drug companies at physicians are thus bypassed.”[177]

With the shift in purchasing decisions, the strategy aimed at selling the product also needs to shift. As Evans notes, economic analyses offer ample opportunities to choose one’s assumptions in order to reach a desired result: “The sponsors have a large economic interest in research outcomes, and the researchers have a professional (and economic) interest in doing research. Bias is inherent in such a structure…”[178] A Task Force on Principles for Economic Analysis of Health Care Technology, which was funded by 12 major pharmaceutical companies to develop guidelines for this research, expresses concerns that the close links to industry have led to mistrust of pharmacoeconomic studies. “A major issue is that the primary source of funding for this research is often the primary financial beneficiary of positive study results.”[179]

Interestingly, this task force obtained funding from pharmaceutical companies but was unsuccessful in obtaining any funding from managed care providers or public funding. Evans believes this is because drug purchasers see little advantage in guidelines to regulate economic evaluations: “They can always hire their own evaluators. If an economic evaluation looks dubious, they don’t have to pay for the product.” He calls pharmacoeconomics, “A pseudo-discipline…conjured into existence by the magic of money”.[180]

A review of economic evaluations of drugs published in English between 1986 and 1991 indicated that the majority found the drug to be more cost-effective than no intervention, and that when drugs were compared to non-drug treatments, usually the drugs were favoured.[181] Did this simply reflect a “positive publication bias” well known in medical science, in which studies showing a beneficial effect are more likely to be published than studies showing that a treatment has no effect? Authors Coyle and Drummond argue that this bias in clinical research should not carry over to economic evaluations because “showing that a given intervention is not cost-effective is potentially just as interesting as showing the reverse.”[182] They were not able to judge the effects of sponsorship as often funding sources were not revealed. However, they raised questions about the increasing priority given to economic evaluations of drugs: “Whether or not a given drug gives good value for money depends critically on the clinical indications and the availability of alternative treatments.”[183]

CONSENSUS GUIDELINES: consensus among and for whom?

The recommendations of consensus conferences, meetings of experts to develop guidelines for treatment of a specific disease or health condition, provide an important source of information for doctors seeking to know how best to treat their patients. Implicit to this model is a sense of trust that the available evidence will be analyzed impartially.

How impartial and independent are consensus conferences? Philip Berger was a participant in a 1996 HIV/AIDS treatment consensus conference organized by the Canadian HIV Trials Network, which is publicly funded and hence presumably independent, "in which company marketing and sales representatives actively and fully participated in the generation of recommendations for when and how to treat HIV-infected persons with the companies' drugs". Seven of the 18 expert group members were pharmaceutical company representatives whose products were being discussed and whose companies stood to gain financially from the recommendations of the consensus conference. Many of the clinicians and researchers present were working on projects funded by these same companies. Berger notes that: "All present denied a conflict of interest". He raises concerns about the implications for patients: "The integrity of the information and recommendations are compromised, yet patients will be making treatment decisions based on a flawed and biased consensus conference…" [(184)]

RECOMMENDATIONS: Consensus conferences

The recommendations of consensus conferences are only useful if independence, accountability and adequate representation can be fully guaranteed, and if all the available evidence is taken into account.

1. Consensus conferences should only include participants without financial links to companies whose products are used to diagnose or treat the condition under discussion.

2. Proceedings and membership of consensus conferences should be fully transparent to ensure public accountability.

3. All consensus conferences should include consumer and patient representatives, again without financial links to the pharmaceutical industry.

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