The Evidence behind our Evidence-Based Decisions: Cheques and Balances

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Evidence-based medicine has become a byword in present-day medical discourse. Its underlying assumption is that clinical decisions are based on unbiased and objective research results. In this issue of *IMAJ* the systematic review by Dr. Liss of 100 published studies on inhaled medications used in diseases of the airways [1] highlights the impact of source of funding on outcomes of clinical trials. Liss reports that industry funding was nearly always (97%) associated with results favoring the sponsor's drug, as compared to only 37% for non-industry-funded studies. These findings are new in the field of respiratory medicine, although the ethics of some industry-supported studies in asthma were questioned previously [2].

The issue is not new; it has been documented for more than two decades in many studies and diverse fields of therapeutics. In psychiatry, where 162 randomized, double-blind, placebo-controlled studies were examined, those reporting financial conflict of interest of one author or more were 4.9 times more likely to report positive results [3]. In studies on oral contraception [4] that compared risks of venous thromboembolism with third- versus second-generation drugs, industry-supported studies showed only a trend towards excess risk, while those funded otherwise showed a significant, more than twofold, increase. In oncology, a survey [5] of all 136 randomized studies of drug therapies in multiple myeloma during the period 1996–98 showed more industry-funded studies comparing innovative therapy to placebo or no treatment than publicly funded studies (60% vs. 21%) with biasing effects on outcomes (see below). With the COX-2 inhibitor saga fresh in mind, it is interesting to note that one of the earlier warnings was in the field of rheumatology – concerning non-steroidal anti-inflammatory drugs in arthritis [6]. The most recent is a review of 324 cardiovascular clinical trial outcomes [7] published by three leading journals in the years 2000–2005, showing significant favoring of newer treatments over standard of care in studies funded by the pharmaceutical industry (67%) compared to studies without commercial funding (49%). The 'flagship' study of the skewing of results [8] was the analysis of 370 drug trials included in 25 meta-analyses, a random sample taken from 167 Cochrane reviews. Trials funded by drug companies were five times more likely to recommend the experimental drug as the treatment of choice, irrespective of differences in real treatment effects or rates of adverse events.

A major ethical and scientific principle upon which clinical trials are based is the uncertainty principle, or equipoise, which states that patients should be enrolled in a randomized controlled trial only if there is substantial uncertainty ("equal bet") regarding which of the trial treatments would benefit them most [5,9]. Violation of this principle, which has been clearly documented, indicates that studies sponsored by industry significantly favor the experimental drug. Thus, in the myeloma trials quoted earlier [5], equipoise between innovative and standard active therapies was sustained when funding was not commercial (53% vs. 47%). Conversely, in the commercially funded studies, innovations were significantly favored over standard treatments (74% vs. 26%) as well as over placebo or no treatment (90% vs. 10%).

Qui bono? It is a fact of life that only 10–15% of newly approved drugs provide important advantages over older drugs in the same category [10]. Nonetheless, a recent report from Canada shows that during the period 1996–2003, most (80%) of the increase in drug expenditure was due to the use of new, patented drugs, which offered little improvement over cheaper alternatives available before 1990 [11]. Furthering awareness of new drugs through multiple, probably redundant, clinical studies enhances utilization [12]. In her 2000 editorial published in the *New England Journal of Medicine*, Marcia Angell comments [13]: "Critics …charge that many industry-sponsored clinical trials are designed more to find small advantages that can be highlighted in promotional campaigns, than to find clinically meaningful effects."

Positive results, then, are more likely to enhance the marketability of a new drug, with obvious implications for the interests of the pharmaceutical industry. In fairness though, it should be noted that when initial studies of novel therapies are positive, the likelihood of further trials (and reports published) is increased, as is that of their being funded by for-profit organizations. In addition, regulatory approval and generation of practice guidelines require replication of clinical trial results, again with obvious impact on sources of funding [7].

Industry, however, is not the only party with potential gain. The medical community – in academic medical centers, and increasingly [2] in community and private practices too – is an active player in the clinical trial industry the world over. Of interest is the Australian experience [14] where industry funding was sought by potential investigators in a 1:2 ratio compared with industry-initiated approaches, for the following reasons: "efficient way to obtain funds" – 66%, "project important regardless of funds" – 60%, "competitive grant unlikely to be successful" – 37%, and "unsuccessful in securing competitive grant" – 13%. Clearly, the individual investigator is motivated to participate in this game, despite the fact that 24% of the 2253 specialists surveyed reported undesirable interactions with sponsors in their research collaboration. The motivation for obtaining research funding, given the stagnant public funding for clinical trials [15], is legitimate. Physicians do clinical research as part of their scientific commitment and need to publish their results for professional and academic recognition. Cooperative effort with the pharmaceutical industry sustains a major proportion of this research [2] and will continue to do so. It should be borne in mind that "it seems unrealistic and wrong to assume that the drug industry can or should develop and test new treatments – without interaction with practicing doctors and clinical academics" [16].

How does the slanting of published evidence occur? Expectations regarding positive outcomes could be reflected in study design (inappropriate comparators such as type or dose of control drug, use of surrogate outcomes), selectivity in data analysis (with undue emphasis on secondary outcome or subgroup analyses), or biased interpretation of trial results. However, poor quality of design has not been shown to selectively typify commercially sponsored studies [4,7]. Publication bias is another likely explanation. Ongoing industry-sponsored studies are often discontinued due to accumulating, apparently negative results, or if completed, these results are not published at all, or only after much delay [4,8].These are sad realities in view of the brave words voiced nearly 25 years ago by the president of Yale University, when discussing academic cooperation with industry research projects: "The university will not accept restriction, inhibition, or infringement upon a member of the faculty's free inquiry or capacity orally to communicate the results of his or her research. In addition, the university will not accept any restriction of written publication, save the most minor delay to enable a sponsor to apply for a patent or license…" [17]. Substitute "hospital" or "clinic" for university and you are left with an aspiration no longer operative in the realm of clinical trials. Finally, medical journals themselves benefit substantially from their commercial links with the drug industry [18] and are responsible, at least in part, for some of the deficiencies in the manuscript approval process, which contributes to the phenomenon of publication bias and cannot be prevented by the current peer review system.

In the end we should remember the dictum coined by the distinguished American social scientist Robert K. Merton: "Science is public, not private. But for science to be advanced, it is not enough that fruitful ideas be originated or new experiments developed or new problems formulated or new methods instituted. The innovations must be effectively communicated to others…In the end, then, science is a socially shared and socially validated body of knowledge" [19].

In order to contend with potentially skewed evidence, we cannot rely naively [20] on author disclaimers. Clinical research must be conducted only under the supervision of institutional review boards, properly equipped to ensure that study designs are not subtly biased, that the researcher maintains full control over his/her original data, and is an active partner in the data analysis process and elaboration of conclusions. Investigators must retain full control over, as well as responsibility for, publication rights and content. Editors (and their reviewers) must examine protocols, insist on trial registration in transparent registries, demand open disclosure of the full role of sponsors in creating the evidence and the written report, and reject manuscripts not fully controlled by the investigator. Above all, major increases in public funding of clinical trials will be needed in order to weaken the links between marketing considerations and the evidence we need to obtain, in order to better inform our decisions for individual patients and society at large. Taken together, all these measures should allow a return to ethical and scientific equipoise, with reestablished faith in the results of clinical studies.

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