Getting it right: industry sponsorship and medical research

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Many of the policies and procedures for the ethical oversight of research were put in place in an era when public funding was much more prominent than it is now. Over the last 2 decades there have been major changes, with increasing pressure on universities, teaching hospitals and individual researchers to seek industry sponsorship for research, and the pharmaceutical industry has become the single largest direct funder of medical research in Canada, the United Kingdom and the United States.[1] At its best, academic participation in the development of drugs leads to effective and safe new therapies. However, conflicts of interest are inevitable at times, because the goals of industry and of academia differ.[2] These conflicts put pressure on researchers to stretch — occasionally to the point of breaking — fundamental principles of ethical and scientific behaviour, and they may result in corporate research agendas, rather than the broader public agenda, being placed centre stage.

When clinical research results are contrary to a company's interests, conflicts are more likely to develop, and there are numerous documented instances in recent years in Canada of attempted suppression of research findings by pharmaceutical companies.[3,4] Companies may be selective in publishing results, and they may delay or not publish unfavourable results at all.[5–7] Clinical trials now often include many centres, and potential for bias is clear, as the company often collates and analyzes the data. The listed authors may not have seen the complete data set.[8] In fact, a recent survey of 108 medical schools in the United States showed that only 1% of the site researchers surveyed had access to all of the trial data and that only 40% had control over publication.[9] Because many multicentre trials take place in Canada and the United States, and because contracts are similar for participating centres, the situation in Canada is likely to be as disturbing. The recent announcement by the Canadian Institutes for Health Research (CIHR) that it is going to conduct an analogous study of Canadian research practices is very encouraging.[10]

Cases of suppression of data and intimidation by industry are troubling, but they are likely only the visible tip of a bigger iceberg. For many academic researchers, the future prospects of their laboratories and careers depend on renewed industry funding. They also may be understandably reluctant to speak out: if they trigger a legal action, it is time consuming and expensive, and it disrupts work and harms reputations. Large pharmaceutical companies, on the other hand, may see such legal expenses as a "cost of doing business."[11] Even if a company ultimately loses an action, in effect they win by delaying publication of adverse findings for lengthy periods, and the case serves as a deterrent to others from acting independently.

Although particular instances of outright suppression are of concern, much more worrying (although less visible) is the well-documented increasing control by industry over design and publication of clinical trials. It makes commercial sense for large drug companies to create their own study designs. It has been estimated that, on average, a manufacturer loses over a US$1 million for each day's delay in obtaining US Food and Drug Administration approval of a new drug.[12] Therefore, we should not be surprised at moves by industry to try to take more control of research, all the way from design and methods, through analysis, data presentation and publication vehicle.[12] Numerous studies and literature reviews show the systemic influence of industry funding, with a correlation between funding by the manufacturers and findings that show results supportive in terms of efficacy and safety of the sponsor's products.[5,13–17] A sponsor's drug at high doses may be compared with lower doses of a competing product, or with a poorly absorbed preparation, or it may be tested in patients who are younger and healthier than patients who typically have the disease, thus reducing the likelihood of adverse events.[18–20]

Industry may influence not only the conduct of clinical trials, but also clinical practice guidelines, which give recommendations on drugs, dosages and criteria for drug treatment and are intended to affect the practice of large numbers of physicians. Clinical practice guidelines have generally been accepted as an objective consensus on evidence. However, in a survey of 192 authors of clinical practice guidelines, about 60% reported that they had financial ties to the companies whose drugs were considered.[21] Disease-specific foundations such as the American Heart Association (which received US$11 million in donations from Genentech, a firm that was very interested in the foundation's guideline on acute stroke management, which recommended the company's product) are heavily funded by industry.[22]

The rapidly increasing trend toward influence and control by industry has become a concern to many. It is of such concern to the Association of American Medical Colleges that the college has issued 2 new documents — one on how to deal with individual conflicts of interest[23] and the other on how to deal with institutional conflicts of interest in the conduct of clinical research.[24] Editorials addressing this important topic are increasing.[25–33] It was of such concern to the ed-

itors of a dozen respected medical journals (including *The Lancet*, the *Journal of the American Medical Association*, *CMAJ* and the *New England Journal of Medicine*), that in September 2001 they set new rules. These journals[34] and, following their lead, other journals[35] now refuse to publish studies unless the responsible author signs a statement that he or she had access to the data, accepts full responsibility for the conduct of the trial and controlled the decision to publish. Unfortunately, the recent review of industry contracts[9] indicates that most researchers in the United States will not be able to meet the new journal requirements unless changes are made; the situation in Canada is unknown.

What can be done to ensure that research involving human subjects conducted by industry or by industry in partnership with academia puts patients' and participants' interests ahead of corporate interests and that society reestablishes its control over the health research agenda? In the United States, well-publicized cases of questionable ethical behaviour in research, such as that of Jesse Gelsinger, who died in a gene therapy trial, and Ellen Roche, who died in a study on asthma, have mobilized institutions to examine and change their policies and have led the US Office for Human Research Protections to temporarily shut down federally supported research at a half dozen prestigious centres in the United States over the last 3 years, because the investigation of these cases showed widespread deficiences.[36,37] The recent requirement of the US Office of Research Integrity (ORI) — that institutions receiving funds or grants for studies involving human subjects have education programs on responsible conduct of research for all researchers — is a step in the right direction.[38] The ORI has supported the development of research ethics instructional Web sites and is taking an approach of continuing quality improvement, helping institutions to come into full compliance.[39] Several Canadian universities are becoming concerned with this issue; for example the University of Toronto and all 8 of its affiliated hospitals have implemented a new policy intended to protect academic freedom and permit disclosure of risks, which they view as "the first step in what will be a continuing initiative."[40]

But more is needed. First, we need to acknowledge the problem. It would be useful to collect Canadian data and to discuss the issues openly. Again, CIHR is taking some initial steps in this direction.[10] It would be helpful if CIHR would require that institutions, as a condition of receiving grants, have in place research ethics education as part of the training of all researchers. Other players, such as Research Ethics Boards, Health Canada, the administrations of universities and research institutions, also have a role to play in protecting the integrity of research.[2]

Lastly, as a society, we need to think about the consequences, for health research as a whole, of the strong focus on academic–industry partnerships to produce marketable products. Few drugs (6%) are classified as "substantial improvements" over other, already available treatments,[41] so it is understandable that companies want to control data collection and dissemination. However, a lack of balance in research activities, with a focus mainly on potential medications, is likely to divert talented researchers from the pursuit of profound scientific questions, or divert them from the pursuit of questions without market relevance but with an aspect of public good. A company has little incentive to support trials evaluating whether inexpensive, off-patent drugs, or whether nonpharmaceutical interventions, could replace their profitable patented drug. When it is easier to fund an industry-supported clinical trial of tamoxifen "look-alikes" to prevent breast cancer than a trial of physical activity or diet for the same reason, it changes the kinds of research questions that are asked. Currently, guidelines are being developed for using expensive drugs for the treatment of obesity,[42] but insufficient attention is being paid to researching effective ways to promote healthy eating and exercise, or to stop the advertising and sale of junk food in schools. It is unrealistic to expect drug companies to stop making drugs to treat diseases that result from lack of physical activity and unhealthy eating or from smoking. But it points up the need for a better balance in funding of health-related research. It also highlights the need for funding of research into new and effective ways to get people to change behaviour, and of research into policies that provide incentives and support for healthier behaviours at a population level.

In conclusion, the increasing influence and control by the pharmaceutical industry brings to attention existing gaps in the current protection of the public interest with regard to the conduct and reporting of clinical trials in Canada. The promise of highly profitable developments in pharmaceutical, biotechnology and genomics research makes it important to have appropriate and transparent resolution of inevitable conflicts of interest.[43] Many new opportunities have been opened up by our new genomics knowledge, but these cannot be explored without the trust of citizens. We cannot afford to lose the confidence of the public in the social contract that allows research involving human subjects in exchange for medical advances. We will all lose — the public, researchers, hospitals and pharmaceutical companies alike — unless we take these lessons to heart.

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