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Industry Sponsored Clinical Trials and Conflict of Interest: Implications for Policy

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1. Introduction

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. But over the last two decades there have been major changes, with increasing pressure on universities, teaching hospitals and individual researchers to seek industry sponsorship for research. Several factors have been instrumental in this. In the late 1980's the federal government got a commitment from the pharmaceutical industry to invest 10% of sales in Canadian based research, in return for longer patent protection. As a result, manufacturers of patented drugs now spend $1B Canadian on research and development in Canada each year. Another factor that has assisted the shift to industry funding is the increasing emphasis on prevention and treatment of chronic diseases. Research trial participants for chronic diseases are likely to have to take drugs for years in order to prevent relatively uncommon disease endpoints. As a consequence, clinical trials now need to be larger and longer, and often they must be carried out at multiple centres in order to get sufficient numbers of patients. Industry is much more able to fund such complex and expensive trials. Lastly, governments in Canada, in an effort to move to a "knowledge based" economy, have vigorously encouraged university/industry partnerships, including those in the area of health research. As a result of these factors, the pharmaceutical industry is currently the single largest direct funder of medical research in both Canada and the United States.

At its best, academic participation in development of drugs may advance knowledge and may lead to effective and safe new therapies. The public has an interest in seeing new, better ways of dealing with disease, and researchers want to make a contribution to that outcome. Drug manufacturers have a strong interest in introducing new therapeutic agents. So on the surface it
seems as if all the players' goals are congruent. But on closer examination, this is not the case. We are fooling ourselves if we do not face the fact that conflicts of interest are inevitable at times, because the goals of industry and of academia differ. The duty of pharmaceutical companies is to make money for their shareholders; the goal of academic research is to seek truth. Industry has to maximize profit, while the aim of academic research is scientific understanding. If clinical trials show unexpectedly poor results, the interests of industry and academia start to diverge. The policies and procedures put in place in another era were not designed to protect the public interest in the face of the sometimes discordant goals of academia and industry. In this changed funding context, we need to be vigilant about protecting the principle that the integrity of the research process and the safety of research subjects in clinical trials, are more important than corporate interests. If industry/academia partnerships are to bring benefits (other than to the partners) there need to be clear rules governing the relationship, rules that protect the right of researchers to publish and communicate findings that may displease the sponsors, and that protect an unbiased reporting of findings. It is important to examine whether the current oversight and practices in Canada are still appropriate. We need to step back, and assess whether the rules of engagement in industry/academic partnerships are clear, are followed, and are protecting the public interest.

2. **The tip of the iceberg**

Many collaborations with pharmaceutical companies are conducted on an appropriate and professional level, but when results are contrary to a company's interests, conflicts are more likely to develop. There are numerous documented instances that demonstrate that the interests of industry and academia may clash and lead to outcomes detrimental to the public interest. For example, in recent years in Canada there are the attempted suppressions by Bristol Myers Squibb and by Astra Zeneca of research findings not in their interest. These companies' drugs
kept their market share during the time interval needed to defend against their interventions to prevent release of data. The example from the U.S. of suppression of information regarding synthroid is now well known, but other, more recent instances show the lessons have not been learned.

The reported incidents of suppression of data and intimidation by industry are troubling, but are likely to be only the "visible" tip of a bigger iceberg. For many academic researchers, the future prospects of their labs and careers depend on renewed industry funding. This encourages their interests to align with those of their sponsors, and encourages them not to make an issue, for example, of subtle changes in wording of a publication. If a larger difference with the industrial sponsor is involved, researchers may be understandably reluctant to speak out - because when they are faced with warnings of legal action, it can be a very long and expensive process, that consumes all available time and energy. Speaking out may cost not only future research funding, but may lead to conflict that disrupts work and harms reputations. A legal case can be ruinous for an individual regardless of the final outcome.

Large pharmaceutical companies, on the other hand, may see such legal expenses as a "cost of doing business". Apotex, for example, spends more than $10m annually on legal fees and is currently engaged in approximately a 100 legal actions. Even if a company ultimately loses an action, in effect they win by delaying publication of adverse findings for lengthy periods. Such legal cases also serve as deterrent examples to others in the research community from acting independently.

3. The rest of the iceberg

Although particular instances of outright suppression are worrying, even more worrying (although less visible), is the documented increasing influence and control of industry over design and publication of clinical trials. It has been estimated that on average a manufacturer
loses over a $1m U.S. for each day's delay in obtaining U.S. Food & Drug Administration approval of a new drug, so we should not be surprised at moves by industry to try to take more control of publications.\textsuperscript{11} There is a lot at stake for them, and a great deal of money involved in the outcome of clinical trials. Some recent figures attesting to that show that in 2001, $155B U.S. was spent on prescription drugs in the U.S., which was a 17\% increase from the previous year.\textsuperscript{12} In Canada in the same year, $11.5B Canadian was spent on prescription drugs, which was a 15\% annual increase.\textsuperscript{1} This substantial increase was facilitated by the approximately $2B spent by the pharmaceutical industry in Canada in 2001 to promote prescription drugs.\textsuperscript{13}

What is the evidence for a less obvious, but widespread influence and control by industry? There are numerous studies that show a systemic influence of industry funding, with a correlation between findings that show positive therapeutic value and funding by the manufacturers of the drugs.\textsuperscript{14,15,16} For example, a review of the English language literature looking at calcium channel antagonists over a 19 month period, found that almost all (96\%) of authors supporting the use of these drugs had financial relationships with the manufacturers. For neutral papers, 60\% of authors had such relationships, while among authors who were critical of the use of these drugs, 37\% had relationships.\textsuperscript{17} Another example of a literature review, this time of pharmacoeconomic studies of cancer drugs, found when industry sponsored the studies, unfavourable conclusions about the company's products were reached only 5\% of the time, whereas 38\% of studies with non-profit funding had unfavourable conclusions about the drug studied.\textsuperscript{18}

Currently, most new drugs, in spite of the promotional claims (and higher prices) actually offer minimal improvement over existing products and may in fact have greater side effects.\textsuperscript{19} Over the last 14 years, just 69 of 1100 new pharmaceutical products in Canada have been classified as "substantial improvements" over other already available treatments.\textsuperscript{20} Since most
drugs that are developed are "me too" drugs, they won't have a major effect on the health of the population, but if effectively marketed and promoted will have a large effect on the revenues of their manufacturers. In a highly competitive context, it makes commercial sense for large drug companies to create their own study designs, and a shift to this practice is happening rapidly. An increasing number of clinical trials are designed, managed and reported by the companies developing the new drug. Even if academics are actually conducting the trial, the drug companies often control the criteria for what patients enter, what drug comparisons are made, and how findings are analysed and reported. Companies may develop studies likely to favour their product, and how this has been done has been vividly described. For example, if a new drug is compared with a lower dose of a competing product, or with a poorly absorbed preparation, the new drug may look better. Patient selection also can make a big difference - if a drug is tested in patients who are younger and healthier than the patients who typically have the disease, it appears more effective. However, incomplete reporting of randomization methods is common in the literature.

Companies may be selective in publishing results, or they may not publish unfavourable results at all. Another tactic that has been observed is that a company may produce multiple publications from one data set if it is favourable, (salami slicing), but under publish studies that do not show benefit. It is not surprising that companies act to ensure that favourable results are widely publicized, while keeping quieter about findings that are harmful to potential sales. Such activities of pharmaceutical companies make commercial sense for them, but what is good for them, may not be congruent with what is good for patients.

Clinical trials now often include many centres, and the lead investigator at each centre may not be able to have an independent concept of what the findings are in the trial overall. He or she often must rely on the company to collate and analyze the data, presenting it back to
investigators at the different centres. Research papers increasingly are being drafted by company employees, and the listed authors may not have seen the complete raw data, but have seen only tables compiled by the company. Potential for bias is clear when the company interprets and reports the data.

Not only clinical trials are influenced by industry, but also what have generally been thought to be objective - clinical practice guidelines. These recommend which drugs, what dosages, and the criteria for drug treatment, and are hoped to affect the practice of large numbers of physicians, so it is important that they be unbiased. However, a recent published evaluation found that conflict of interest, or at least perception of one exists, because 59\% of clinical practice guideline authors had some form of financial relationship with the specific companies whose drugs were considered in the guideline they authored. Over half (53\%) of the guideline authors said the process they were involved in had no provision for declaring industry relationships.

Another issue is that doctors and the public are likely to rely on guidelines for drug use produced by credible non-profit associations, so it is important that the process such organizations use is transparent and appropriate. Many people therefore, found it disturbing when the American Heart Association produced guidelines for thrombolytics in stroke, yet didn't disclose that during the decade before they published the guidelines, they accepted $11m U.S. in donations from Genentech, which produces a thrombolytic which was recommended in the guidelines for use. Six of the nine guideline panelists had ties to the manufacturer. There was one dissenter from the recommendation to use their drug (alteplase) for stroke, and he had no industry ties. His dissent was not mentioned in the published AHA guidelines.

Other non-profit associations, such as the American Cancer Society, and the National Alliance of the Mentally Ill, are also sponsored by large pharmaceutical companies. So it is
important they put in place transparent processes as to how their public statements and guidelines are produced.

4. Reactions to the increase in industry influence

This rapidly increasing trend to influence and control by industry has become of concern to many. It was of such concern to the Association of American Medical Colleges that it issued two new documents - one to deal with individual and the other to deal with institutional conflicts of interest in the conduct of clinical research.\(^{28, 29}\) Editorials addressing this important topic are increasingly appearing.\(^{30, 31, 32, 33, 34, 35, 36}\) It was of such concern to the editors of a dozen respected medical journals (including Lancet, JAMA, CMAJ, and the NEJM), that in September 2001 they set new rules. These journals now refuse to publish articles based on studies that allow the sponsor to control the data or allow them to withhold publication. They now ask the responsible author to sign 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. In addition, they require contracts with industry to give researchers a substantial say in trial design. And as before, authors must disclose any conflicts of interest to the journal and also to study participants.\(^{37, 38}\)

Unfortunately, most researchers will not be able to meet the new journal requirements unless changes are made. A recent study which reviewed industry contracts in over a 100 medical schools in the United States found the new standards required by this International Committee of Medical Journal Editors were not adhered to.\(^{39}\) For example only 1% ensured that authors of reports on multicentre trials had access to all trial data, and most contracts did not address data collection and monitoring. The situation is not likely to be different in Canada, as many multicentre trials involve both countries and contracts are similar for participating centres. The authors recommend an urgent re-evaluation of the process of contracting for clinical research by academic institutions.
The conflicts of interest are starting to be taken seriously in the U.S., which has recently set up an Office of Health Research Protections. The Office has temporarily shut down federally supported research at a half a dozen prestigious centres in the U.S. over the last three years, including Duke University, the University of Illinois, and Johns Hopkins.\textsuperscript{40} Investigation in these instances had shown there was a threat to the potential well-being of research participants.

5. Measures that are needed

Clearly, the unfettered action of the free market does not serve the public health well. In the face of the threats to the integrity of clinical trials in a research environment strongly influenced by industry, what is needed to protect the public interest? There are several measures that would be of benefit.

• First, we need to acknowledge the problem. Governments have placed pressures on universities to link up with industry, but the pitfalls to such partnerships in an area like health care haven't been adequately recognized, discussed, and guarded against. We need to openly acknowledge that there are pitfalls to industry/academia partnerships, and that clear rules of engagement are needed in order to protect the public interest.

• We need to build a self reinforcing culture that understands the importance of scientific independence, and of putting patient safety first in interactions with industrial sponsors. Such attitudes need to be incorporated into education at all institutions doing research. Heightened awareness by clinical researchers of potential conflicts of interest when sponsored by industry is needed in order to protect the public. Researchers need to adopt the attitude that conflict of interest regulations, and Research Ethics Board (REB) requirements, are not just rules that "get in the way" of research, but are there to protect the public interest.
• Resources for research oversight offices and for REB’s across the country need to be increased. They are under resourced and overburdened. Service on these needs to be more valued. Additional expertise is needed - for example, contracts with industry are often complex, and as well as ethical review, legal expertise is needed to evaluate them for appropriateness.

• We need a more vigorous regulatory environment. Over the last twenty years there has been a well documented decline in the level of Health Canada oversight of pharmaceutical research, development, marketing and sales. This is not a trend that will protect the public. Putting in place a united regulatory stance with nationwide standards for industry contracts is needed and would avoid any race to the bottom. If some institutions or individuals are known to be more lenient and available, pharmaceutical manufacturers could stop carrying out projects at universities and institutions that ask for greater independence and few restrictions on publication. Individually, clinical researchers are easy pickings for the industry, but a regulated standard for industry contracts that protected the independence of researchers, would mean they were backed up. Currently researchers in Canada are continuing to sign contracts with clauses that are too restrictive. Another measure that would be useful is registration of all clinical trials in an accessible database.

• Universities and academic health centres should act promptly and firmly to protect their ethos to seek truth, as well as to protect the public, when an industrial partner tries to influence or suppress research findings. Counter balancing forces coming from public institutions and the medical profession are needed to counteract industry influence. Individual researchers cannot do it on their own.

We should attend to the fact that conflict of interest in industry/academia partnerships may be institutional. If a company is a major donor to a hospital or to a university and supports large numbers of research projects at an institution - it may make that institution more reluctant
to displease the research sponsor by protecting its researcher who is threatened. This needs to be brought into the open, and the recent recommendations of the AAMC are useful in this regard.\textsuperscript{29} They note that institutional conflicts are difficult to manage, but that ensuring REB’s are truly independent is important, and that an outside, arm's length entity to make some decisions may be helpful.

- **Legislation to protect whistle blowers.** Given the detrimental consequences to speaking out, it would be desirable for legal protections to be in place for those who do so.

- Lastly, as a society, we need to think about the consequences for health research as a whole as a result of the strong focus on academic/industry partnerships. This focus may divert talented researchers from the pursuit of profound scientific questions, or it may divert them from pursuit of questions without market relevance but with a public good aspect, to research that is more immediately product driven. A company has little incentive to support trials evaluating whether inexpensive, off patent drugs, or whether other non pharmaceutical 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 get asked and carried out. In a context where most of the funding comes from industry, research questions become ones that are likely to lead to answers that are marketable products. For example, currently guidelines are being developed for using expensive drugs for treatment of obesity, but we do not have sufficient attention to research on effective ways to promote healthy eating and exercise, or to stop advertising and sale of junk food in schools.\textsuperscript{41} 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 smoking. But it points up the need for balance in funding, and highlights that funding is badly needed for research on new and effective ways to get people to change behaviour, and for
research on policies that provide incentives and support for healthier behaviours at a population level. We need much more research in these areas, and there is relatively little funding for it.

6. 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, in conjunction with the tighter fiscal reality of hospitals and universities, makes it very important to have appropriate and transparent resolution of inevitable conflicts of interest. Many new opportunities have been opened up by our new genomics knowledge but these cannot be explored without the trust of citizens. Future research projects will need access to well characterized populations, and DNA samples from normal and affected sub-groups, to use the new genomics knowledge to understand disease pathways, and how they might be changed.

Our society depends on the trust and voluntary participation of citizens in clinical trials to make progress to more effective treatments. We cannot afford to lose the confidence of the public in the social contract that allows research on 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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