

Monitoring Contracts with Industry: Why Research Ethics Boards Must be Involved

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Introduction

Industry-university collaboration is an increasingly common phenomenon in Canada. A recent study on university-industry partnerships in this country indicated that the amount of research funded by private companies jumped from 2% in 1976 to 13% in 1996.¹

Critics have raised concerns that such research may have an underlying bias in favour of its sponsors.² To compound the problem, institutional research ethics boards (REBs) are often not privy to contracts negotiated between the institution and the industry sponsor.³

Such contracts may contain ethically questionable clauses, and it is therefore imperative that REBs be able to view them before deciding whether a given research protocol is deserving of ethics approval. Without access to contracts and related documentation, an REB is precluded from making an educated decision on the matter. This could result in research proceeding that is unethical in nature, putting subjects at risk. It may further result in publication restrictions and other constraints on the investigator, jeopardizing the scientific integrity of the research.

REBs and the Regulation of Research in Canada

There is no single regulatory regime that governs research conduct in Canada. Most research is regulated indirectly

through requirements of the three major federal funding agencies (CIHR, SSHRC, and NSERC). The *Tri-Council Policy Statement*, which governs federally funded research, requires that all research be approved by a local REB before investigators can proceed.⁴ However, not being federal public entities, pharmaceutical companies and thus industry-sponsored research are not subject to the *Tri-Council* guidelines. While most academic institutions have in place requirements for REB approval of all research, the lack of official and formal regulation of ethics review by the Canadian government renders the situation somewhat murky in terms of what is, and is not, acceptable.

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Research ethics boards are generally composed of individuals from different areas of expertise. Most include a lawyer; an ethics expert; at least one person with expertise in the research area under review; and a member of the community unaffiliated with the institution.⁵ The mandate of REBs is to scrutinize research protocols and related documents (e.g., consent forms) for ethical acceptability. Protocols that are deemed unacceptable must be resubmitted with the necessary changes made.

Several principles should guide REBs in making their decisions. These include the respect for persons, beneficence, and justice.⁶ REB members must closely examine submitted protocols for such things as improper informed consent, deception, unnecessary exposures to risk, and any other harms that could be incurred by participating subjects. The purpose of such ethical scrutiny is primarily to protect subjects from injury or harm of the kind suffered by human research subjects in such notorious historical events

as human experimentation by the Nazis, or the Tuskegee Syphilis Study.

Research Contracts: A Cause for Concern?

A research contract is an agreement by a host institution to conduct research on behalf of a company in exchange for the payment of all related costs.⁷

The terms of the contract dictate how the research will be carried out. Research contracts are currently not standardized. There is therefore no “universal” contract that is acceptable to all parties. This lack of standards is problematic, since it could translate into a discrepancy in practice even between different sites in the same industry-sponsored multicentre trial. Further, unlike peer-reviewed grants from public funding agencies like CIHR, industry-sponsored research contracts are generally initiated by pharmaceutical companies and are therefore necessarily profit-motivated. Good scholarship and scientific integrity may be secondary to this goal. As well, investigators contracting with industry may stand to profit from their involvement with the company. Such an occurrence puts the investigator in a conflict of interest, which could result in harm for research subjects. In the Jesse Gelsinger case at the University of Pennsylvania, for example, issues of conflict of interest were raised after the young man died in a gene therapy study.⁸ While there was no research contract per se, the investigator stood to benefit financially from the protocol. Such tragedies underscore the importance of unbiased, conflict-free research.

Problematic Clauses and Publishing Restrictions: The Nancy Olivieri Case

Lack of standardization with respect to research contracts may result in certain clauses in a given contract being seriously problematic. In the Nancy Olivieri case, for example, the pharmaceutical company she contracted with to study deferiprone, a thalassemia drug, had a “3-year gag clause” in their contract, preventing the unauthorized release of any findings.⁹ When Olivieri became concerned that there

were adverse effects associated with the drug, the drug company decided she was incorrect. She then went to the hospital’s REB, which required she change the consent forms so as reflect the new concerns. The drug company subsequently ended the study in Toronto, and terminated Olivieri. Olivieri went ahead and published her findings regardless, and was sued by the company.

Phillips and Hoey write that the most remarkable thing about the “gag clause” was “that it came to be written at all”.¹⁰ The Hospital for Sick Children, where the research was

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conducted, stated that it had not been aware of the contracts until after they had been signed, when it was already too late to intervene. This lack of a mechanism in place for the review of research contracts at an internationally renowned

academic hospital is disturbing. Had the institutional REB been privy to the contract before it had been signed, they might have been able to prevent the entire incident from taking place. This case underscores the need for contract review by REBs. A research contract that contains unconscionable or unethical clauses compromises the ethical integrity of the entire protocol. A prohibition on the reporting of negative results, for example, puts patients at risk of harm. It also translates into a lack of proper informed consent, as consent that is not based on all relevant information cannot be considered to be full and informed. These are both conventional grounds for the decline of approval by an REB for a given research protocol. If the REB does not see the contract, however, and the remainder of the protocol appears perfectly acceptable, ethics approval may be granted. This is extremely worrisome. Indeed, in the *Report of the Committee of Inquiry on the Case Involving Dr. Nancy Olivieri, the Hospital for Sick Children, and Apotex Inc.*, it was stated that, in the future, research ethics boards should be “vigilant against restrictions on communication in the wording not only of protocols but also of contracts and investigator agreements”.¹¹

Protecting Subjects from Unethical Research

The history of human subjects research is littered with examples of horrifying and unethical research practices. One



shocking episode involved young boys at a school for the mentally challenged in Waltham, Massachusetts.¹²

Beginning in 1949, the boys were fed small doses of radioactive substances. The study was sponsored by the Quaker Oats Company, the National Institutes of Health, and the Atomic Energy Commission, and was aimed at determining whether chemicals used in breakfast cereal interfered with the body's ability to absorb calcium and iron. Neither the boys nor their parents were informed of the radiation experiment.

The past 50 years have thus seen a dramatic change in the way research on humans is conducted.¹³ Today, research participants are required to provide full and informed consent in order to enroll in a study. Monitored by watchdog REBs, investigators must disclose all relevant information to an individual considering research participation. The informed consent standard for research in Canada is therefore very high, and an investigator's financial ties to a clinical trial would certainly be considered information that must be included in a consent form. Ensuring that all information regarding conflicts of interest is passed along to subjects is the duty of the REB. Without access to research contracts, however, the REB may not be aware of all potential conflicts of interest. The REB is then precluded from fulfilling its responsibility to protect subjects, and such subjects may be unwittingly subjected to harm.

Industry, Research, and Scientific Integrity

In 2002, in an attempt to demonstrate goodwill and a commitment to scientific integrity, the Pharmaceutical Research and Manufacturers of America (PhRMA) released a set of four principles it has adopted voluntarily with respect to the clinical research process.¹⁴

The first principle is a commitment to protecting research participants. PhRMA indicates that its interactions with research subjects and investigators must be governed by this principle. The second principle is that clinical trials must be conducted in accordance with the any relevant laws and regulations, as well as "locally recognized good clinical practice".¹⁵ Specifically, it is stated that ethics boards will have independent decision-making authority, and that all safety issues should be tracked and monitored. The third principle is a commitment to ensuring objectivity in research. It is explicitly stated that contracts should not interfere with the independence of individuals and entities

involved in the clinical research process. The fourth principle is a policy of public disclosure of clinical trial results. PhRMA states that it is committed to the timely communication of new information to the medical profession and the public.

However, while this is a step in the right direction, elements of the PhRMA document are nonetheless quite disconcerting. It is stated that the sponsor is the ultimate owner of the database, and therefore has the discretion to decide who will have access to the database. As well, it is stated that sponsors have the right to review manuscripts before they are submitted for publication. This is problematic, since authors must have independent access to all data if the scientific integrity of the study is to be preserved. In a critical editorial in 2001, editors of major medical journals took a stand against such practices, criticizing contracts that deny investigators the right to independent examination of data or require sponsor approval for all manuscripts.¹⁶ The most important reason why these industry guidelines do not address the issue of scientific integrity directly enough is that adherence is voluntary, and there is no mechanism to mandate compliance. Other policies adopted by pharmaceutical companies on this matter have similar problems. The "Good Publication Practice" or GPP guidelines released in May of 2003 are intended to complement the guidelines set forth by the International Committee of Medical Journal Editors (ICMJE).¹⁷ However, these guidelines continue to permit companies the right to review all potential manuscripts prior to submission for publication. This may jeopardize author independence, threatening the scientific integrity of manuscripts associated with industry-sponsored trials. Finally, guidelines published by the pharmaceutical industry include items discouraging ghost authorship and duplicate publication. These practices have long since been deemed unacceptable by medical journal editors, suggesting the industry is behind the times with respect to its policies.

Research contracts may therefore restrict author independence and data access, hallmarks of the scientific integrity of a research study. A trial that cannot guarantee investigator independence and unrestricted publication rights cannot be considered ethical, since the underlying industry-control points to the likelihood of a bias in any results. Indeed, a recent systematic review by Lexchin *et al.* reported that studies sponsored by pharmaceutical companies are more likely than those sponsored by other sources to report findings favourable to the sponsor.¹⁸ Financial pressures can result in biases in design, outcome, and reporting of results.¹⁹

Conclusions

A signed contract is a legally binding document. A research contract between academic institutions and industry therefore dictates the terms on which the research will proceed. The profit motives of pharmaceutical companies may lead to the inclusion of clauses in the contract that restrict the rights of the investigators, jeopardizing the scientific integrity of the research and possibly putting subjects at risk of harm. Research ethics boards have long been in place in universities and affiliated hospitals to monitor research protocols and ensure that all studies carried out in an ethical fashion. However, without access to research contracts, REBs cannot completely fulfill this task. Even a protocol that passes ethics review could be under the auspices of a research contract that is restrictive and unethical. Until a mechanism is put in place to ensure that all research contracts are reviewed by REBs, the ethics review process will continue to be incomplete and insufficient. However, at the same time, individuals who volunteer to participate in research will continue to rely on the REB to ensure their safety. In the interests of protecting human research subjects, then, together with the goal of preserving scientific integrity, research ethics boards should be required to review all research contracts prior to ethics approval.

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