3.4.3 Personal Conflict of Interest in Medical Research: What Is It? What Can Be Done About It?

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Educational Objectives

1. To understand the concept of conflict of interest in the context of medical research
2. To understand why conflicts of interest have to be addressed
3. To learn what types of remedies exist to deal with conflicts of interest

Case

Dr. Reed is an academic researcher with over 400 publications. He is on the advisory boards of professional organizations as well as pharmaceutical companies. He holds a Chair in Cardiology at the University of Port Hope. He obtained a contract from the pharmaceutical company Selaserom to conduct a phase 3 double-blind randomized controlled trial comparing Selaserom's drug Lovrux with another hypertension drug in the University of Port Hope's General Hospital. Dr. Reed has been paid as an expert consultant during the development of Lovrux. The contract provides a lump sum of $9,000 per patient to Dr. Reed and his team for all administrative and research-related costs, payment for research equipment and a half-time salary for a research coordinator. Dr. Reed will receive stock options in Selaserom. The contract stipulates that blood samples and clinical data will be analyzed at the General Hospital's research laboratory and that the data will be forwarded to Selaserom's research unit, which will keep the randomization codes. Selaserom will organize the final analysis and will coordinate, in collaboration with Dr. Reed, all public communications related to the project.

Questions

1. What is a conflict of interest?
2. How can we identify conflicts of interest in medical research?
   a. What are the primary professional obligations of researchers?
   b. What types of financial conflicts of interest exist in medical research?
   c. How can the professional obligations to conduct research and to protect the integrity and well-being of human subjects be affected by these financial interests?
3. What remedies are there to deal with conflicts of interest?
4. What conflicts of interest affect Dr. Reed?
5. How should Dr. Reed's conflicts of interest be dealt with?

Discussion

Q1. What is a conflict of interest?

A conflict of interest is best defined as a situation in which a primary professional obligation tends to be unduly affected by other interests. A determination of a conflict of interest does not require concrete evidence that it affects people's behaviour. Conflict of interest rules are based on the experience that, in similar situations, professional duties are often affected by additional interests that are not necessarily "inappropriate." Having a conflict of interest is not an ethical violation per se, yet failing to deal appropriately with one is.

The following questions have to be asked in the context of research: (1) What are the primary professional obligations of researchers that can be affected by conflicts of interest? If there is more than one professional obligation, how should researchers rank them in order of importance? (2) What secondary interests can exist, and how can professional obligations be affected? (3) What are the available regulatory and professional tools to deal with conflicts of interest?

Q2. How can we identify conflicts of interest in medical research?

Q2a. What are the primary professional obligations of researchers?
Protecting the rights and well-being of the research subjects remains the most important duty. The Helsinki Declaration\(^1\) (principle 6) and various other ethics guidelines clearly recognize this. The obligation does not necessarily clash with researchers’ commitment to conduct good research. Very often patients do better when enrolled in a clinical trial. Yet, research also involves risks. It exposes patients to unknown side effects and to the risk of receiving inferior therapies. When the interests of subjects and the interests of research collide, the obligation toward subjects takes priority.

**Q2b. What types of financial conflicts of interest exist in medical research?**

In clinical research, per capita payments are often used as financial incentives to stimulate recruitment. Researchers and research personnel are also often paid for the time spent with the research subjects, for filling out questionnaires and forms, for blood and tissue collection, and for other administrative costs. Payments given for the sole purpose of recruiting patients are termed “finder’s fees.” Finder’s fees are often a hidden part of general payments. Sometimes, researchers are offered recruitment bonuses for fast recruitment or for recruiting extra research subjects. Researchers can also be paid a general amount for a project or receive a per annum payment as consultant to a pharmaceutical sponsor. They may receive research equipment, books or payment for participation at conferences. Many researchers are members of speaking bureaus or sit on advisory boards of pharmaceutical sponsors, who often pay thousands of dollars per year for such services.

Researchers may own shares or receive stock options in a company, which gives them a direct financial interest in speeding up the process of drug discovery and in obtaining study results that will increase the stock price.

**Q2c. How can the professional obligations to conduct research and to protect the integrity and well-being of human subjects be affected by these financial interests?**

First, financial interests may have a negative impact on the protection of the rights and well-being of the research subjects. Researchers may be tempted to disrespect inclusion criteria or to delay withdrawing subjects from a study, which may put subjects’ health at risk. Researchers may be tempted to pressure their patients to sign a consent form. Sometimes, sponsors pay extra premiums for fast recruiting or for recruiting an extra 10 patients. Payments to researchers may depend in part on keeping patients in a clinical trial, which can result in pressure on research subjects to remain in a study, even when they are not doing well and want to withdraw.

Second, commercial interests threaten the integrity of the research process. Financial interests can influence the design, the conduct, the collection and interpretation of research data, and the presentation of the final results. Empirical studies establish a statistically significant link between source of funding and research outcome. Industry-sponsored research is more likely than non-commercially sponsored research to lead to a conclusion that a new therapy is better than the standard therapy. There is also evidence of positive result-dependent overreporting and of underreporting of industry studies of new drugs where adverse effects are discovered.

Moreover, research is increasingly coordinated by specialized contract research organizations, which either conduct research in their own specialized research centres or involve a multitude of clinicians to conduct the research. Sponsors thereby increasingly control the design of the study, the recruitment of subjects, the collection and analysis of data, and the publication of the results. Results of studies are often written by ghostwriters (i.e., authors who do not appear in the final publication), offered as easy publications to established academics in the field and published in the most prestigious medical journals. Academic authors lend their name to give credibility to the publications. Instances of such practices have recently been documented again in the controversy surrounding the withdrawal of Vioxx from the market.

Third, financial interests can also distort the research agenda. Growing commercial incentives in research affect what research is being undertaken. Pharmaceutical sponsors are more likely to offer payments for clinical trials. Other research studies (for example, on neglected diseases) do not have the budget to compete with the recruitment strategies of industry-sponsored studies.

**Q3. What remedies are there to deal with conflicts of interest?**

**General**

Detailed provisions on conflicts of interest exist in research ethics guidelines and regulations by various organizations, institutions and agencies. Some conflicts of interest may also violate specific pieces of legislation, such as those related to securities. Canadian provinces have detailed rules surrounding medical practice, through
bylaws of colleges of physicians and surgeons. Regulations enacted under Ontario’s Medicine Act, for example, contain detailed rules about conflict of interest, focusing on medical practice (Ontario Regulation 114/94). The regulation prohibits, for example, kickbacks or the charging of referral fees. In 2006, the College of Physicians and Surgeons of Ontario enacted a specific guideline on conflict of interest in the context of recruiting subjects for research studies.2 Under the Medicine Act, the College has the power to take disciplinary action when these rules are violated.

Remedies can be distinguished according to the following categories: disclosure, review by research ethics boards (REBs) or by specialized conflict of interest committees, monitoring of conflicts of interest, and outright prohibition. Registration and results-reporting obligations are also part of the solution.

**Disclosure**

Disclosure is the most basic requirement. Researchers have to disclose financial interests to REBs, to research subjects, in publications and in all presentations of their findings. Respect for research subjects requires that they are informed of all issues that may impact on the research. Subjects have to be fully informed of potential financial interests that may affect researchers' behaviour. Disclosure is a necessary, although clearly not always sufficient, condition for dealing with conflict of interest. The "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans" (TCPS2)3 mandates disclosure of "the presence of any real, potential or perceived conflicts of interest on the part of the researchers, their institutions or the research sponsors" (TCPS2 p. 31) in the informed consent process when recruiting research subjects. Other guidelines, for example those of the College of Physicians and Surgeons of Ontario, also require such disclosure.2

Research subjects have to be informed of the nature of the study, of the source of funding for the study (name of funding agency or pharmaceutical sponsor), of the fact that physicians are paid to participate in the study, and — to the extent that it is allowed — of the fact that researchers have other financial relations with the sponsors of the study (e.g., consultancy, funding for research).

Most established medical journals now have disclosure policies in place, obliging authors to reveal all financial relations with sponsors. Conflicts of interest also have to be declared in presentations of the research.

In Canada, a research group led by Paula A. Rochon published in 2010 an extensive checklist for clinical research studies, which contains detailed questions about all possible conflicts of interests that may affect the design, conduct, analysis and reporting of clinical research. This checklist is an excellent tool to obtain standardized information about COIs and could be used by institutions, REBs, and conflict of interest committees to determine what remedies are required.3

In the United States, several states have enacted legislation which mandates pharmaceutical and medical device companies to disclose payments and gifts to physicians, including payments for involvement in clinical research. In 2009, a similar so-called Sunshine Act was also introduced in the US Congress, which would make such disclosure part of a national disclosure system.4 The Canadian federal and provincial governments should consider similar measures to promote transparency of relations between industry and medical practitioners.

**Review Procedures**

Disclosure is the basis of other procedures. Academic institutions, journals and funding agencies submit conflict of interest situations to a review process. Based on this review process, researchers can be told to disclose the conflicts or to make required changes to, for example, the informed consent procedure.

The TCPS2 further requires that researchers declare conflicts of interest in the protocol submitted to the REB, so that the REB can "determine the appropriate steps to manage the conflict of interest" (TCPS2 art. 7(4)).5 REBs have to receive the appropriate information to fulfill this task, including access to the budget of research protocols and to financial relations between researchers and sponsors. Particularly in clinical trials, an analysis of the budget by REBs, or by a specialized organization that reports on this analysis to the REB, is crucial. It is therefore essential that REBs themselves are not affected by conflicts of interest.

Conflict of interest committees have been set up in various academic institutions, particularly in the United States. This is a valuable initiative and should be considered in all academic institutions that receive industry funding. A conflict of interest committee can assist an REB in analyzing budgets and in discussing conflicts of interest in an institution. It can make recommendations and inform an REB of specific financial relations to which the REB would otherwise never have access.

Review of research contracts is certainly necessary to avoid having researchers enter into contracts that limit their
academic freedom or that create contractual obligations that may affect the protection of research subjects.

**Ensuring Independent Oversight of the Research Process**

Conflict of interest committees or REBs may request that the informed consent process be conducted by a person independent of the investigator; that an independent investigator be added to a research project; and that an independent data monitoring committee be established to monitor the safety of clinical trials, analysis of data and presentation of findings. The REB may also set up specific monitoring procedures for the informed consent process and for other research procedures. The procedures set up by the REB should be proportionate to the risk that the conflicts of interest may affect the research or the protection of human subjects.

**Prohibitions**

Financial conflicts of interest may be deemed so significant that a prohibition is warranted. The Association of American Medical Colleges recommends that institutions introduce in their conflict of interest policies a rebuttable presumption that researchers with significant financial interests ought not to be involved in the research and that institutions with significant conflicts of interest ought not to have research take place in their establishments. National or regional regulatory agencies, funding agencies, or professional organizations should introduce the same presumption and provide guidance on what conflicts of interest fall under this presumption. Stating that as a principle means that exceptions to this rule have to be justified and based on solid and publicly defensible reasons.

Some conflicts of interest may be the subject of specific prohibitions. Many academic centres and professional organizations, for example, have issued guidelines prohibiting the use of finder's fees, even if they allow for reasonable compensation in line with standard practice compensation. Academic institutions, which have a clear public mandate, should also be stricter with respect to potential financial interests of their researchers. There is, for example, no reason why researchers who receive a full-time salary from their institutions should receive additional payment for including research subjects in research projects.

Some forms of payment to investigators are also prohibited by law or regulation. National authorities should consider prohibiting certain cash payments to researchers, for example, pure finder's fees, or payments that create significant incentives to keep patients in clinical trials. In some provinces, regulations related to the health professions may already provide tools to prohibit some of these payments.

**Registration of Clinical Trials and Results Reporting**

Two important new regulatory initiatives are also worth mentioning: the mandatory registration of all clinical research and the mandatory reporting of all research results. These measures aim at promoting transparency. Although the primary focus of these initiatives has been on promoting research integrity, there is obviously also a direct impact on the protection of research subjects. Access to all relevant information is needed to assess the potential risks and benefits of research and to avoid duplication of research efforts. When pharmaceutical sponsors and researchers use human subjects in research and subsequently hide the results because of financial interests, they may be using human subjects as instruments in misleading promotional campaigns. This instrumental use of subjects without regard for the public value of research seems an affront to their inherent dignity.

Trial registration and results reporting are now required according to the 2008 version of the World Medical Association's Declaration of Helsinki (principles 17 and 30). In Canada, TCPS2 now explicitly requires trial registration and results reporting of all research. The International Committee of Medical Journal Editors has also taken the position that it will only publish the results of studies that have been registered prior to the recruitment of human subjects.

REBs, when reviewing research protocols, should therefore require registration of clinical trials prior to any recruitment of human subjects and should ask researchers for a clear strategy for publicizing the results. REBs should also request a final report of the research results of any study that they approve. REBs thus have an important role to play in that context, particularly since strict regulation related to registration and result reporting is not yet in place in Canada.

**Q4. What conflicts of interest affect Dr. Reed?**

Dr. Reed has a clear conflict of interest flowing from his financial relations with Selaserom. He has been involved in the development of the product as an expert. More information will have to be provided to the conflict of interest committee or the REB regarding the payments he received for his work as consultant. Dr. Reed is also on several boards of pharmaceutical companies. More information has to be made available within the institution to the
Because of these direct and significant financial interests, the REB should prohibit Dr. Reed from being involved in the research related to this product. It should also evaluate whether other researchers in the institution can be sufficiently independent from Dr. Reed to ensure the integrity of this clinical trial and the protection of research subjects. The REB has to look at Dr. Reed's official position within the university department or hospital. Does he exercise a position of authority? Do the other researchers who could undertake this study report to him in any capacity? If so, the REB should rule that the research cannot take place in the hospital or that external researchers be invited to conduct the research.

There are also specific conflict of interest problems associated with the research contract. The stipulations that Selaserom will keep the randomization codes, that it will organize the final analysis and that it will be directly involved in the "coordination" of the communication of findings raises serious concerns about the sponsor's control over the analysis and reporting of results. These stipulations suggest that the researchers do not have full control over the research, that they may not be guaranteed access to all the data and that ghostwriters may be involved in writing up the final results. The institution should have reviewed this contract and should not have allowed these clauses in the contract in the first place. The REB should not accept that research takes place under such conditions, which seriously undermine the independence of the research and undermine academic freedom.

A conflict of interest also seems to be embedded in the payment structure of the research contract. A conflict of interest committee or the REB has to inquire about the justification of the per capita payment for each patient recruited. What are the procedures that will take place? What is the breakdown of all the different costs involved in the clinical trial? A $9,000 payment per patient is high and creates a significant incentive to recruit patients in the trial. Part of this payment seems to constitute a finder's fee, that is, a financial reward for the mere recruitment of patients. Finder's fees are generally considered unacceptable and are prohibited by many conflict of interest guidelines. Payments to physicians for referring patients to clinical trials may also violate existing professional regulations. The TCPS alerts to the danger created by per capita payments and states that payments should be comparable to standard professional fees that professionals would receive for comparable activities (see TCPS discussion under Article 11.3). Recovery of costs, particularly in a publicly funded hospital, is obviously also appropriate and even required.

As with any other type of clinical trial, the REB also has to ensure that the source of funding of the research and all potential conflicts of interest that remain are appropriately disclosed in the informed consent procedures. Finally, the REB has to explicitly request that the clinical trial be registered prior to recruiting human subjects. It also has to ensure that there is an appropriate disclosure strategy in place for the final results of the study. The REB should request that a final report of the publication of the study be submitted to its office within a specific period of time after the finalization of the project.

Conclusion

There is a growing recognition, resulting in part from various empirical studies, that financial conflicts of interest can impact on the design, conduct, analysis and reporting of clinical research. It is also increasingly recognized that disclosure of conflicts of interests is not sufficient to deal with the potential impact on the protection of research subjects and the integrity of research. Dealing with such conflicts is complex, and various institutional and regulatory measures have been developed to address the problem. Researchers, institutions, governmental agencies and REBs have to work together to reduce the potential negative impact of conflicts of interests.

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