3.4.1 Institutional Conflicts of Interest

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Educational Objectives

1. To understand the concept of Institutional Conflict of Interest
2. To understand the potential impact of institutional COI
3. To learn how to deal with institutional COI

Case

Dr. X is an expert on the treatment of colon cancer. She is also the vice president (VP) of research at one of Canada's major research-oriented hospitals, the General Hospital of Bancroft. Nearly three years ago, a pharmaceutical company, Lanaflux Inc., signed a contract with Dr. X and her institution for a multisite, three-year study on the efficacy and safety of a new medication for the treatment of colon cancer. The research contract is now coming to an end.

The company, apparently happy with the work delivered so far, proposes to establish a closer collaboration with the General Hospital and with the University of Central Bancroft, to which the General Hospital is attached. It will provide a $10 million fund for research on colon cancer to a specialized cancer research unit. It will also fund a research chair in colon cancer, the Lanaflux Chair. The research chair will be for a two-year probationary period, with possible renewal for subsequent three-year periods. Dr. X will probably be the chair holder. Lanaflux Inc. will have a priority right over the commercialization of any research findings coming out of the specialized research unit during the period of funding. In exchange, the General Hospital will receive 25% equity shares in the company. Researchers who have been involved in a study that has its findings commercialized will receive a total of 15% in equity, to be divided among those involved.

Questions

1. What is a conflict of interest (COI)?
2. What is an institutional COI?
3. Why is it important to deal with COIs in research?
4. What regulatory and policy options are available to deal with COIs?
5. How do trial registration and results reporting help us to deal with some aspects of COI?

Discussion

Q1. What is a conflict of interest?

A COI has been defined in the medical context as "a set of conditions in which professional judgment concerning a primary interest tends to be unduly influenced by a secondary interest." The literature on COIs originally focused primarily on personal COIs, but increasing attention is being paid to institutional COIs.

An institutional COI can be defined as a set of conditions in which the primary mandate of an institution tends to be unduly affected by other, secondary interests. In the medical context, "institutions" means health care institutions and the universities with which these institutions are affiliated. For example, an institutional COI can exist when financial interests compromise or may be perceived to compromise the integrity of health care practices within that institution. A COI can also exist between an institution's research mandate, its teaching mandate and the clinical mandate of academic teaching hospitals.

There would clearly be a COI in the case presented if, for example, the hospital pharmacy were to start stockpiling pharmaceutical products that are produced by the sponsoring company and directly or indirectly urging physicians to prescribe the medication. A COI can also exist when the research activities of an institute are affected by the financial interests of a sponsor. Financial interests could, for example, push this institution to give priority to Lanaflux in accessing patients to recruit them into clinical trials involving Lanaflux's products. Although commercial
interests are not the only source of potential tension between an institution’s mandate and other interests, several reasons justify the focus on financial COIs. First, it is widely known that money motivates more than most other rewards in life. People are influenced by monetary gain.

Second, financial interests in research have exponentially increased over the last few decades as a result of legislative and funding-agency initiatives that promote commercial matching funding. Medical research is being increasingly submerged in the competitive context of a lucrative biotechnology industry.

Third, many significant recent controversies that have affected the public trust in the practice of medicine and in medical research enterprise have also raised questions about the independence of academic institutions from commercial sponsors.\(^3,^4\)

Fourth, an array of reports, initiatives and regulations emanating from official organizations and governmental agencies has reflected a comprehension that the potential negative impact of financial interests is a serious cause for concern.\(^5^-^8\)

Fifth, academic teaching hospitals do not have a single mandate. It is, in fact, not so easy to separate (for example) the research and teaching mandates from the health care mandate of these institutions. They are to some extent inseparable, even though proper organizational measures have to be taken to allow institutions to fulfill each mandate appropriately.

Financial interests are more objective, tangible and measurable, and can often—at least in theory—be separated from the conduct of research and the practice of medicine itself.\(^1\) In addition, the different mandates of teaching hospitals may actually, when appropriately organized, be complementary and feed each other. Indeed, patients should benefit from the expertise available in academic teaching hospitals. Studies also show that patients often do better in clinical trials in these institutions.

**Q2. What is an institutional conflict of interest?**

As mentioned, institutions may receive industry funding for an important part of their activities. They may be financially dependent on these sponsors for funding some aspects of the health care they provide, social activities for patients and staff, academic chairs and/or research or educational activities. Institutions may have stock in a company, which can be affected by medical research undertaken or decisions made within the institution.\(^4\) An institution may also obtain financial interests as a result of negotiations related to technology transfer. It may obtain an equity position in the company, in addition to licensing fees and royalties. This is typically the case when researchers connected to an institution form a start-up company.

Holding a significant amount of stock in a company can create concerns about the potential impact of this institutional interest, or the perception of such an impact, on decision-making within the institution. Decisions about which drugs to prescribe, research priorities, allocation of research space, assigning research mandates, promoting specific research agendas, and providing priority access to patients within a health care institution, could be (or could be perceived to be) influenced by these financial interests.

As highlighted in the case presented, an institutional COI can also exist when a company or individual donates a significant amount of money to an institution, and when research or decisions within the institution may affect the financial interests of that company or individual. The concern would be that the institution has an interest in keeping the donor satisfied and happy.

A final form of institutional COI occurs when an official with decision-making power within the institution has a personal COI (e.g., through investments or other financial ties). This “official” might be a board member, trustee, senior executive or a member of decision-making committees, such as COI committees or research ethics boards (REBs). The Association of American Medical Colleges (AAMC) emphasizes that in such cases, a personal COI becomes an institutional COI.\(^5\)

**Q3. Why is it important to deal with conflicts of interest in research?**

**Safety and well-being of patients and research subjects**

Institutional COIs may lead to inappropriate clinical practice, for example when decisions about available pharmaceutical or other health care products and devices are influenced by financial gain, and not by priority-setting related to the quality of a product and the available resources.
When an institution has a significant financial interest, loyal employees may—consciously or unconsciously—take this interest into consideration in their decision-making:

- Physicians may feel inhibited to be critical about the safety or efficacy of a product.
- In the research context, physicians may feel pressured to move quickly into clinical trials of a product that could bring valuable equity to the university, or they may avoid conducting studies that raise questions about the efficacy or safety of a product.
- REB members, who have to evaluate the risks and potential benefits of a study, may be under pressure to approve studies that will financially benefit the institution.
- Researchers may be inclined to go along with a sponsor's demands, even if these demands go against appropriate research practice and against the public interest in independent research.

Distortion of the research agenda

The increase of industry funding and the growing commercial focus of funding agencies also impact the health research agenda. Researchers who are funded to conduct research with a commercial focus are not available for other research endeavours. Since commercial sponsors are able to offer higher recruitment incentives to researchers and research subjects, it may become harder to launch other studies.\(^9\)

Research integrity

When an institution has very close ties to an industry sponsor it may, for example, be hesitant to take appropriate action to protect individual investigators who have a COI about access to research data. Institutions may be more reluctant to protect their researchers against corporate sanction.\(^10\) The mere perception that they are not backing their researchers can have a shilling impact on academic freedom.

Q4. What regulatory and policy options are available to deal with conflicts of interest?

Many universities, professional organizations and medical journals have established guidelines that reflect a precautionary approach (i.e., an approach that aims at preventing the potential negative impact of COIs). COI guidelines are further introduced by funding, drug regulatory and health care agencies. There may also be legislative provisions that determine the possible sources of income for institutions and the types of activities they can engage in. In addition, growing attention is being paid to the use of criminal law and professional misconduct rules by the professional bodies of the different health professions to deal with COIs.\(^9,11\) The procedural mechanisms introduced by these organizations and agencies include disclosure of COIs, management of COIs through review by REBs or specialized COI committees and outright prohibition of COIs.

Disclosure

Disclosure is the most basic remedy and is also the basis of other regulatory measures. The idea behind disclosure as a stand-alone remedy is that informed people can make an appropriate judgment about the potential impact of the disclosed COIs.

In the case of institutional COI, disclosure can be difficult to achieve as an independent remedy. Indeed, while disclosure of the financial sponsors of institutions seems important at a general level, it may be impractical to impose a duty to accurately inform every patient and every research subject of every specific institutional "secondary" interest. Overall, however, transparency within institutions about the existence of different mandates and different sources of income remains important. An institution's sources of funding should be available on its website and in publications and official documents coming out of the institution. Legal requirements regarding annual reporting reflect the importance of public accountability. In some cases, specific disclosure obligations could exist. It would seem appropriate to inform research subjects in consent forms or information sheets that an institution has significant financial ties to the company sponsoring the study. Even if the institutional official who obtained the funding is not directly involved in the study, institutional dynamics may impact on the research. It seems ethically required that research participants are informed of these interests.

Disclosure is also the basis of other procedures. Health care institutions, academic institutions, journals and funding agencies submit COI situations to review processes. Based on these review processes, researchers can be told to disclose their COIs; change contractual provisions; change, for example, the informed consent procedure; create a buffer between those who have a COI and others who are involved in clinical, research or management decisions; add independent investigators to a research project; or establish an independent data-monitoring committee to monitor the safety of clinical trials, analysis of data and presentation of findings.
Prohibition

The financial COI may be deemed so significant that a prohibition is warranted. The AAMC,\textsuperscript{5} for example, recommends that institutions introduce to their COI policies a rebuttable presumption that researchers with significant financial interests in a particular research project should not be involved in that research. It also recommends that when institutions have significant COIs, the research in which this COI occurs should not take place in those establishments. Some university hospitals in Canada have set up COI committees, outside of the REB, to review such situations. These committees may recommend, for example, that a clinical trial should not take place in a hospital that has significant institutional COIs. They should also recommend that institutional officials with significant COIs do not participate in conflicted research projects.

Many COI rules aim to create a wall between those who have a direct institutional role in fundraising and the generation of income and those who make health care or research decisions that could impact on those fundraising or income-generating decisions. For example: the person or administrative body that governs research and promotes ethics should not be situated within the technology transfer office\textsuperscript{12}; those involved in fund-raising in academic institutions should not set research priorities or be involved in hiring a new research director or in deciding who should become a chair holder; and the person in charge of the purchase of pharmaceutical products in a health care institution should not be involved in negotiating donations from a pharmaceutical company.

Conflicts of interest committees

It is crucial that the COI review is exercised by a truly independent body. COI committees should be established within each institution.\textsuperscript{5} The COI committee should be independent from the institutional official who has a direct role in financing and fundraising. The committee should report to the board of governors of the institution or to another body within the institution that ensures its independence and reflects its important role.

The committee should include a substantial number of people who are not employees of the institution. Its members should be offered a fixed appointment for a specific period of time. Officials in charge of technology transfer and fundraising within the institution should report to the COI any possible financial relationship between the institution and potential sponsors of research. The COI should review these financial relationships, determine their potential impact and make recommendations as to how the COIs should be dealt with. An institutional link should be created between the COI committee and the REB. The REB should be aware of potential institutional interests and of the decisions made by the COI committee.

Research ethics boards

The need for REB independence should also be emphasized in this context. REBs have an important role to play in determining whether COIs affect research undertaken in the institution. They should be independent from those who have an institutional interest in the research or in the financial aspects of that research.

The potential lack of independence of REBs and REB members has been highlighted by several commentators.\textsuperscript{7,8,13,14} It can be argued that most Canadian institutional REBs are too tightly integrated within institutions and insufficiently regulated to consider themselves as adequately independent. Many REBs report to the VP of research within their institution, who has a direct mandate to attract and promote research. In the absence of a better regulatory structure for REBs, reporting to the board of an institution or to those with an institutional commitment to the health care of patients would seem more appropriate.

Research Ethics Board Members

COIs of REB members must also be addressed. A US survey of such members [REFERENCE: Campbell EG, Weissman JS, Vogeli C; et al. Financial relationships between institutional review board members and industry. \textit{N Engl J Med}. 2006;355(22):2321-2329.] revealed that 36.2% had had a financial relationship with industry in the year prior to the survey, which was higher than the percentage of researchers who had had relationships with industry. Institutions should request full disclosure of REB members' financial interests and exclude those with financial interests associated with the studies they are reviewing. Institutions should make additional efforts to remove those with financial interests from REBs. Institutions should also alert REB members to the fact that they could be exposed to criminal sanctions if they use insider information obtained as member of an REB for investment purposes.

Novel approaches

Many of the remedies mentioned here have been in place for some time without eliminating major controversies. Several authors have called for more radical and stricter COI approaches, such as an increase in public funding for
research. An institution should promote as vigorously as possible funding from sources that do not create COIs. Institutions should strive to have a balanced funding portfolio in all of their research units, and should encourage researchers to obtain non-industry funding through institutional rewards and recognition.

Q5. How do trial registration and results reporting help us to deal with some aspects of conflicts of interest?

The idea of mandatory registration of clinical trials has been gaining ground. Trial registration been recommended by the International Committee of Medical Journal Editors,15 a group of international experts,16 and the World Health Organization.17 Trial registration would track trials before they begin to avoid secrecy and ensure full reporting of results.

Registration and results reporting has been introduced as a regulatory requirement in the United States for all clinical trials, with the exception of some phase I trials. Participation in clinical registration and results reporting is a major step toward transparency and accountability, but should not be regarded as a panacea to COI concerns.

REBs could take important steps in this area by explicitly requiring that all research involving human subjects must be registered prior to subject recruitment, and by requesting a report on how the research is to be publicized at the end of the project (e.g., publication in a journal or registration of results reporting on a publicly accessible website).

The Case

In the presented case, the collaboration established between the institution and the sponsor clearly creates COIs. At a minimum, an independent, arms-length COI committee should be established by the institution with the mandate to review the potential impact of these institutional interests on the conduct of research. The institution should also ensure that proper procedures are in place to safeguard the independence of its investigators. It should establish a complaints procedure that will allow individual investigators to report potential negative issues that arise from the significant interests at stake.

The COI committee should document its evaluations, make recommendations about how to deal with the COIs and make these recommendations publicly available. It should ensure proper communication with the REB.

The university should, in my view, resist the temptation to accept the chair offered by the company. Renewable contracts create a situation of dependence. It speaks for itself that people who receive the chair (with its accompanying significant financial benefits and prestige), knowing that the renewal of this chair depends on the satisfaction of a pharmaceutical sponsor, may be less critical of the sponsor's products. They would certainly be perceived to lack independence.

Even if the chair holder is not driven to skew data, present study results prepared by the sponsor as their own or sign a paper written by a ghost author, they may not be in a position to stand up to the sponsor if issues of interpretation and results reporting arise. Alternatively, they may simply avoid talking about the sponsor's products if they think the products are inferior or when safety issues arise. They lack the necessary independence to be seen as fully independent academic researchers.

In this particular case, the fact that the VP of research has a close connection to this important research sponsor—and that she is also the person who will receive the chair—indicates significant institutional confusion of roles. The VP of research should not be involved in negotiating this contract and should remove herself from such personal COIs.

The institution should, at a minimum, be able to convince the pharmaceutical sponsor to donate a fixed amount of money to be used for an endowment that does not depend on the yearly goodwill of the sponsor. Not all problems will be solved by this approach. Indeed, the expectation that future funding may be coming can clearly influence an institution's behaviour. However, if such funding is deemed acceptable then I would expect to see at least the creation of a buffer between the institutional interests and the day-to-day research and teaching activities of the staff. The institution should also implement policies to strengthen the independence of its oversight bodies, in line with the recommendations above. The presented case clearly shows why the COI committee and the REB should not report to the VP of research in this institution.

The institution should ensure that all research contracts within the institution are verified to ensure that researchers are free to publish the results of the study and to share the data with other investigators. It should
implement policies to ensure compliance with several other initiatives to promote transparency and accountability of research, including trial registration and registration of results.

The institution should further ensure that researchers who have direct financial interests in the outcome of the research are not involved in the study. Following this approach, the chair holder should not be involved in any research funded by this industry sponsor. It would also seem appropriate, following the recommendations of the AAMC, to see if the research sponsored by Lanaflux Inc. can take place in another institution that does not have such a significant equity share in the company.

References


Further Reading

- Bekelman JE, Li Y, Gross GP. Scope and impact of financial conflicts of interest in biomedical research: A


