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ONTARIO CANCER RESEARCH ETHICS BOARD
GUIDELINES FOR ASSESSING AND MANAGING CONFLICTS OF INTEREST

Purpose

Conflict of interest policies and guidelines are attempts to ensure that professional decisions are made on the basis of primary interests and not secondary interests.

The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), which governs human clinical research, specifically addresses conflict of interest (COI) and requires Investigators and research ethics board (REB) members to "disclose actual, perceived or potential conflicts of interest to the REB". It further requires REBs to develop mechanisms to address and resolve COI declared by Investigators by obtaining full information on the COI; assessing the likelihood that the Investigator's judgement may be influenced; and assessing the seriousness of harm that is likely to result. Failure to address these issues could lead to an erosion of public trust and accountability in research.

In addition to the TCPS2, the "*National Standard of Canada, Research ethics oversight of biomedical clinical trials*", and non-Canadian regulatory organizations (e.g., USA Department of Health and Human Services and the Food and Drug Administration), also establish COI-related requirements that may apply to Canadian Investigators.

As a supplement to the standard operating procedure (SOP) 105B, the Ontario Cancer Research Ethics Board (OCREB) has prepared a set of guidelines to assist Investigators when submitting an application to OCREB. These Guidelines are complementary to and do not detract or diminish from the requirement to adhere to OCREB policies and SOPs, and to any funding and institutional requirements. These Guidelines also signal to the broader community OCREB's commitment to minimizing the potential impact of COI.

These Guidelines also provide assistance to OCREB reviewers in assessing COI and will facilitate a consistency in approach by OCREB to managing COI**.** However, it is acknowledged that dealing with COI can be a grey area, and there will need to be a case-by-case review of these situations.

Application/Responsibility

These Guidelines apply to Investigators, Co-Investigators, and any other persons affiliated with research that is reviewed by OCREB.

Definitions

OCREB SOP 105B

Conflicts of interest, including real, potential, or perceived conflicts of interest, arise when an individual is in a position of trust in which there are competing professional or personal interests. Such competing interests may influence his or her professional judgment, objectivity and independence, and potentially can influence the outcome of a decision. A conflict of interest may exist even if no unethical or improper act results from the conflict.

TCPS2

Investigators' conflicts of interest may arise from interpersonal relationships (e.g., family or community relationships), financial partnerships, other economic interests (e.g., spin-off companies in which Investigators have stakes or private contract research outside of the academic realm), academic interests or any other incentives that may compromise integrity or respect for the core principles of this Policy. Conflicts may arise from an individual's involvement in dual and multiple roles within or outside an institution. While it may not be possible to eliminate all conflicts of interest, researchers are expected to identify, minimize or otherwise manage their individual conflicts in a manner that is satisfactory to the REB.

An institutional COI involves a conflict between at least two substantial institutional obligations that cannot be adequately fulfilled without compromising one or both obligations. Conflicts may occur when pursuing particular goals, for instance, the pursuit of two different "goods," such as an effort to obtain general infrastructure funding from a donor that conflicts with an effort to promote research that the donor does not wish to support. For example, if the institution has a financial/proprietary interest in the study or the outcome of the study these potential conflicts of interest should be declared.

General Guideline Statement

Investigators and the research staff should identify declare and eliminate or manage conflicts of interest to maintain the public confidence and trust and to maintain the independence and integrity of the ethics review process. If a conflict of interest cannot be avoided, procedures should be in place to manage and/or to minimize the impact of the conflict.

The perception of a conflict of interest may, in many cases, be as damaging as a real conflict. The REB should assess the likelihood that the Investigator's judgment may be inappropriately influenced, or perceived to be influenced, by private or personal interests. It should then determine the magnitude of harm that is likely to result from such influence or from the perception of undue influence.

Once a declaration has been made, the Board may request that the Investigator eliminate or manage a conflict, require formal oversight procedures for the research (e.g., audits, independent data safety monitoring processes, regular reports to OCREB), or may disapprove the research altogether. The Board may also inform the Investigator's institution about the conflict of interest. Depending on the nature of the COI, it may be a requirement to inform research participants of significant conflicts of interest in the consent form.

In addressing conflicts of interest, disagreements between the REB and the Investigator may arise about the scope and reach of disclosure, including disclosure of new information to participants, or other aspects of managing the conflict. Resolution of disagreements should be guided by the paramount principles of Respect for Persons and Concern for the Welfare of participants. If the Investigator and the REB cannot resolve their disagreement, they should use the institutional conflict of interest mechanisms to arrive at a solution. (TCPS2).

Types of Conflict of Interest

It is difficult to classify specific categories of conflict of interest declarations. The categories are fluid and in some senses, arbitrary. The same type of conflict may fall into more than one category.

In order to better describe COI, four categories or types of COI have been identified: Financial; Direct Status/Career Benefit; Undue Influence; and Competitive Interest. These categories provide a framework for thinking about which situations may lead to a conflict of interest.

(i) Financial

This is the most obvious form of COI. If the Investigator or anyone connected to him/her through their interpersonal relationships stands to gain financially in the undertaking or outcome of research, there will likely be a financial conflict of interest.

The following are examples of financial conflicts of interest:

- The Investigator or someone connected to him/her through their interpersonal relationships has financial or other economic interests in the outcome of the study;
- The Investigator stands to gain from the research in terms of gifts, favours or gratuities;
- The Investigator will receive a bonus for positive results;
- The Investigator may receive financial incentives from the sponsor (e.g., recruitment incentives, enrolment target incentives, spin-off companies in which the Investigators have stakes, or private contract research outside of the academic realm);
- If the Investigator achieves significant results, there may be opportunities for participation in a conference, or other involvement with the sponsor (e.g., consultancy).

(ii) Direct Status/Career Benefit

If the Investigator or someone connected to him/her through their interpersonal relationships stands to gain through direct rewards in respect of his or her status (for example career status) in the undertaking or outcome of research, there will likely be a direct status benefit conflict of interest.

The following are examples of direct status conflicts of interest:

- The Investigator stands to gain from the research in terms of promotions (e.g., tenure/professorship) or other special considerations;
- The Investigator will be promoted or hired by the sponsor, or be invited to participate in paid activities by the sponsor if the research is successful.

While it is recognized that undertaking research usually will be viewed positively in terms of enhancing career advancement, the question is whether the link between career enhancement and the outcome of the research is so strong as to bring into question the objectivity of the Investigator, in the research process and outcome.

(iii) Undue Influence/Dual Roles

This category refers to situations in which the position of the Investigator is such that the Investigator may exert an undue influence over the research, because of his or her position, or because of the vulnerability of other persons involved in the research as participants. This influence may be due to a personal or professional relationship between the affected individuals.

The following are some examples of situations in which undue influence may constitute a COI:

- The research is Investigator-initiated and thus the Investigator is also the Sponsor of the study. This is particularly notable when an Investigator-Sponsor would like to waive one or more eligibility criteria in order to enrol his/her own patient to a study;
- The Investigator has a patient who may benefit from a drug being tested;

- Recognizing the particular challenges of conducting research in small subspecialties, if the Investigator recruits participants from among his/her patients, the Investigator may exert an undue influence (even subtly) on the patients' consent to participate;
- If the Investigator recruits participants from among his/her employees, students, or immediate colleagues, the Investigator may exert an undue influence on potential participants based on the employment relationship.

(iv) Competing Interest - Investigator
This category of COI refers to situations in which the Investigator may be influenced to draw conclusions against the interest of the sponsor or another interested party to the study because the researcher or someone connected to them through their interpersonal relationships has an adverse interest related to the research.

The following are some examples of a competing interest which may constitute a COI:
- The Investigator is a party to a legal suit against the research company or sponsor;
- In the instance of peer review, a lack of impartiality or bias toward an academic competitor/colleague;
- The Investigator may have a financial interest in another treatment or product which is used to treat the same medical condition as the subject matter of the research.

(v) Competing Interest - Institution
Although economic partnerships between industry and academia are now routine for cancer research, there is particular risk for conflict of interest when partnerships extend beyond an organization's corporate interests to involve institutional decision makers. Institutions and institutional decision makers are expected to fully disclose such financial interests and relationships, and Investigators that are aware of such interests should also disclose them to OCREB.

The following are some examples of competing interests which may constitute an institutional COI:
- The hospital and its chief executive officer have financial interests in a medical device firm whose primary product was used at the hospital and promoted by its surgeons;
- The Chair of a university department receives substantial consulting payments from pharmaceutical companies and attracts industry funds for department career awards, endowed chairs, and other gifts.

OCREB Procedures for Dealing with Conflict of Interest

Declaration and Review of the COI

Investigators submitting research applications to OCREB shall disclose to OCREB any real, potential or perceived conflicts of interest, and strategies for the management of the COI, as well as any institutional conflicts of interest of which they are aware that may have an impact on their research.

a) The Investigator is required to make a full COI declaration to OCREB (on behalf of themselves and the research team) as part of their initial application for OCREB approval, at each period of Continuing Review, and whenever a conflict of interest arises, such as changes in responsibilities or in financial circumstances;
b) If there is a conflict or potential conflict of interest, the Investigator should propose strategies to eliminate, reduce or manage the COI;
c) OCREB review of the COI declaration may include consulting with experts and with the institution, particularly when sizable financial amounts are involved;

d) OCREB will need to make three determinations: 1) Is there a conflict of interest, and 2) if there is, can it be managed, and 3) if so, how will it be managed.

OCREB Considerations when Determining the Probability and Severity (Magnitude of harm) of the COI

In determining the appropriate action, OCREB may take into consideration information such as:

- The nature of the research;
- The magnitude of the interest or the degree to which the conflict is related to the research;
- The extent to which the interest could affect the research;
- The fact that a specific individual is unique in his/her clinical or scientific qualifications to conduct the research;
- The degree of risk to the human participants involved in the research that is inherent in the research protocol; and/or
- The management plan for the COI proposed by the researcher.

Outcome of OCREB Review of the COI

Upon discussion with the Investigator and the institution, OCREB shall determine the appropriate steps to manage the conflict of interest. In assessing COI, OCREB should strive for a proportional management strategy. With the establishment of an appropriate plan to eliminate or to manage the conflict, OCREB may approve the research.

Actions required by OCREB may include, but are not limited to:

- Divestiture or termination of relevant economic interests;
- Mandating Investigator recusal from a study;
- Modifying or limiting the participation of the Investigator-Sponsor in all or in a portion of the research (e.g., requiring an independent determination for eligibility waivers involving the Investigator's own patients);
- In cases involving equity, by imposing a bar on insider trading or requiring the transfer of securities to an independent financial manager or blind trust, or limiting the timing of sales or distributions;
- Monitoring research, i.e. independent review of data and other retrospective review for bias, objectivity, comprehensiveness of reporting (versus withholding data);
- Independent clinical review of appropriateness of clinical care given to research participants, if applicable;
- Monitoring the consent process;
- Disclosure of the conflict to institutional committees, research participants, journals, and the data safety monitoring boards, and /or;
- Disapproval of the research application.

OCREB Response to Reports of Non-Compliance

Any deviations from the COI plan must be reported to OCREB. Action taken in response to confirmed non-compliance with the OCREB approved COI management plan will be guided by relevant OCREB SOPs.

References

1. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement; Ethical Conduct for Research Involving Humans (TCPS2);
2. National Standard of Canada, Research ethics oversight of biomedical clinical trials;
3. U.S. Office for Human Research Protections (OHRP) "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection;
4. U.S. Food and Drug Administration (FDA) Guidance for Clinical Researchers, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators;
5. OCREB SOP 105B - Conflicts of Interest – Investigators;
6. OCREB SOP 903 – Non-Compliance.