

Ontario Cancer Research Ethics Board: Lessons Learned From Developing a Multicenter Regional Institutional Review Board

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A B S T R A C T

Purpose

We describe issues and outcomes in the development of a specialized, central institutional review board (IRB) for multicenter oncology protocols.

Numerous authoritative bodies have called for a change to the ethics review system to better manage multicenter trials in terms of quality, timeliness, and efficiency. In 2003, the American Society of Clinical Oncology proposed a network of regional IRBs for cancer. Previous experience with central IRBs has been met with mixed success.

Methods

We took a bottom-up approach to organizing a province-wide IRB, which was led by an IRB chair and a clinical investigator at one cancer center. Participation on the part of institutions was voluntary.

Results

Uptake in the first 2 years was modest and increased from 11 clinical trials in year 1 to 21 in year 2. In the third year, there was an apparent upsurge in the number of involved centers (14) and in the number of submitted clinical protocols (54).

Conclusion

Sponsors and investigators are loath to risk development of a novel IRB until there is a clear demonstration of quality, efficiency, and timeliness of decision. Development of a regional, specialized IRB requires considerable efforts to develop and maintain the trust of sponsors, investigators, and institutions despite prior demands for more efficient and timely ethics review. Voluntary institutional participation, clear delineation of roles and responsibilities, and effective execution promote development of this trust.

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INTRODUCTION

The research ethics oversight system in North America does not optimally manage human participant protection in multicenter trials (MCTs)¹⁻⁴. By failing to adapt to the growing MCT environment, the traditional research ethics system is fraught with redundancy,³ in which multiple individual institutional review boards (IRBs) review the same research and use increasingly strained resources.¹ Because of a 42% increase in the volume of studies reviewed by IRBs during a 5-year period, the Office of the Inspector General (OIG) of Human Health Services (HHS) describes the IRB system as “in jeopardy”; IRBs “review too much, too quickly, with too little expertise.”¹ For investigators and sponsors, IRB review has become a formidable barrier to the timely initiation and conduction of MCTs. For IRBs, the costs and workload are becoming unmanageable. A

regional, centralized Research Ethics Board (REB; Canadian terminology equivalent to IRB) was created to provide consistent, excellent, and efficient ethics review and oversight of MCTs in the Canadian province of Ontario.

Genesis of the Ontario Cancer Research Ethics Board

Ontario, which has a population of more than 12 million and an area greater than 1,000,000 km²,⁵ delivers cancer treatment at 28 community and teaching hospitals, which includes 14 Integrated Cancer Programs (ICPs) that provide specialized treatment. The ICPs work together with their host hospital and with Cancer Care Ontario, the provincial cancer agency that steers and coordinates Ontario's cancer services and prevention efforts. Accordingly, Ontario was seen as an ideal setting in which to test the feasibility of a central IRB.

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Research ethics board (REB) is the Canadian terminology equivalent to Institutional Review Board (IRB). The terms REB and IRB are used interchangeably in this paper.

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There were four key motivations that fostered the establishment of a central, cancer-specific IRB in Ontario: (1) the need to provide excellent scrutiny of cancer clinical trials by creating an oncology-specific IRB; excellence was a *sine qua non* for any success of the project; (2) the requirement to effect more timely and efficient approval of MCTs across multiple sites by centralizing the review process; (3) the need to reduce duplication in the management of external serious adverse event (SAE) reporting; and (4) the potential that a central IRB would have more influence in dealing with sponsors in MCTs than individual, local IRBs.

In addition, the project could serve as a proof-of-concept of a central IRB in any discipline across any large geographic area.

The Ontario Cancer Research Ethics Board (OCREB) proposal was comprised of three key elements. The first was a desire for excellence in terms of policies, procedures, and people. It was presumed that excellent, timely decision making on the part of OCREB was key to its success and that a well established, specialized, central IRB could provide more depth of scientific and clinical expertise than could most local IRBs. A second key element was that OCREB would have to continuously win the support of the institutions, because the use of OCREB (instead of the local IRB) would be voluntary and because the benefits of a central IRB model could only be realized with the participation of a critical mass of sites. In particular, OCREB would have to win early adopters through the promotion of the potential long-term benefits of the model. The third element of the proposal was that the new IRB would have its own funding and would therefore not affect the existing financial arrangements of local institutions.

A consultative meeting was held with REB representatives and clinical trials managers from each cancer center. There was broad diversity in the perceived need for OCREB (from urgent to none). The potential barriers that were identified related to concerns about institutional risk and infringement on local REB jurisdiction.

The formal creation of OCREB stemmed from extensive provincial and national consultation. Other models of central ethics review were researched, and legal opinion was obtained. OCREB was established in compliance with applicable regulatory requirements and included medical and radiation oncologists; nurses with experience in oncology research; informed community members and/or cancer survivors; and members with expertise in research ethics and relevant law, including privacy legislation, pharmacy, epidemiology, biostatistics and other related disciplines when necessary (e.g., surgical oncology). Membership consisted of broad representation from across Ontario, and each institution was encouraged to select a local representative to serve on OCREB.

METHODS

Developing the OCREB Model

After completion of the organizational and developmental efforts, OCREB began reviewing protocols in January 2004. Initially, there were two options for OCREB review: facilitated review and board of record. In facilitated review, the local IRB remained the board of record and used OCREB's expert oncology review findings to assist in its own review. In the board-of-record option, OCREB is registered under the institution's federal-wide assurance, and OCREB contracts with the institution to serve as its IRB on a study-by-study basis for initial review and for ongoing oversight. The local IRB is not involved in the study when OCREB is the board of record. Before IRB review, the institution conducts an administrative review of the research to

assess study impact, adequacy of local resources, investigator competence, and any other local issues.

Ultimately, the facilitated-review process was found to be unattractive, particularly by investigators and sponsors, as it delayed the review process by requiring an additional, sequential review layer. However, it proved valuable in that it introduced OCREB to clinical trial sites and allowed them to assess the quality of OCREB reviews. Sites that initially used the facilitated-review process eventually moved to the board-of-record option. This experience is consistent with the assessment of Enzle and Schmalz,⁶ who saw that a successful central IRB system "must avoid serial review processes while engendering trust by local institutional authorities and REBs."

RESULTS

In its first year of operation, OCREB met 12 times and reviewed 19 multicenter cancer protocols (Fig 1): 11 clinical trials and eight regional epidemiologic studies. In the five centers that used OCREB as their IRB of record, the average time from receipt of the protocol to OCREB approval was 29 days. Of note, two of five board-of-record centers initially restricted their use of OCREB to specific, cooperative-group studies as a means of piloting OCREB.

By the end of its second full year of operation, the number of institutions that used OCREB increased to seven, and the number of new submissions increased by 64% to 31 (ie, 21 clinical trials and 11 epidemiologic or chart review studies). The average time from receipt of protocol to OCREB approval climbed to just greater than 3 months for the board-of-record option; the facilitated-review option was already falling out of favor. This increase in approval time can be attributed to delays in the receipt of investigator responses to the OCREB review letters, to delays in the receipt of regulatory documents required to issue approvals (eg, Health Canada "No Objection" Letters), and to incremental increases in the number of active studies that resulted in a cumulative increase in the OCREB administrative workload (eg, amendments and renewals that required full OCREB review, numerous external SAEs). The time from the receipt of protocol to

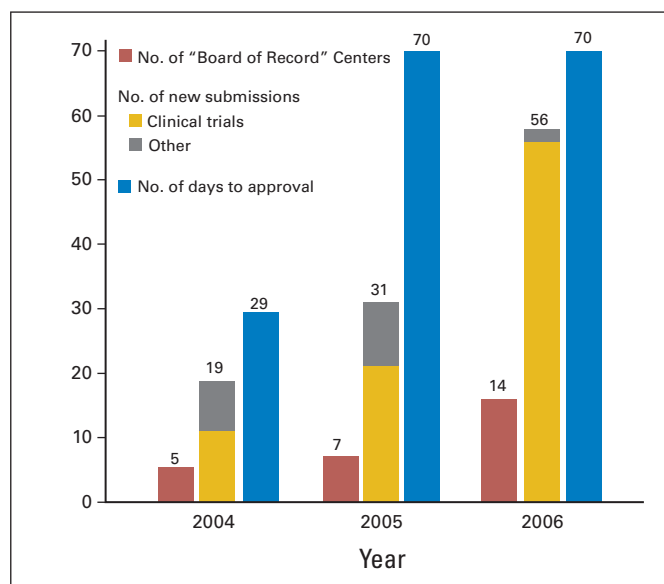


Fig 1. Number of new submissions to Ontario Cancer Research Ethics Board (OCREB) and number of centers using OCREB as their institutional review board of record.

approval remained constant in 2006 (mean, 70 business days), although 38 of those days accounted for the average time spent waiting for investigator responses.

By the end of 2006 (ie, year 3), 14 institutions had a formal relationship with OCREB, and two of the three centers that began with restricted use of OCREB had authorized the use of OCREB for any MCT, as decided locally on a study-by-study basis. There were 56 new submissions in 2006 (all but two were clinical trials), and nearly 90% of all trials submitted since OCREB's inception remained active.

The average number of participating centers per clinical trial remained constant at 1.4 for 2004, 2005, and most of 2006, which is an indication that OCREB had not yet achieved a critical mass of institutions that were participating in the same trials. Because many of the studies submitted to OCREB are leading-edge, early-phase, drug development trials, the low number of centers per trial was expected. The advantage to accepting early phase trials despite the fewer centers is that Ontario then will have gained the experience that will attract the later-phase, follow-up trials. The number of centers per trial did increase to 2.6 in the latter part of 2006, which brought the overall average for 2006 to 1.8 centers per trial (Fig 2).

DISCUSSION

Multiple reviews by individual IRBs do not provide any clear advantage compared with a central, expert review.⁷ Studies that examined differences in responses among IRBs within the same protocol reveal an unexplained variation among IRBs and a costly process of review.⁸⁻¹⁰ McWilliams et al.¹⁰ observed that MCTs increased more than 10-fold between 1984 and 2003, whereas the number of studies in general less than doubled. These investigators proposed the use of central IRBs as a possible solution. In short, there is evidence that there are negative effects of the system of institutionally based IRBs in MCTs.¹¹⁻¹³ Wood et al.¹⁴ called for supplanting the IRB system with a network of regional ethics organizations.

There have been four high-level, North American documents that reflect a growing support for central ethics review. The American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research¹⁵ advocated a network of regional IRBs for cancer. A 2005 workshop convened by the Secretary's Advisory Committee on Hu-

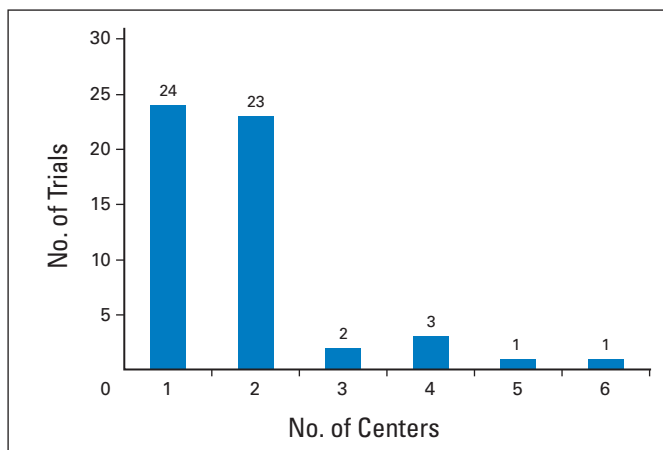


Fig 2. Number of trials v Ontario centers per clinical trial in 2006.

man Research Protections reviewed a number of innovative models of IRB review, including three examples of central ethics review of MCTs.² The focus was on the improvement of the quality of review and on the reduction of an excessive IRB workload. The US Food and Drug Administration issued a guidance document on central ethics review of MCTs that particularly addressed efficiency and timeliness.⁴ In addition, the US Office of Human Research Protection (OHRP) guidance document "IRB Knowledge of Local Research Context" contains alternative ways to incorporate knowledge of the local context into the central IRB model.¹⁶ Importantly, both the Canadian and US regulations and guidelines that govern research ethics allow for central ethics review.¹⁷⁻¹⁹

There are already a number of precedents for central IRB review.²⁰⁻²³ One example is the Multi-Center Academic Clinical Research Organization (MACRO),²⁰ a consortium of major academic health care centers with reciprocity agreements to facilitate ethical and administrative approval of MCTs that involve the five universities. Ethical approval at any one site constitutes ethical approval at all five. The proposal, although appealing in principle, has not succeeded in attracting many trials.

Another example is the National Cancer Institute Central IRB (NCI CIRB).²² The NCI CIRB involves 263 participating adult-oriented and 128 pediatric-oriented institutions. One review is done centrally for each study, and a facilitated review is conducted by the local IRB chair/subcommittee, which concentrates on local issues. The CIRB serves as the board of record and is responsible for the continuing review and the subsequent amendments and SAEs.²⁴ The local IRB is responsible for the review of local SAEs and for the oversight of local conduct of the study. More than 116 phase III, adult, cooperative-group oncology protocols have been reviewed since January 2001. OCREB adopted a model that is similar but not identical to that of the NCI CIRB.

From the perspectives of quality and efficiency, a specialized central IRB intuitively makes sense. Specialization provides the expertise required for complex reviews, and centralization promotes efficient use of resources. In addition, conflicts-of-interest in supporting the work of the institution's own investigators is lessened or eliminated³; the central IRB truly is at an arm's length from the institution.

At the outset, OCREB was rapidly adopted by nonacademic hospitals that had limited oncology-specific research ethics expertise. Subsequently, large nonacademic and small university hospitals followed suit; a few large academic hospitals were testing the waters with a small number of trials. Large academic hospitals were the last to adopt OCREB, which perhaps reflected a greater satisfaction with their status quo.

During the first three years of operation, OCREB faced several challenges: (1) a substantial effort required to win support from each institution; (2) the adaptation and development of operational processes specific to a central IRB model; (3) the recognition of the large cumulative workload for an oncology-specific IRB, and the provision of appropriate staffing levels; and (4) education and communication to assist institutions in adapting to different processes required with a central IRB model.

Presently, 14 of the 27 institutions that conduct oncology trials in Ontario have authorized a board-of-record relationship with OCREB and are actively using OCREB for multicenter cancer studies. Additional sites are planning to opt for this relationship, which is an indication that OCREB is fulfilling a need and is considered a central IRB model that works.

In conclusion, OCREB, functioning as a regional IRB, was initially promoted by an IRB chair and a clinical oncologist who worked conjointly with a provincial program that promoted clinical cancer research: in large part, a bottom-up approach. There was extensive consultation with institutions, IRBs, sponsors, and investigators. Initially, there was considerable concern regarding the lack of jurisdiction of OCREB. However, OCREB is earning the trust and support of affiliated institutions through its performance, through the quality of its reviews, and through the maintenance of effective communication with its stakeholders. Timeliness of review, measured in terms of time from submission until approval, has room for improvement, and OCREB is poised for substantial growth. OCREB will address its internal procedures and will seek to improve its coordination with investigators and sponsors. OCREB will reach its full potential only when it is the board of record for a large number of sites per study. OCREB is working to improve the quality and efficiency of research ethics review, thereby enhancing human participant protection and making Ontario a more attractive region to conduct cancer clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked

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REFERENCES

- Office of the Inspector General. Institutional Review Boards: A Time for Reform. <http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf>
- National Institutes of Health, Office for Human Research Protections, Department of Health and Human Services, Association of American Medical Colleges, American Society of Clinical Oncology: Alternative Models of IRB Review: Workshop Summary Report. <http://www.hhs.gov/ohrp/sachrp/documents/AltModIRB.pdf>
- Emanuel EJ, et al: Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals. *Ann Intern Med* 141:282-291, 2004
- Food and Drug Administration. Guidance for Industry: Using a centralized irb review process in multicenter clinical trials, March 2006. <http://www.fda.gov/cber/gdlns/irbclintrial.pdf>
- Government of Ontario. About Ontario: Ontario Ministry of finance census highlights 2005. <http://www.gov.on.ca/mbs/english/about/geography2.html>
- Enzle ME, Schmaltz, R: Ethics Review of Multi-Centre Clinical Trials in Canada. *Health Law Rev* 13:51-57, 2005
- Gold JL, Dewa CS: Institutional Review Boards and Multisite Studies in Health Services Research: Is There a Better Way? *Health Serv Res* 40:1:291-308, 2005
- Redshaw ME, Harris A, Baum JD: Research Ethics Committee Audit: Differences between committees. *J Med Ethics* 22:78-82, 1996
- Stair TO, Reed CR, Radeos MS, Koski G, et al: Variation in Institutional Review Board Responses to a Standard Protocol for a Multicenter Clinical Trial. *Acad Emerg Med* 8:636-641, 2001
- McWilliams R, Hoover-Fong J, Hamosh A, Beck S, et al: Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study. *JAMA* 290:360-366, 2003
- Burman WJ, Reves RR, Cohn DL, Schooley RT: Breaking the Camel's Back: Multicenter Clinical Trials and Local Institutional Review Boards. *Ann Intern Med* 134:152-157, 2001
- Burman W, Breese P, Weis S, Bock N, Bernardo J, Vernon A, and the Tuberculosis Trials Consortium: The effects of local review on informed consent documents from a multicenter clinical trials consortium. *Control Clin Trials* 24:245-255, 2003
- Schneider EC, Epstein AM, Malin JL, Kahn KL, Emanuel EJ: Developing a System to Assess the Quality of Cancer Care: ASCO's National Initiative on Cancer Care Quality. *J Clin Oncol* 22:2985-2991, 2004
- Wood A, Grady C, Emanuel EJ: Regional ethics organizations for protection of human research participants. *Nat Med* 10:1283-1288, 2004
- American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research. *J Clin Oncol* 21:2377-2386, 2003
- US Department of Human Health Services, Office for Human Research Protections. IRB knowl-
- edge of local research context, August 27, 1998 (updated July 21, 2000). <http://www.hhs.gov/ohrp/humansubjects/guidance/local.htm>
- Tri-Council Policy Statement. Ethical Conduct for Research Involving Humans, August 1998 (2000, 2002, 2005 amendments). http://www.pre.ethics.gc.ca/english/pdf/TCPS%20October%202005_E.pdf
- US Food and Drug Administration. Code of Federal Regulations Title Part 56. Institutional Review Boards Subpart C: IRB Functions and Operations 56.114—Cooperative Research, revised April 1, 2006. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=56&showFR=1&subpartNode=21:1.0.1.1.21.3>
- US Food and Drug Administration. Code of Federal Regulations Title 45 Part 46. Protection of Human Subjects 46.114: Cooperative Research, revised June 23, 2005. <http://www.nihtraining.com/ohsr/site/guidelines/45cfr46.html#46.114>
- Vanderbilt Clinical Trials Center Home Page. Clinical Trials Center. <http://www.mc.vanderbilt.edu/ctc/macro.html>
- Biomedical Research Alliance of New York: BRANY IRB. <http://www.branyirb.com>
- National Cancer Institute: The Central Institutional Review Board Initiative. <http://www.ncicirb.org>
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. <http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf>
- Christian MC, Goldberg JL, Killen J, Abrams JS, et al: A Central Institutional Review Board for Multi-Institutional Trials. *N Engl J Med* 346:1405-1408, 2002