

Ethics Review of Multi-Centre Trials: Where Do We Stand?

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It has been a decade since the Office of the Inspector General, U.S. Health and Human Services (OIG), issued its landmark report, *Institutional Review Boards: A Time for Reform*.¹ The OIG report talked of major changes in the research environment, with more multi-centre trials (MCTs) and increased commercialization of research. The purpose of this article is to review recent developments in terms of ethics² review of MCTs within the Canadian context.

The OIG report described a number of important findings, all of which apply to the Canadian context as well:

- The number of studies reviewed by each REB has increased enormously, without a commensurate increase in resources and with continued lack of appropriate expertise on IRBs.
- Insufficient attention was given to monitoring the study after initial approval.
- Healthcare institutions have become dependent on revenues from commercially sponsored clinical research.
- There is concern about lack of independence of REBs and institutional pressure to approve trials, resulting in concern about conflict of interest.
- There was insufficient training for investigators and Board members.

The OIG called for a variety of measures to improve the system, including an increased role for Data Safety Monitoring Boards (DSMBs). However, the OIG did not advocate centralization of IRB function.

In a previous article in this journal, Enzle and Schmaltz reviewed the issue of MCTs in the Canadian context, and focused on the issue of centralization of ethics review.³ They observed that article 1.2 of the Tri-Council Policy Statement (TCPS)⁴ could be interpreted to limit the possibility of central review of MCTs. The TCPS initially assumed that an REB would be under the purview of an individual institution. Although this was later amended to allow delegation, Enzle and Schmaltz addressed multiple reasons why an institution might choose to use its own REB for ethics review of all studies involving the institution or its personnel, including regulatory compliance, management of liability, and quality of review. They noted that there was no regulatory or other requirement for ethics review within the institution. Rather, there was the requirement that the institution be accountable for research done under its auspices. Concern of the institution regarding liability was intertwined with a desire on the part of the institution to maintain control of ethics review as part of a broader administrative oversight of what is done in the institution. Finally, Enzle and Schmaltz addressed the inherent strengths and weaknesses of multiple ethics review. Strengths included a greater possibility of identification of key issues if more eyes observed a trial. However, concomitant weaknesses included redundant use of resources and inconsistencies between sites which could result in delays to the research. Although they reviewed examples of centralized REBs at that time, there was limited experience in this regard.

The key issue with moving toward centralized REB review can be summarized as follows. Under the current system of individual REB review, the opinion of each



REB represents the consensus opinion of a number of individuals. However, centralizing ethics review to one REB necessarily means that there is only one consensus opinion. Multiple REB reviews mean that there will be more variability in response. A key issue is whether this variability is desirable.

Enzle and Schmaltz observe that differing REB opinions provide an opportunity for the critical study of a concern arising from a lone dissenter at a single REB, which could potentially be recognized by the REB as a whole in its decision. The authors however do not provide supporting data. There are abundant arguments

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to the contrary.⁵ Numerous studies from disgruntled investigators address inefficiencies, inconsistencies and other negative consequences of multiple reviews of their trials. Burman *et al.* address consent form changes proposed by multiple REBs in a multi-centre trial of therapy of tuberculosis, resulting in errors and increased complexity to the forms.⁶ Of the median 46.5 changes per form per REB, only 1.5% were thought to reflect local issues and only 1.7% were thought to be of potential general relevance to all sites. Gold and Dewa reviewed problems with ethics review of MCTs, and cite the huge costs, delays, and inconsistencies of institutional-based review.⁷ They believe the differences are unrelated to substantive criteria. A systematic review by Greene and Geiger identified a total of 40 peer-reviewed articles and 6 commission or advisory reports regarding ethics review of MCTs.⁸ The same problems were repeatedly identified in multiple studies. There were proposals for solutions with limited empirical data to support them. Of note, education and training of REB members and investigators were thought to be a key element of

addressing MCTs. The problems with the REB system jeopardize research and squander scarce funds; costs are estimated at \$1000 per site per review.⁹

Structurally, a negative response from one of a large number of institutional REBs reviewing a particular study does not impact the study as a whole; rather, it impacts that site, which will not participate, while the study goes ahead at the other sites. Dissenting opinions from individual REBs may be disregarded by the sponsors simply by bypassing the dissenting institution. The question arises, then, is the one review per centre model a source of quality or is it a reason for diminution of quality?

The OIG report painted a picture of REBs flooded with work and responding with rapid and presumably inadequate reviews. In other words, the preponderance of information at this point suggests that the institution-based system results in compromise of quality of decision-making at each site because of excessive volumes and lack of ethics expertise.¹⁰ Inconsistencies in review between REBs are not substantive, not based in regulation or principle, and result in problems with consent forms. Other issues include the lack of training of REB members in research ethics and lack of expertise in the multiplicity of subject areas addressed.

What has changed with regard to centralized review of MCTs in the three years since Enzle and Schmaltz submitted their report? What lessons can be learned for the Canadian context?

There have been two major proposals in the United States regarding regionalization of REB function. The American Society of Clinical Oncology proposed a system of regional REBs for cancer cooperative studies.¹¹ One REB would review a given protocol for the entire region. These REBs would use standard forms for initial applications, adverse event reporting, etc. They would work in concert with DSMBs with respect to adverse events and interim analysis. Local REBs would have limited, administrative responsibilities in MCTs. High standards of training would be expected of all parties to research, including investigators and REB members.

Wood, Grady and Emanuel propose a network of regional ethics organizations (REOs) across the United States, each with a Protocol Review Committee (PRC) which would serve as a regional REB for MCTs, but also which



would serve as a national REB for MCTs originating in the region.¹² Each PRC would be well trained, have at least 25% lay members, and have a number of experts who would meet frequently and be paid for their time. The REOs and PRCs would supplant local REBs. This proposal, while similar to ASCO's, is broader in subject area and more profound in the change it requires, for example change in regulation. Such a model could be adapted to Canada.

A workshop convened by the Office of Human Research Protections (OHRP), the Association of American Medical Colleges (AAMC), and the American Society of Clinical Oncology (ASCO) explored issues around centralization of ethics review.¹³ It identified five key challenges: assurance of review quality; sensitivity to local context; liability; control and accountability; and loss of resources. Its proposal emphasized the need for clear delineation of local roles and responsibilities. A number of recent documents from governmental agencies in both the United States and Canada represent an apparent shift of opinion towards more acceptance of centralization of review.

The Food and Drug Administration (FDA) in the United States issued a guidance regarding centralized ethics review which cites issues related to the institutional review model. It states: "Use of a centralized IRB review process is consistent with the requirements of existing IRB regulations," citing 21 CFR 56.114. They address different aspects of community attitudes which should be sought and different fashions of achieving this input.¹⁴

In Canada, the Experts Committee of the Sponsors' Table addressed governance of research ethics in Canada.¹⁵ This committee identified a list of familiar concerns relating to the status quo, including conflict of interest, inconsistency of reviews and lack of expertise on REBs, as well as administrative burden, cost and delays. It rejected the development of regional and national REBs in lieu of local REBs but did not address an integrated system mixing the regional and national REBs with institutional ones.

The most recent document regarding this issue in the Canadian context comes from the recently released draft update of the TCPS.¹⁶ In this document, it is acknowledged that differing decisions "may delay or jeopardize the implementation of the research." A number of different models of streamlining of multi-centre ethics review

are discussed. The Inter-Agency Panel on Research Ethics allows for REBs specialized by content area (e.g., cancer clinical trials) or by methodology (e.g., qualitative research), or not specialized. They propose as options *de novo* REBs, common REBs for two or more institutions, or reciprocal review arrangements among multiple institutions. They stress the importance of clear delineation of roles and responsibilities among institutions and involved REBs.

An alternative model for MCT review has been instituted recently by OCREB. OCREB is supported by the Ontario Institute for Cancer Research (OICR). OCREB and OICR have sought to play a leadership role in terms of

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research ethics and more broadly in terms of conduct of clinical research across Ontario and across Canada. While other proposed models of centralization have taken either a top-down or bottom-up approach, OCREB has adopted a market-driven, bottom-up approach.

In the OCREB model, a *de novo* REB was established which attempts to compete with the status quo of institutional REBs in regard to MCTs.¹⁷ OCREB has a formal agreement with 17 of the 27 institutions (cancer centres/hospitals) in Ontario that conduct oncology MCTs. It initially served either an advisory role to a local REB ("facilitated review" option) or was delegated by the institution to act for the institution as its REB for the study ("REB of record"). Since 2006, it has discontinued the facilitated review option, which was intended to serve as a means of developing a relationship between OCREB and institutions, but was perceived by sponsors, investigators and local (institutional) REBs alike to represent an added layer of bureaucracy. OCREB serves



as the institutional REB on a study by study basis. Each institution does a local administrative review both to address local issues and to allow the institution to determine the feasibility of conducting the study. Despite tremendous attention to the OCREB model by investigators and sponsors, initial growth was slow and manageable but has since accelerated. OCREB reviewed 73 clinical studies in 2007, each involving an average of just over two sites.¹⁸ These included a number of single-site Phase I trials.

An increasing number of universities have developed processes for streamlining ethics review with their affiliated hospitals. There are such arrangements at various levels of development at McGill University, University of Ottawa, University of Toronto, and University of British Columbia. These local arrangements are generally relevant to smaller multi-centre trials.

It is our view that the barriers to greater efficiency of the REB system are unchanged from four years ago. Institutional desire for control of the REB process and concerns about liability remain.

One province – Newfoundland – has legislated relationships among REBs: a top-down approach. In Newfoundland, there is one designated health REB for the province and the option of designating others, excluding for-profit REBs.¹⁹ In Quebec, an administrative scheme was implemented in April 2008 by the Ministry of Health and Social Services for multi-centre trials involving hospitals. It is a two-tiered approach, with one REB of record for the province (any approved REB may fill this role), with input from each involved REB.²⁰ Recently, the Ministry has agreed to exempt certain projects from the scheme.

It is our view that the barriers to greater efficiency of the REB system are unchanged from four years ago. Institutional desire for control of the REB process and concerns about liability remain. It is difficult for the institution to ascertain the quality of people, process or policies of an outside organization. There is no

accreditation system. A limited number of REB leaders know their peers through attendance at regional or national meetings such as the National Council on Ethics in Human Research (NCEHR) and the Canadian Association of Research Ethics Boards (CAREB), but this is informal and inconsistent. There is lack of trust on the part of Canadian REB chairs and members in the work of other REBs.²¹ A majority of American medical schools are against using a central REB, preferring the status quo of local review.²² From an institutional perspective, the development of central REBs cannot supplant the need for local REBs and implies the need for added administrative oversight. There is concern that development of *de novo* REBs will diminish resources at the local institution without a commensurate reduction of REB workload at the institution.

An important potential role of the REB is in the education of all local stakeholders in research ethics and its importance. There is no generally accepted metric of how this should be done, nor in how well it is being done. Education is a particular area where larger REBs with broader reach have an opportunity to work with local REBs to support research ethics education.

There has been continued discussion of the need for an accreditation system for research ethics, recently reiterated by the Experts' Committee. Accreditation is particularly important to centralization of REB function through delegation by institutions. In the absence of a generally held standard of function of REBs or the ability of the institution to ensure some form of reciprocal indemnification provisions, it is difficult for the institution to delegate.

A few key issues remain to be addressed. What elements of the oversight of a study require REB review and what can be done by a knowledgeable and expert individual? Do we need an entire committee to assess investigator competence, concerns about overtaxing a particular set of patients, or impact on local resources? How does a local REB represent or address diverse cultural and religious values of diverse local populations and how does this differ from a central REB? In short, when is administrative review sufficient in lieu of full REB? How do they best engage each other to identify particular cultural, religious or linguistic issues?

Centralization of ethics review puts particular responsibility on the central REBs for excellence of



decision-making. There is a particular need for standards of training of members. Similarly, the conduct of a study ultimately is in the hands of the investigator and his/her staff. There is a broad need to instill a culture of research ethics and scientific integrity in all those involved in human subjects' research. Well-functioning central REBs can support institutions in their educational efforts, but the prime agent of educational efforts and maintenance of standards at a local level must remain with the institution.

All stages of a study should be interpreted in light of their ethical impact. Investigators can be expected to identify ethical issues in their studies in protocols and in the REB application process, and to propose means by which to manage these issues. The monitoring process gives the opportunity to further assess the study and to address whether any changes are required to better manage risk and benefit. Every project should have a final report which should be widely and publicly available.

Emanuel and colleagues proposed seven requirements for clinical research which form a framework for assessment: social or scientific value; scientific validity; fair subject selection; favorable risk-benefit ratio; independent review; informed consent; and respect of potential and enrolled subjects.²³ Most clinical research is focused on broader issues than local ones, but many may be usefully viewed with knowledge of local circumstances.

Conclusion

There have been modest advances in terms of ethics oversight of multi-centre trials. We have moved beyond criticism of the problems inherent in the ethics system to proposals for change. There is recognition at the regulatory level in the United States (i.e., by the FDA and OHRP) and at a similar level in Canada (i.e., by the Sponsors' Table) of the need to better manage MCTs.

Concrete, functioning models of change are few and far between. How do we promote a robust but streamlined system to address MCTs? A first step is a thorough review of the functions of an REB – protocol review, monitoring of trials, education, policy development – and an assessment of what functions are appropriately centralized, what local functions require an REB, and what requires the local REB. A second step is assessment and management of barriers to change. For example,

expert analysis and public discussion of institutional liability for research and the impact of central REBs are clearly required. The absence of standards for REBs and independent, standardized assessment of them and of their host institutions in regard to human subjects protection makes it difficult for an institution to delegate to an external REB. We need standards, particularly for education of REB members and investigators, and an accreditation system. Finally, we need empirical data regarding innovation. We must evaluate new models of research ethics and build new ethics structures based on evidence.

The REB system in Canada must adapt to the realities of multi-centre trials. Not to do so shall jeopardize Canada's position as a leader in human subjects research.

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Endnotes

- 1 U.S., Department of Health and Human Services, *Institutional Review Boards: A Time for Reform* (Washington, D.C.: Office of Inspector General, 1998).
- 2 In this paper, we shall generally use the term "research ethics board" or "REB;" American documents use the term "Institutional Review Board" or "IRB." The two entities are essentially the same.
- 3 Michael E. Enzle & Rodney Schmaltz, "Ethics Review of Multi-Centre Clinical Trials in Canada" (2005) 13:2-3 Health Law Review 51.



- 4 Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans* (Ottawa: Public Works and Government Services Canada, 1998 with 2000, 2002, 2005 amendments), art. 1.2, online: Interagency Advisory Panel on Research Ethics (PRE) <<http://www.pre.ethics.gc.ca/english/policystatement/section1.cfm#1B2>>.
- 5 See for example: William Burman *et al.*, "The effects of local review on informed consent documents from a multicenter clinical trials consortium" (2003) 24 *Controlled Clinical Trials* 245; Jennifer L. Gold & Carolyn S. Dewa, "Institutional Review Boards and Multisite Studies in Health Services Research: Is There a Better Way?" (2005) 40 *Health Services Research* 291; M.E. Redshaw, A. Harris, & J.D. Baum, "Research ethics committee audit: differences between committees" (1996) 22 *Journal of Medical Ethics* 78; Thomas O. Stair *et al.*, "Variation in Institutional Review Board Responses to a Standard Protocol for a Multicenter Clinical Trial" (2001) 8 *Academic Emergency Medicine* 636; Rita McWilliams *et al.*, "Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study" (2003) 290 *Journal of the American Medical Association* 360.
- 6 Burman *et al.*, *ibid.*
- 7 Gold & Dewa, *supra* note 5.
- 8 Sarah M. Greene & Ann M. Geiger, "A review finds that multicenter studies face substantial challenges but strategies exist to achieve Institutional Review Board approval" (2006) 59 *Journal of Clinical Epidemiology* 784.
- 9 Jeremy Sugarman *et al.*, "The Cost of Institutional Review Boards in Academic Medical Centers" (2005) 352 *New Eng. J. Med.* 1825.
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- 11 American Society of Clinical Oncology, "American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research" (2003) 21 *Journal of Clinical Oncology* 2377.
- 12 Anne Wood, Christine Grady & Ezekiel J. Emanuel, "Regional ethics organizations for protection of human research participants" (2004) 10 *Nature Medicine* 1283.
- 13 U.S., National Institute of Health *et al.*, *Alternative Models of IRB Review: Workshop Summary Report* (Washington, D.C.: Department of Health and Human Services, 2005), online: Department of Health and Human Services <<http://www.hhs.gov/ohrp/sachrp/documents/AltModIRB.pdf>>.
- 14 U.S., Department of Health and Human Services *et al.*, *Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials* (Rockville, Md.: Food and Drug Administration, 2006), online: Food and Drug Administration <<http://www.fda.gov/cber/gdlns/irbclintrial.pdf>>.
- 15 A group of organizations that shares a common interest in promoting research involving humans that meets the highest standards in excellence and ethics, the Sponsors' Table for Human Research Participant Protection in Canada consists of:
- Alberta Ministry of Health and Wellness,
 - The Association of Canadian Academic Healthcare Organizations,
 - The Association of Faculties of Medicine of Canada,
 - The Association of Universities and Colleges of Canada,
 - Canada's Research-Based Pharmaceutical Companies,
 - The Canadian Federation for the Humanities and Social Sciences,
 - The Canadian Institutes of Health Research,
 - Fond de la recherche en santé du Québec,
 - Health Canada,
 - Health Charities Coalition of Canada (since June 2007)
 - The Michael Smith Foundation for Health Research (since August 2007)
 - Research Canada (since June 2007)
 - The Natural Sciences and Engineering Research Council,
 - The Social Sciences and Humanities Research Council, and
 - The Royal College of Physicians and Surgeons of Canada.

The Sponsors' Table will

Establish an Experts Committee to provide expert advice on the development of a system for human research participant protection in Canada, considering accreditation and alternative models, and taking into account different levels and types of risk in research. This process will include an assessment of existing means of ensuring human research participant



protection for various types of research and of the gaps that such a system would address.

See Sponsors' Table for Human Research Participant Protection in Canada, "Home," online: Sponsors' Table for Human Research Participant Protection in Canada <<http://www.hrppc-pphrc.ca/english/sponsors.html>>. For the Experts Committee's final report, see Experts Committee for Human Research Participant Protection in Canada, *Moving Ahead: Final Report of the Experts Committee for Human Research Participant Protection in Canada* (Ottawa: Experts Committee for Human Research Participant Protection in Canada, 2008), online: Sponsors' Table for Human Research Participant Protection in Canada <<http://www.hrppc-pphrc.ca/english/movingaheadfinalreport2008.pdf>>.

- 16 Interagency Advisory Panel on Research Ethics, *Draft 2nd Edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: Interagency Advisory Panel on Research Ethics, 2008) at 81-90.
- 17 Raphael Saginur *et al.*, "Ontario Cancer Research Ethics Board: Lessons Learned From Developing a Multicenter Regional Institutional Review Board" (2008) 26 *Journal of Clinical Oncology* 1479; M.R. Chaddah, "The Ontario Cancer Research Ethics Board: a central REB that works" (2008) 15:1 *Current Oncology* 49.
- 18 See Ontario Cancer Research Ethics Board (OCREB), *Ontario Cancer Research Ethics Board: 2007-2008 Annual Report* (Toronto: Ontario Cancer Research Ethics Board, 2008), online: <http://www.oicr.on.ca/ocreb/documents/OCREB_AR0708.pdf>.
- 19 *Health Research Ethics Authority Act*, S.N.L. 2006, c. H-1.2.
- 20 See Sante et Services Sociaux Quebec, "Unite de l'ethique," online: Sante et Services Sociaux Quebec <<http://ethique.msss.gouv.qc.ca/site/166.0.0.1.0.0.phtml>>.
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- 23 Ezekiel J. Emanuel, David Wendler & Christine Grady, "What Makes Clinical Research Ethical?" (2000) 283 *Journal of the American Medical Association* 2701.

