

# Ethics Review of Multi-Centre Clinical Trials in Canada

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Human research conducted at institutions receiving funding from any of the three federal Canadian funding agencies must be reviewed and approved in advance by a human research ethics board (REB). The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*<sup>1</sup> (TCPS) requires that each institution be fully responsible for the ethics review of human research conducted under its auspices (Article 1.2).<sup>2</sup> This provision has been interpreted to mean that one institution cannot *pro forma* accept the REB decision of another institution when the same research is proposed for conduct at both institutions. This interpretation is most clearly at issue in cases of multi-centre clinical trials, wherein researchers from two or more institutions are invited to participate in trials using standardized research protocols.

Many researchers, research ethics boards, clinical trial sponsors, and institutional administrators have complained informally about several inter-related consequences of TCPS Article 1.2. They argue that this Article has resulted in institutions and their REBs being concerned that reliance on another institution's REB decision would either constitute non-compliance with the TCPS, or would expose them to unknown, and therefore unacceptable, liability risks.

Other critics argue that the multiple reviews resulting from this state of uncertainty about institutional responsibility are unnecessarily redundant in view of the common standards for protection of human subjects established by the TCPS. They claim that this redundancy creates wasted human resources, wasted material resources, and wasted time.

Another concern centres on decision consistency, because it is possible for one REB to reject the same proposal judged acceptable in whole or part by another REB. Thus, the same protocol can be found acceptable for implementation at one site, but not at another.

Pharmaceutical companies and investigators<sup>3</sup> also complain that they receive many demands for protocol revisions from different REBs, some of which are diametrically opposed to one another. Such demands pose difficult challenges for the designers and sponsors of multi-centre trials, as homogeneity of methods across sites is a critical element of scientific control.

The critics of multiple REB reviews for multi-centre trials also cite a negative public health consequence: Research with important health implications may be delayed unnecessarily, or even discouraged, thereby indirectly depriving the populace of the best possible healthcare.

There have been three main reactions to these criticisms and warnings. One response is that redundancy and the attendant costs of multiple REB reviews is justified and desirable, as the effect is to enhance the protection of human research subjects. A second is that a national, centralized, system of review for multi-centre clinical trials should be established. The third reaction, a *fait accompli*, is an amendment to the TCPS Article 1.2 that permits institutions to form affiliations in which mutual acceptance of each other's REB findings can occur.<sup>4</sup>



## 1. Benefits of Redundancy

Despite the apparent validity of the inefficiency and inconsistency arguments about multiple REB reviews, we have suggested elsewhere that multiple reviews may promote human research protections.<sup>5</sup> Critics of decentralized multiple reviewing implicitly claim that inconsistency among REB decisions amounts to poor reliability among REBs. They argue that a common, easily understood set of standards exist in the TCPS, and that inconsistency therefore represents a misapplication of the standards by REBs. This approach assumes, moreover, that minority opinion is wrong and reflects a lack of expertise or negligent application of ethics standards. We do not think that this is necessarily the case. Our reasoning stems from a common phenomenon at REB meetings – that in which a single REB member identifies a significant ethical issue, and persuades all remaining members of the REB that the protocol requires substantial changes or should be rejected. Thus, the minority opinion may be the incisive and decision-determining view for the local REB. The TCPS itself recognizes this possibility in its promotion of decision-making by consensus rather than by majority vote.<sup>6</sup> We believe that a similar dynamic might well operate at the level of multiple REBs. That is, the minority opinion of one or more REBs may sometimes be the better one. Where multiple REBs might overlook a subtle but significant point and approve a protocol, a small number of REBs might identify that critical point and reject the proposal, or call for revisions. The underlying problem is that although the TCPS does establish a common set of ethical principles, procedures and standards for researchers and REBs, there currently is no assurance system (e.g., accreditation) that establishes and oversees consistent implementation and application of those principles, procedures and standards.

## 2. Benefits of Centralized Review

### *The 2000-2002 Health Canada Initiative*

Several years ago, Health Canada launched an ethics governance consultation process that included a multi-centre review trial balloon. This response appeared to accept the criticisms of multiple REB reviews as legitimate, but also reinforced that the primary concern of the TCPS was the protection of human research subjects. Discussion papers for that exercise cited a number of potential advantages for a national level of ethics review.<sup>7</sup> The Health Canada documents suggested that a national and central REB for

multi-centre trials could provide a high level of review for proposals requiring specialized expertise, with a resulting enhancement of human subject protections. The papers also focused on increasing efficiency by reducing multiple reviewing of multi-centre trials. A key component of the system would have been a quality assessment and improvement system designed to ensure that all accredited REBs, including a national central REB for multi-centre trials, would meet a common and high level of human subject protections.

The consultation papers suggested that the centralized review envisioned by the Health Canada actors of the day would have been a two-stage process. Protocols for multi-centre trials would have begun with a central national review mechanism followed by local review. In other words, a central REB could be created which would be expert in the review of pharmaceutical trials. Protocols for multi-centre trials would enter the system for first review with the central REB. Following approval from the central REB, the protocol would then be passed on to local REBs of researchers who wished to participate in the multi-centre trial.

The public rationale for secondary review by local REBs is that relatively site-specific and regional details known to the local REB about researchers (e.g., currency of licensure and competency to conduct the research), laws (e.g., provincial privacy legislation) and resources (e.g., the availability of specialized resuscitation equipment), require consideration in judging the overall ethical acceptability of a protocol. The Health Canada initiative underwent a significant downscaling in late 2002 or early 2003. There currently is no national consultation by Health Canada on centralized review for multi-centre clinical trials. Nevertheless, there are informal indications that the federal government maintains an interest in centralized review through Health Canada,<sup>8</sup> and that the three federal funding agencies are concerned with the issue of multi-site ethics reviews.<sup>9</sup>

A number of centralized review systems already exist in other countries (e.g., the United Kingdom) and provincial jurisdictions (e.g., Alberta, Ontario, and Quebec). None of the systems are complete general-purpose review structures for multi-centre trials. The Ontario Cancer Research Ethics Board handles only cancer-related trials. The United Kingdom and Alberta systems are multiple-entry point systems, in which any one of several REBs may serve in practice as a central review agent for the others. Nevertheless, there is much to be learned from the experiences of, and reactions to, these variations on central ethics review.



### United Kingdom (1997-2004)

Until October of 2004, the United Kingdom operated a system in which several regional multi-centre research ethics committees (MRECs) carried out national reviews followed by reviews at local institutional research committees (LRECs).<sup>10</sup> The principal investigator for a multi-centre trial submitted the trial protocol and application materials to the MREC responsible for his or her geographic region. (The five geographic regions each included approximately 5 million people.) Once the MREC approved a protocol, the project principal investigator supplied the responsible investigator at each local research site with the MREC approval documentation. These local investigators then applied to their LRECs using these materials. An executive committee of each LREC was then supposed to expedite the review of the protocol.

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LRECs through their executive committees were supposed to refuse a protocol under their jurisdiction for only three reasons: insufficient expertise of local researchers to properly conduct the research, unsuitable local site or facilities, or inappropriate use of local subjects (e.g., where the target subject population had been overused). Moreover, LREC executive committees were permitted to require changes *only* to the subject information sheet (which discusses issues of voluntariness, confidentiality, risks, and benefits of participation) and the consent form, and then only for matters related to local institutional conditions. If an LREC executive committee identified what it believed was a significant ethical issue beyond its review authority, it was to convey its concerns to the responsible MREC. Once these steps were concluded, the MREC was to take whatever action it deemed appropriate on the basis of feedback from LRECs, and the local investigator could then commence enrolment of subjects and initiation of the trial protocol.

How did the U.K. experiment with multi-centre review fare? It was met with considerable criticism from researchers. The complaints were about the very problems the system had been designed to cure. A number of reports claimed that the centralized U.K. system increased rather than decreased inefficiency, duplication of effort, and costs.<sup>11</sup> Some writers provided evidence that many LRECs reached beyond their assigned scope of local concerns by conducting detailed

reviews of entire protocols<sup>12</sup>, thereby undermining the rationale for the centralized review itself. It also appears that many LRECs did not develop an executive committee for expedited review of MREC-approved applications, and instead referred all MREC-approved protocols to full LREC hearings.<sup>13</sup> Whatever advantage could have been afforded by expedited review was obviated by this failure. The fact that studies could not commence at any trial site until the MREC received all LREC reports meant that the efforts of LRECs that previously had timely review processes were lost to the reporting times of the slowest REB in the nation.

The U.K. system did not engender the respect of either researchers or ethics committees. Clearly, many of the LRECs did not trust the MRECs to provide adequate protection of trial subjects. The LRECs continued to conduct full reviews of protocols and to act

on basic ethical issues, despite government policy to the contrary.

This issue of trust among human research ethics committees is a salient one. In Canada, Beagan<sup>14</sup> cited the same issue in her report of interviews with REB members. Many REB members believed that a centralized system of review for multi-centre clinical trials would have value, but are concerned that another REB might not protect subjects under their jurisdiction as well as they would. Beagan and McDonald<sup>15</sup> revisited these interviews, and concluded that,

There is significant agreement across sites about the fundamental principles and standards of research ethics, and about substantive ethical issues. It appears, however, that when members of one REB do not know *how* another REB arrives at its decisions, whether a protocol is subjected to the same level of scrutiny, they have no evidence upon which to base trust in other REBs.

In fact, no evidence has been offered, one way or the other, about the effectiveness of the U.K. system in doing what it is supposed to do – protect human research subjects. For example, did the MRECs bring greater expert opinion to bear on safety issues? Were more perspicacious ethicists



working on the MRECs (on average) than on the LRECs? Did informed consent materials become more understandable to prospective subjects? We do not know. We do note, however, that criticisms of the efficiency of the system led to contemporary policy changes in the U.K., changes which Cave and Holm (2002) believe subjugated the interests and welfare of subjects to that of industry sponsors and their researchers. Those changes, now nullified, were designed only to reduce paperwork inefficiencies. We will return to the U.K. model, which was dramatically altered in late 2004, in a later section of this paper.

### **U.S. National Cancer Institute (NCI) Central Institutional Review Board (CIRB)**

At the beginning of 2001, the U.S. National Cancer Institute (NCI)<sup>16</sup> and Office for Human Research Protections (OHRP) jointly implemented a voluntary centralized review process for NCI-funded clinical trials. Each NCI trial is first submitted to the Central Institutional Review Board (CIRB) for review. Once the CIRB has granted final approval to an application, local investigators who wish to enroll subjects in the study then obtain the protocol, informed consent documents, and the CIRB application from the NCI website and submit these materials to their local IRBs, if the local IRB has agreed voluntarily to participate in the program. Each local IRB may designate one or more voting members to conduct a “facilitated review”, i.e., an expedited review, of the protocol based on the CIRB’s review and approval. Designates decide whether to accept the CIRB reviews, or to require full local board reviews. If they send the protocol to full local review, the local IRB has effectively withdrawn from the central review system for that protocol. If the local designate elects to accept the CIRB approval, the local IRB may add stipulations or local requirements to protocols, but may not contradict any substantive protocol requirements.

In summary, the NCI CIRB system is very much like the 1997-2004 U.K. centralized structure. The main differences are that it is voluntary and that its jurisdiction is limited to cancer-related clinical trials. It would not be surprising if some of the same criticisms of the U.K. system were directed against the NCI program. Some researchers do in fact complain that having to wait for CIRB approval has led to longer start-up times for trials than when only their local IRB was responsible for ethics review.<sup>17</sup> And there are concerns that the multi-layered process will eventually cause purposeless delays merely because the system is more complex than the typical local IRB regime.<sup>18</sup> Importantly from our perspective, one writer wonders whether local IRBs will

be sufficiently trusting of the CIRB to fully implement the facilitated review process.<sup>19</sup> In other words, there is concern that the reality of U.K. system could become that of the CIRB system. Adding to these potential problems is the unknown effect on local institutional liability of accepting CIRB decisions.<sup>20</sup>

### **Ontario Cancer Research Ethics Board (OCREB) Pilot Program**

In May of 2000, the Tri-Council Panel on Research Ethics modified the effect of TCPS Article 1.2 by the following addition to the commentary that accompanies the Article:

Each institution is accountable for the research carried out in its own jurisdiction or under its auspices. An institution can authorize its REB(s) to accept the review of other REBs constituted under the Tri-Council Policy Statement if it so wishes. This might involve specific agreements between institutions for sharing the work.<sup>21</sup>

This revision, though lacking in important details and direction, permitted a number of experiments with local and regional centralized systems. The OCREB system is one, and we later discuss other examples from Alberta and Québec.

The OCREB pilot program began in late 2003. Similar to the NCI CIRB system, local institution REBs in Ontario can choose to use the OCREB central review decisions for an expedited review process. In such cases, the OCREB review is a recommendation, and local REBs may substitute any changes to the protocol and consent materials, or conditions for approval, that they wish. Alternatively, on a case-by-case or general basis, local REBs may completely delegate ethics review responsibility to the OCREB, which then acts as the REB-of-Record. The OCREB decision in such cases is apparently binding, and local REBs may not require changes to the protocol or consent materials.

The OCREB project has been in effect for only a short time, and it is not currently possible to evaluate reactions to it by researchers and REBs. However, the OCREB system does seem to avoid most of the problems we have identified with the U.K. and NCI systems. For instance, the possibility of complete delegation by local REBs to the OCREB introduces a potential for increased efficiency. Heslegrave and Stacey<sup>22</sup> report that between January and August 2004 sev-



eral institutions had adopted OCREB as their REB-of-Record for cancer trials. The effects of this centralized system on protection of research subjects are understandably unknown at this time. There currently does not exist in Canada a general governance or accreditation system by which the quality of human protections can be assessed. But the fact that subject protections have a central place in the goals and guiding principles of the OCREB system bodes well.

### **The University of Alberta, Capital Health region, and Caritas Hospitals Group Affiliation Agreement**

In 1997, the University of Alberta, the Alberta Capital Health Regional Authority and the Caritas Health Group which is sponsored by the Alberta Catholic Health Corporation, agreed to end redundant ethics reviews of biomedical and social science health researchers affiliated with their sites. Most University of Alberta Faculty of Medicine and Dentistry faculty members also work at Capital Health or Caritas hospitals. These multiple affiliations led to ethics review by several REBs for the same protocols because each hospital and the University were diligently attempting to meet their autonomous obligations under the TCPS for the ethical acceptability of research conducted under their auspices. The three institutions decided that these repeated reviews did not enhance the protection of human subjects. To solve this perceived problem of unproductive redundancy, a joint Health Research Ethics Board (HREB) was formed that is contractually enabled to act for all three institutions. Membership is drawn from all three of the institutions, and the HREB reports to each institution through a joint oversight body in addition to the individual administrative structures of the institutions.

This arrangement has operated for many years, with demonstrable enhancement of efficiencies. For example, because virtually all University of Alberta researchers hold appointments at one or more Capital Health or Caritas hospitals, multiple reviewing for those researchers was completely eliminated. We believe that the system provides for

enhanced protections of research subjects as well, owing largely to the combined pool of expert scientific members and specialists in ethics and in law that resulted from the affiliation of the three institutions. We believe that an important ingredient in this apparent success is the relative ease in which trust among the institutions was accomplished. The institutions already had effective affiliation agreements in place regarding other research matters, and before the introduction of the TCPS often informally accepted the results of each others' research ethics panels.<sup>23</sup>

Questions of liability and insurance were resolved through the affiliation agreement. A quality assurance and improvement program is in preparation with which to evaluate and promote the effectiveness (i.e. human subjects protects and efficiency) of this arrangement.

### **McGill University Faculty of Medicine and McGill Affiliated Hospitals**

The McGill University Faculty of Medicine and its Affiliated Hospitals have signed mutual REB Authorization Agreements that give legal force to a centralized system of review. When more than one Hospital joins the same clinical trial, the

McGill Faculty of Medicine REB conducts a binding review for all sites. When a McGill faculty member or trainee is involved in a trial at one of the Hospitals, the Hospital REB conducts a binding review for the Hospital and for McGill University Faculty of Medicine. As well, each Hospital REB may conduct a binding review for all of the Hospitals. The system contains no formal provision for local re-review once the first review is completed, although REB chairs may communicate to resolve differences of opinion on an informal basis.

The McGill system is very similar in intent to the University of Alberta-Capital Health-Caritas model. It relies on a binding agreement among the institutions, and requires a level of trust that obviates the need for local re-review. From the perspective of its administrators, the McGill system works well, and a quality assurance and improvement program has been developed.<sup>24</sup>

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## **Alberta Province-Wide Reciprocal Approval Process**

Another approach to central review is in progress in Alberta. The four primary Research Ethics Boards in the Province<sup>25</sup> committed themselves to forging a reciprocity agreement whereby a protocol approved by one REB would be subject to expedited review by the others. On surface, the system is similar to the McGill model, but has not been fully implemented. One institution has not joined the agreement because its risk managers and insurers do not believe the affiliation agreement is sufficiently strong for the institution to accept the consequences of errors at the other institutions.

### **General Assessment**

Central REBs have been proposed and implemented to accomplish two very different sets of goals. On the one hand, it has been argued that central review boards can permit a greater concentration of expertise to be brought to bear on proposed clinical trials, with the effect being greater protection of potential subjects. On the other hand, researchers, research institutions and industry sponsors look to centralized review as a means of reducing costly redundancies in the human protections system.

We have discussed a variety of models, some of which are well-established and some of which are nascent. Little direct evidence exists with which to evaluate how well the systems protect human subjects, beyond the intuitive conclusion that affiliations among institutions can result in a larger pool of experience and expertise than that available to any one institution, on average, on its own. We are reasonably confident that any success that may exist in this regard for central REB systems is grounded on trust among institutions and REBs that they will each do the right thing where research subject safety, dignity, and rights are concerned (again, see Beagan & McDonald). We are also convinced that when institutions are geographically dispersed, as in the case of the Alberta Province-Wide system, trust is difficult to forge without a rational system to ensure that trust is well-placed. The quality improvement and accreditation system proposed by the National Council on Ethics in Human Research<sup>26</sup> could provide this assurance, but at this writing has not as yet been accepted by stakeholders.

It is easier to estimate the success of centralized systems on costs and efficiency. The original U.K. system seems to have faltered in large measure because of its use of a serial review process in which local REBs became responsible for subject welfare after centralized review was completed.

Many local REBs appeared to have been unwilling to cede authority to the central REB over protocol and consent issues, and the entire system ended with greater redundancy than that with which it began. In October 2004, the U.K. Central Office for Research Ethics Committees (COREC) announced the end of local REB review for multi-site trials.

The apparently healthy centralized systems in fact seem to have avoided combining central and local review authorities. The University of Alberta and regional hospitals did so by establishing a joint REB for the institutions. The McGill University and Affiliated Hospitals unconditionally accept each others' REB decisions. The Ontario Cancer Research Ethics Board appears to be thriving through its REB-of-Record delegation provision. We believe that a successful national system of review for multi-centre trials must be based on the elements of success that have already emerged. The system must avoid serial review processes while engendering trust by local institutional authorities and REBs. To do so, the system must obviously demonstrate competency to consider the multiplicity of local site concerns as well as competency to review protocols and protect prospective subjects. To ensure the confidence of local institutions to rely on the decisions of a centralized board, a system of quality improvement and accreditation must be considered. The system must also respect, and likely incorporate, existing provincial and regional models that work. Forthcoming from these writers is a proposal for such a system.

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1. Tri-Council, *Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (with updates of May 200 and September 2002)* (Ottawa: Tri-Council, 1998), online: <[http://www.pre.ethics.gc.ca/english/pdf/TCPS%20June2003\\_E.pdf](http://www.pre.ethics.gc.ca/english/pdf/TCPS%20June2003_E.pdf)>.
2. *TCPS*, Article 1.2: "The institution in which research involving human subjects is carried out shall mandate the REB to approve, reject, propose modifications to, or terminate any proposed or ongoing research involving human subjects which is conducted within, or by members of, the institution, using the considerations set forth in this Policy as the minimum standard."



3. T. Ferris discusses how confidentiality concerns and policies make certain inconsistencies among REBs difficult to resolve. T. Ferris, "Industry-sponsored pharmaceutical trials and research ethics boards: Are they cloaked in too much secrecy?" (2002) 166 Canadian Medical Association Journal 1279.
4. *Ibid.*
5. Michael E. Enzle & Rodney Schmaltz, "National Human Ethics Review and Stem Cell Research" presented at the *Symposium on Bill C-56: The Assisted Human Reproduction Act* (University of Alberta, September 21, 2002).
6. *Supra* note 2, commentary to Article 1.9.
7. See Health Canada, *Towards a National System of Oversight for the Governance of Research Involving Humans* (Ottawa: Health Policy and Communications Branch, 2002).
8. See, for example, Health Canada's Health Policy Division, online: <<http://www.hc-sc.gc.ca/english/about/org.html#hpb>>.
9. Canadian Institutes of Health Research, "Virtual Scholar: A need to amend multi-centered research ethics review under the TCPS?", online: CISH <[http://www.pre.ethics.gc.ca/english/publicparticipation/applicationsandproposals/requestforproposals\\_26\\_05\\_04\\_B.cfm](http://www.pre.ethics.gc.ca/english/publicparticipation/applicationsandproposals/requestforproposals_26_05_04_B.cfm)>
10. T. Smith, *Ethics in Biomedical Research*, (Cambridge: Cambridge University Press, 1999) at 12-49.
11. See N. Dunn, A. Arscott & R. Mann "Costs of Seeking Ethics Approval Before and After the Introduction of Multicentre Research Ethics Committees" (2000) 93 *Journal of the Royal Society of Medicine* 511; I. Larcombe & M. Mott, "Multicentre Research Ethics Committees: Have They Helped?" (1999) 92 *Journal of the Royal Society of Medicine* 500; N. Maskell, E. Jones & R. Davies, "Variations in Experience in Obtaining Local Ethical Approval for Participation in a Multicentre Study" (2003) 96 *QJM: An International Journal of Medicine* 305.
12. See I. Larcombe and M. Mott, *ibid*; see also J. Tully, *et al.*, "The New System of Review by Multicentre Research Ethics Committees: Prospective Study" (2000) 320 *British Medical Journal* 1179-1182.
13. See N. Maskell, E. Jones and R. Davies, *supra* note 11; See also Tully, *ibid*.
14. Michael McDonald *et al.*, "The Governance of Research Involving Human Subjects" (Ottawa: Law Commission of Canada, 2000) at 11.
15. Brenda Beagan & Michael McDonald, "Evidence-based Practice of Research Ethics Review?" School of Occupational Therapy, Dalhousie University, 2005.
16. National Cancer Institute, online: <<http://www.nci.nih.gov/>>.
17. J. Randal, "Growing Pains: Central Review Board Project Still Developing" (2003) 95 *Journal of the National Cancer Institute* 636.
18. See E. Emanuel *et al.*, "Oversight of Human Participants Research: Identifying Problems To Evaluate Reform Proposals" (2004) 141 *Annals of Internal Medicine* 282.
19. M. Christian *et al.*, "A Central Institutional Review Board for Multi-Institutional Trials" (2002) 346 *New England Journal of Medicine* 1405.
20. Rebecca Pentz, "The Future of Institutional Review Boards: Centralized IRBs" (2004) 4 *The Lancet Oncology* 325 at 327.
21. Tri-Council Panel on Research Ethics, online: <<http://www.pre.ethics.gc.ca/english/policystatement/addenda02.cfm>>.
22. R. Heslegrave & S. Stacey, "Investigators Using OCREB for Ethics Review" (2004) 5 *OCREB Newsletter* (<[http://www.ocrn.on.ca/ocreb\\_newsletters.htm](http://www.ocrn.on.ca/ocreb_newsletters.htm)>).
23. This trust may have been promoted as well by geographical proximity of the institutions, and by the fact that many researchers are affiliated with both institutions.
24. Personal interview with D. Cournoyer, 6 November 2004
25. The four boards are the University of Alberta Health Research Ethics Board (including the Capital Health Region); the University of Calgary Conjoint Health Research Ethics Board (including the Calgary Health Region); the Alberta Cancer Board Research Ethics Board; and the Alberta College of Physicians and Surgeons Research Ethics Board.
26. National Council of Ethics in Human Research, online: <<http://www.ncehr-cnerh.org>>.

