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VARIATION IN ETHICS REVIEW OF MULTI-SITE RESEARCH INITIATIVES[+]

Timothy Caulfield, Nola Ries** and Graham Barr****

Introduction

The factors that affect health status and the development of disease are complex and multi-factorial. Understanding the causes, treatment and prevention of disease requires methods that allow the exploration of a wide range of variables. As a result, there is a trend in the health research community toward large, multi-site interdisciplinary research projects – such as longitudinal cohort studies that include the collection of personal information and, increasingly, biological samples, from participants. This type of multi-site research raises numerous ethical and legal issues, including a need for a research ethics board (REB) review at multiple institutions and a need to understand and comply with applicable legislation in each jurisdiction.[1] The collection, long-term retention, and use of personal information and biological samples raise concerns about consent for continuing use of information and samples and the need for robust data/sample handling and security protocols.

Over the last 20 years there has been a nine-fold increase in the number of multi-site studies, as compared to the one and one half increase in single site studies.[2] REBs were created during a time when there was a particular focus on studies at single institutions. The rise of multi-site studies has heightened the policy significance of REB variability and the inconsistency of REB decisions.[3] While it has been noted that REB variation can be a useful way to surface the range of ethical issues that can be associated with complex studies,[4] there seems to exist a consensus in the literature that unjustifiable variation should be minimised because it allows for uneven protection of research participants, can result in a lack of scientific validity, and is inefficient and costly.[5]

[+] *This work was supported by AllerGen NCE Inc. (the Allergy, Genes and Environment Network), a member of the Networks of Centres of Excellence Canada program and guided in part by members of the AllerGen staff and participants from the December 17th, 2009 AllerGen workshop centred on research ethics challenges. We would also like to acknowledge the support of the Interdisciplinary Chronic Disease Collaboration (ICDC) – Improving the Efficient and Equitable Care of Patients with Chronic Medical Conditions, funded by the Alberta Heritage Foundation for Medical Research Team Grant. And finally we would like to thank the staff of the Health Law Institute at the University of Alberta for their input and support.*
** Timothy Caulfield, LL.M., F.R.S.C., is a Professor in the Faculty of Law and the School of Public Health, Canada Research Chair in Health Law and Policy and Research Director of the Health Law Institute at the University of Alberta.*
*** Nola M. Ries, B.A. (Hons.), LL.B., M.P.A., LL.M., is a Research Associate with the HLI and an Adjunct Assistant Professor at the University of Victoria.*
**** Graham Barr, B.A., LL.B. (Hons.), LL.M., is a Research Associate with the HLI.*

[1] For consistency, the term 'Research Ethics Board' (REB) is used throughout this paper and is understood to encompass alternate terms such as 'institutional review board' or 'research ethics committee'.

[2] R. McWilliams, J. Hoover-Fong, A. Hamosh, *et al*., 'Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study', *JAMA* 2003-3, pp. 360–366.

[3] H. Silverman, S. Hull & J. Sugarman, 'Variability among Institutional Review Boards' Decisions within the context of a Multicenter Trial', *Crit Care Med* 2001-2, pp. 235–241.

[4] M. Michael & R. Schmaltz, 'Ethics Review of Multi-Site Clinical Trials in Canada', *Health Law Rev* 2005-2/3, pp. 13-57.

[5] D.J. Willison, *et al.*, 'Access to Medical Records for Research Purposes: Varying Perceptions across Research Ethics Boards', *J Med Ethics* 2008-4, pp. 308-314; S.M. Greene & A.M. Geiger, 'A Review Rinds That Multicenter Studies Face Substantial Challenges But Strategies Exist to Achieve Institutional Review Board Approval', *J Clin Epidemiol* 2006-8, pp. 784-790; C.D.

In this commentary, we focus on the issue of REB variability. Indeed, variation in ethics review across multiple REBs appears to be the rule rather than the exception.[6] Studies from around the world have found substantial variation across REBs, and even among members on the same REB, when reviewing the same protocol. The studies summarised in Table 1 indicate that this variation can occur across several dimensions, including how REBs assess consent processes and documents and how they apply the concept of minimal risk. In addition to variation in the results of the review, the length of time required for review of studies varies substantially. The growth in the number of privacy laws may also contribute to variability in ethics review. The majority of REB members do not have legal training. As such, attempts to understand and comply with legislative requirements may contribute to variability as each committee may interpret the laws in a slightly different manner. Each of these topics is discussed in more detail below. The overall goal of the paper is to draw together existing literature – including relevant empirical studies – to examine the issue of REB variation and identify emerging policy reform themes. Some specific examples are drawn from the Canadian context to offer points of comparison for international readers.

I. Variability in REB Review

REBs review ethical aspects of research involving human participants, considering matters such as voluntary and informed consent, inclusion in research, privacy, and conflicts of interest. The REB has authority to set terms and conditions of the research and require changes to the protocol, such as requesting an alteration in the proposed consent process. One of the most significant challenges for multi-site studies is the need to obtain REB approval from multiple institutions. This process can require significant time and resources, particularly when the review process is not uniform, for example, where different committees ask for different approaches to consent.

While the studies in Table 1 are from a wide range of jurisdictions, the data remains broadly relevant as the reasons for variation appear relatively common to all REBs, regardless of jurisdiction. First, "[t]he very existence of ethics review by committees, which are made up of people with different backgrounds, expertise, and values, may explain and even justify some differences in REC [research ethics committee] values."[7] Further, "[v]ariability among IRBs [institutional review boards] regarding their approved research practices can be expected, because IRBs are given discretion in interpreting and applying these regulations."[8] Variation may also be a result of ambiguity in research ethics guidelines and the need for REB members to interpret how to apply principles and general rules to particular protocols. As an illustration of this point, the Canadian Tri-Council

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Newgard, S.H. Hui, P. Stamps-White & R.J. Lewis, 'Institutional Variability in a Minimal Risk, Population-Based Study: Recognizing Policy Barriers to Health Services Research', *Health Serv Res* 2005-4, pp. 1247-1258; L.A. Green, J.C. Lowery, C.P. Kowalski & L. Wyszewianski, 'Impact of Institutional Review Board Practice Variation on Observational Health Services Research', *Health Serv Res* 2006-1, pp. 214-230; J.L. Gold & C.S. Dewa, 'Institutional Review Boards and Multi-site Studies in Health Services Research: Is There a Better Way?', *Health Serv Res* 2005-1, pp. 291-307.

[6] P. Glasziou, 'Ethics Review Roulette: What Can We Learn? That Ethics Review has Costs and One Size Doesn't Fit All', *BMJ* 2004, 328, pp. 21-122.

[7] S.J.L. Edwards, T. Stone, T. Swift, 'Differences Between Research Ethics Committees', *Int Soc Technol Assess Health Care* 2007-1, pp. 17-23.

[8] Silverman *et al.* 2001, *supra* note 3, pp. 235-241.

Policy Statement on the Ethical Conduct of Research involving Humans (TCPS) points out that:

> Often, more than one principle will apply to a specific case. This is due in part to the diversity of research and in part to the range of fundamental values upon which the research ethics enterprise is founded. If the application of principles yields conflicts, then such conflicts properly demand probing ethical reflection and difficult value choices. Such choices and conflicts are inherent in the ethics review process.[9]

I.1 Consent

One of the greatest challenges in research ethics is the issue of informed consent. As a general principle common to many research ethics guidelines, potential participants (who have mental capacity) must make a voluntary and informed decision to participate in research. This requires that researchers provide a full explanation of the research purpose, along with reasonably predictable risks and potential benefits of participation. Some policies permit REBs to approve a departure from this consent standard where specified criteria are satisfied; for example, that the research involves no more than minimal risk, that it could not practicably be conducted if specific, informed consent were required, and that the research does not involve a therapeutic intervention.

With the growth of longitudinal, multi-site research initiatives, an alternative approach to consent has been proposed. This approach involves continuing use of information and samples on the basis of a more general broad or open consent,[10] which does not specify in detail the future research that may incorporate the research participant's data. Researchers seek permission to depart from a standard of needing specific, informed consent from each participant for each use of their information and biological samples for the practical reason that this standard can be impossible or infeasible to meet over a long-term project. REBs vary in their requirements for consent and their views on the acceptability of deviating from the standard of specific, informed consent for each use of data and samples (see Table 1).

I.2 Minimal risk

Of critical importance to research ethics review is the REB's assessment of the degree of harm or risk associated with a research proposal. Table 1 shows that there is often wide variation among REBs in categorising the level of risk. This variation is not surprising where the definition of 'minimal risk' in ethics guidelines are stated in imprecise terms that necessitate exercise of subjective judgment.[11] Removing subjectivity in risk assessment exercises is an unattainable goal, but striving to reduce the breadth of variation is a feasible objective.

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[9] *Tri-Council Policy Statement. Ethical Conduct for Research Involving Humans.* 90 Ottawa, ON: Medical Research Council of Canada Natural Sciences and Engineering Research Council of Canada Social Sciences and Humanities Research Council of Canada 2003. Section G, p. i.9.

[10] T. Caulfield, J. Kaye, 'Broad Consent in Biobanking: Reflections on Seemingly Insurmountable Dilemmas', *Med Law Int* 2009, 10, pp. 85-100.

[11] According to the TCPS, for example, research involves minimal risk if the participants "can reasonably be expected to regard the probability and magnitude of possible harms implied by participation in the research to be no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research." See Tri-Council Policy Statement 2003, *supra* note 13, section C1, p. 1.5.

I.3 Compliance with legislative requirements

Researchers and REBs alike must be aware of and comply with applicable legislation and different interpretations of statutory requirements may also lead to REB variation across jurisdictions. In general, prospective studies that seek to collect information from individuals with their consent for a specific research purpose will accord with privacy laws. Broader consent that purports to authorise unspecified future uses of identifiable information, however, may fall outside the letter – and spirit – of privacy laws. Once personal information is in the hands of researchers, they should be aware of legislative requirements for secure retention of information and limits on further use or disclosure without participant consent.

Many privacy laws, such as those in Canada (see Table 2), have specific rules governing disclosure of personal information for research purposes. For example, researchers who seek access to identifiable information held by a government body must meet specific criteria before that body is legally permitted to release the information without obtaining consent of the individual about whom the information relates. These criteria typically include requirements to obtain approval from an REB or privacy commissioner, limit use of information to specific purposes, and ensure secure storage of data.

We are unaware of any Canadian studies that examine REBs' perceptions and knowledge of privacy legislation and its application to research involving human participants, though recent research has examined views of health professionals, health researchers and data custodians.[12] A 2008 study by Willison et al. found wide variability among Canadian REBs in consent requirements for secondary use of medical records for research. While this study did not focus specifically on REB members' understanding of privacy legislation, the authors suggest that their "findings may also reflect an initial cautious response to new legislation."[13] Research on REB knowledge and application of privacy laws would be useful, particularly to understand the extent to which variation in REB requirements for consent processes and access to and use of information, driven by compliance with legislation, introduces another source of REB variation across jurisdictions.

II. Addressing REB Variability

What strategies may be useful in addressing variability in REB review and decisions about research protocols? Section A in Table 3 summarises potential reform strategies identified in recent literature, including calls for better training, harmonisation initiatives (such as development of standardised REB application forms), earlier involvement of REBs to provide guidance at design stages of complex, multi-site studies, and delegated review to specialised boards. Centralisation of REB review is a specific reform proposal discussed in studies noted in Section B of Table 3.

Some organisations in Canada are exploring new approaches to research ethics review. In the province of Ontario, the creation of the Ontario Cancer Research Ethics Board (OCREB) - a disease specific review panel that mimics the National Cancer Institute Central IRB (NCI CIRB) in the United States - provides an example of how expertise and resources can be harnessed to provide quality and efficiency to the REB process.[14] In the province of

[12] R. Saginur, S.F. Dent, L. Schwartz, R. Heslegrave, S. Stacey, J. Manzo, 'Ontario Cancer Research Ethics Board: Lessons Learned From Developing a Multicenter Regional Institutional Review Board', *J Clin Oncol* 2008-9, pp. 1479-1782.
[13] Willison *et al.* 2008, *supra* note 5, p. 312.
[14] Saginur *et al.* 2008, *supra* note 16, pp. 1479-1782.

British Columbia, the work of the Michael Smith Foundation for Health Research on the British Columbia Ethics Harmonisation Initiative (BCEHI) calls for the creation of a hybrid ethics review system consisting of reciprocity, common tools/processes and collaboration in order to improve quality, access, efficiency, capacity and consistency.[15] A 2009 draft revision to the national ethics policy statement proposes new guidance on multi-jurisdictional review that permits alternate models for ethics review. For example, one or more institutions may enter written agreements that permit delegated or reciprocal ethics review processes.

A modest, and immediately applicable, approach to improving the REB process is to encourage researchers to engage with REBs (or REB chairs) early in the review process. Our analysis of relevant literature found numerous studies that identified collaborative dialogue with REBs as one of the most effective and efficient means of ensuring efficient reviews.[16] For example, Gilbert et al. conclude that "[i]nstead of viewing IRBs [REBs] and institutional administrators as potentially adversarial, customised solutions can be identified by engaging them in collegial discussions that identify common ground within regulatory bounds".[17] Although time consuming, an upfront effort by the research team to the review process will, in the long term, benefit all by helping to ensure an efficient and effective review process that protects the interests of the research participants.

Harmonisation, delegation and centralisation may also be impeded by legal liability risks of REBs and research institutions. The accountability (and, to a large degree, the legal liability) for research ethics decisions remains with institutions and their REBs.[18] This reality can make the delegation, centralisation or harmonisation of the process more difficult. For example, REB 'A' may wish to simplify the review process for a particular multi-site protocol by accepting reviews by REB 'B'. But regardless of the nature of the agreement between 'A' and 'B', REB 'A' remains ultimately accountable (and liable) for the decision they produce. As a result, REB 'A' may feel compelled to do its own de novo review, thus ensuring it is satisfied the research ethics standards have been met (or, at least, an appropriate review process has been completed). Indemnity agreements, where one institution agrees to protect another against legal claims seeking compensation, might moderate liability concerns.

In the Canadian province of Newfoundland and Labrador, the development of new provincial legislation is aimed at overcoming this issue and establishing a legal framework that centralises review.[19] While this is an interesting model, it is not clear whether it could be adopted in other regions with larger biomedical research communities. Also, for multi-site projects that span more than one jurisdiction, approval from multiple REBs remains

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[15] *B.C. Ethics Harmonization Initiative Introductory Workshop. Report on Proceedings.* Vancouver, BC: Michael Smith Foundation for Health Research 2008.

[16] See J. Blustein, M. Regenstein, B. Siegel, J. Billings, 'Notes From the Field: Jumpstarting the IRB Approval Process in Multicenter Studies', *Health Serv Res* 2007-4, pp. 1773-82; Green *et al.* 2006, *supra* note 8; Greene & Geiger 2006, *supra* note 6; E. Chaney, L.G. Rabuck, J. Uman, D.C. Mittman, C. Simons, B.F. Simon, M. Ritchie, M. Cody, L.V. Rubenstein, 'Human Subjects Protection Issues in QUERI Implementation Research: QUERI Series', *Implement Sci* 2008, 3, p. 10.

[17] G.H. Gilbert, V. Qvist, S.D. Moore, D.B. Rindal, J.L. Fellows, V.V. Gordan, O.D. Williams, 'For the DPBRN Collaborative Group. Institutional Review Board and Regulatory Solutions in The Dental PBRN', *J Public Health Dent* 2010-1, p. 19.

[18] L.E. Hutt, 'Protecting the Protectors: Indemnification Agreements for REB Members', *CMAJ* 2006-10, p. 1229.

[19] Health Research Ethics Authority Act, S.N.L. 2006, c. H-1.2.

necessary. Researchers, institutions and REBs may also wish to develop collaborative relationships that increase the efficiency of the review process.

Conclusion

Numerous studies have identified variation in REB review in multi-site studies as a problem that requires attention. Some degree of variation is expected and the process of review by multiple boards can be beneficial to the extent that more than one review process can help fully identify and address ethical concerns. Indeed, the fundamental purpose of ethics review is to provide oversight to ensure the ethical conduct of research. While facilitation of research cannot take priority over the ethical conduct of research, the two goals are not necessarily mutually exclusive. The newly updated Canadian national research ethics policy states: "This Policy aims to strike an appropriate balance between recognition of the potential benefits of research, and protection of participants from research-related harms" and speaks directly to the need for "reducing unnecessary impediments to, and facilitating the progress of, ethical research."[20]

Variations in REB review create unnecessary delays and may compromise the comparability of results across sites when different REBs require modifications to a protocol. This has the effect of altering the original research objective of replicating the same study across multiple sites. Researchers leading long-term, multi-site initiatives should be prepared to work with REBs early in the process to develop strategies that minimise variability, such as agreements to use a common submission process and identification of core elements of the protocol that, for optimal scientific validity, should be consistent across all the jurisdictions. Harmonisation and centralisation of review are longer-term strategies worth pursuing and study of existing centralised review bodies can provide instructive lessons. Further training for REB members and measures for recruitment and retention of experienced members are also important strategies for enhancing ethics review and reducing variability in time taken to review protocols.

[20] Second Edition of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2), Ottawa, ON: Interagency Secretariat on Research Ethics, 2010, p. 11.

Appendix 1

Table 1: Studies Relevant to Variability in Multi-Site Ethics Review		
Author	Nature of Study	Findings
SECTION A: CONSENT		
Willison et al. (2008) *J Med Ethics*	To study variation in REB consent requirements for retrospective chart review and who has access to the medical record for data abstraction.	Large variation was found for consent for research involving access to medical records. 14 sites (47%) required individual patient consent. 11 sites (38%) did not require consent. 16 (53%) allowed external extraction.
Burman et al. (2003) *Contr Clin Trials*	To evaluate the effects of the local review process at 25 study sites on the consent forms from two studies with a multicentre trials group.	A median of 46.5 changes (range 3–160) were made in the centrally approved forms. Errors were commonly introduced (11.2%of changes), and 33 of 50 (66%) locally approved consent forms had at least one error.
White & Gamm (2002) *Account Res*	To determine whether IRBs vary in their informed consent requirements.	Results indicate that IRB practices vary substantially.
Silverman et al. (2001) *Crit Care Med*	To determine the extent of the variability among different IRBs on informed consent forms within the context of a multicenter trial.	Within a multicenter trial, IRBs varied in several of their approved research practices and in the extent to which the basic elements of informed consent were included in their consent forms.
Mammel & Kaplan (1995) *J Adolesc Health*	A national survey of IRBs was conducted to determine the current practices of IRBs concerning consent for adolescent minors.	There is a broad spectrum of interpretation. 70% of IRBs required parental consent for all research on minors, and IRBs reviewing more than 10 adolescent protocols per year were less likely to require parental consent.
SECTION B: VARIABILITY REGARDING ASSESSMENT OF 'MINIMAL RISK'		
Mansbach et al. (2007) *Acad Emerg Med*	To investigate the variability of IRB responses to a multicenter observational study of children presenting to emergency departments.	Substantial variation in IRB assessment of a standard protocol was present in this study. Ninety-one percent of IRBs considered the protocol to be minimal risk.
Sherwood et al. (2006) *Otolaryngol Head Neck Surg*	To describe the process of obtaining regulatory approval for a minimal risk genetic study in a multi-center setting.	Institutions varied considerably in their requirements and in the issues that were raised. Despite uniform federal standards, all local IRBs required unique and individualised submissions.
Lenk et al. (2004)	To examine whether there was certainty in	Risks deemed to be clearly higher than "minimal" caused

J Med Ethics	German REC's determinations of minimal risk.	chairpersons of German RECs to differ widely on their decisions.
Shah et al. (2004) *JAMA*	To determine how IRB chairpersons apply the federal risk and benefit categories for pediatric research.	Application of the federal risk and benefit categories for pediatric research by IRB chairpersons is variable and contradicted by the available data on risks and the regulations themselves.
McWilliams et al. (2003) *JAMA*	To document the burden imposed by review of multicenter studies and to determine the variability among local institutional review boards (IRBs) in the approval of a multicenter genetic epidemiology study.	Review of a protocol for a multicenter genetic epidemiology study by local IRBs was highly variable. Evaluation of risk by 31 IRBs resulted in 7 expedited reviews (23%) and 24 full reviews (77%). 15 IRBs (48%) required 2 or more consents.
Rogers et al. (1999) *IRB*	To examine the practices of 11 different IRBs reviewing one common study protocol recruiting minor adolescents.	The review experience of this multicenter study demonstrates that the definition of minimal risk research by local IRBs is variable and not always consistent with the regulations.
SECTION C: TIME TAKEN TO REVIEW PROTOCOL		
Ezzat et al. (2010) *BMC Health Serv Res*	The applications forms of 16 different REBs were abstracted for a list of standardised items. The application process across sites was compared. Correspondence between the REB and the investigators was documented in order to: construct a timeline to approval, identify the specific issues raised by each board, and describe how they were resolved.	Overall, it took a median [range] of 42 days [4-443] to receive final REB approval. When CPN ?? underwent expedited review (n = 9), the median time to approval was 33 days [8-239]. When local hospital approval was given separately from REB approval, the additional median time to approval was 32 days [4-197]. Ten REBs had no issues with the proposal: their median time to approval was 33 days [8-251]. For the site which required 251 days to receive approval despite no ethical concerns, REB approval took 54 days, but then local hospital approval took a further 197 days. Six REBs requested more information: their median time to approval was 178 days [55-443].
Dyrbye et al. (2007) *Acad Med*	To compare how different IRBs process and evaluate the same multi-institutional educational research proposal.	The findings suggest variability in the timeliness and consistency of IRB review. Review by IRB administrator/IRB member (range 1–101 days) by IRB committee (range 6–115 days).
Mansbach et al.	To investigate the variability of IRB	Substantial variation in IRB assessment of a standard

(2007) *Acad Emerg Med*	responses to a multicenter observational study of children presenting to emergency departments.	protocol was present in this study. IRBs returned initial applications in a median of 19 days (IQR, 11–34 d). Of n=34, 13 = no changes, 18 = conditional approval, and 3 were deferred. Initial submission to final approval had a median 42 days (IQR, 27–61 d).
Dziak et al. (2005) *Health Serv Res*	To document the IRB review process and to explore the impact of different patient notification procedures.	IRBs at 15 sites varied in days from submission to approval (5–172). 4 sites required patient notification in advance of the study; 2–11% of patients refused in opt-out sites and 37 percent in the single opt-in site.
Larson et el. (2004) *J Nurs Scholarsh*	To compare IRB processes in 68 U.S. hospitals for the same multicenter study.	Current IRB review time varies widely. Time from submission to approval averaged 45.4 days (range, 1-303 days), and the majority of reviews were "expedited" (61.8%). Expedited reviews required more time (m= 54.8 days) than did exempt (m=10.8 days) or full (m= 47.1 days) reviews.
al-Shahi & Warlow (1999) *J R Coll Physicians Lond*	To assess the practices of local research ethics committees (LRECs) in their review of a multicentre study approved in Scotland.	The median delay to review an application at an LREC meeting was 28 days (range 14-97), the median delay from application to the time of LREC final approval was 39 days (range 21-109) and a total of 5,789 A4 pages (26.9 kg) were required to complete the application process.

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Appendix 2

Table 2: Legislation governing collection, use and disclosure of personal information in Canada

	Information & privacy legislation (public and private sector)	Health information legislation	Other privacy statutes
Yukon	Access to Information and Protection of Privacy Act, R.S.Y. 2002, c. 1		

British Columbia	Freedom of Information and Protection of Privacy Act, R.S.B.C. 1996, c. 165 Personal Information Protection Act, S.B.C. 2003, c. 63	E-Health (Personal Health Information Access and Protection of Privacy) Act, S.B.C. 2008, c. 38	Privacy Act, R.S.B.C. 1996, c. 373 (establishes statutory tort of invasion of privacy)
Alberta	Freedom of Information and Protection of Privacy Act, R.S.A. 2000, c. F-25 Personal Information Protection Act, S.A. 2003, c. P-6.5	Health Information Act, R.S.A. 2000, c. H-5	
Saskatchewan	Freedom of Information and Protection of Privacy Act, S.S. 1990-91, c. F-22.01	Health Information Protection Act, S.S. 1999, c. H-0.021	Privacy Act, R.S.S. 1978, c. P-24
Manitoba	Freedom of Information and Protection of Privacy Act, C.C.S.M. c. F175	Personal Health Information Act, C.C.S.M. c. P33.5	Privacy Act, R.S.M. 1987, c. P125
Ontario	Freedom of Information and Protection of Privacy Act, R.S.O. 1990, c. F.31	Personal Health Information Protection Act, 2004, S.O. 2004, c. 3, Sch. A	
Quebec	Act Respecting Access to Documents Held by Public Bodies and the Protection of Personal Information, R.S.Q., c. A-2.1		Charter of Human Rights and Freedoms, R.S.Q., c. C-12 Act Respecting the Protection of Personal Information in the Private Sector, R.S.Q., c. P-39.1 Civil Code of Quebec
New Brunswick	Protection of Personal Information Act, S.N.B. 1998, c. P-19.1	Personal Health Information Privacy and Access Act, S.N.B. 2009, c. P-7.05.	
Prince Edward Island	Freedom of Information and Protection of Privacy Act,		

	R.S.P.E.I. 1988, c. F-15.01		
Nova Scotia	Freedom of Information and Protection of Privacy Act, S.N.S. 1993, c. 5	Personal Health Information Act, S.N.S. 2010, c. 41.	
Newfoundland and Labrador	Access to Information and Protection of Privacy Act, S.N.L. 2002, c. A-1.1	Personal Health Information Act, S.N.L. 2008, c. P-7.01.	Privacy Act, R.S.N. 1990, c. P-22
NWT	Access to Information and Protection of Privacy Act, S.N.W.T. 1994, c. 20		
Nunavut	Access to Information and Protection of Privacy Act, S.N.W.T. 1994, c. 20		
Federal	Privacy Act, R.S.C. 1985, c. P-21		Personal Information Protection and Electronic Documents Act, S.C. 2000, c. 5

Appendix 3

Table 3: Potential Reform Strategies	
Author	Recommendation
SECTION A: STRATEGIES TO ADDRESS REB VARIATION	
Gilbert et al. (2009) *J Public Health Dent*	Instead of viewing IRBs and institutional administrators as potentially adversarial, customised solutions can be identified by engaging them in collegial discussions that identify common ground within regulatory bounds. Although time-intensive and complex, these solutions improve acceptability of practice-based research to patients, practitioners, and university researchers.
Finch et al. (2009) *Arch Pediatr Adolesc Med*	When considering future reforms, the national human subject protections system should consider the potential redundancy and effect on generalisability, particularly regarding enrolment of poor urban children, related to local IRB review.
Willison et al. (2008) *J Med Ethics*	REBs could benefit from training in best practices for protecting privacy and confidentiality in health research. An REB forum for research chairs could also reduce variation in decisions.
Saginur et al. (2008) *J Clin Oncol*	Development of a regional, specialised 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.
Driscoll et al. (2008) *J Clin Nurs*	Development of a national ethics application form with full ethical review by the first Institutional Research Ethics Committee (IREC) and compulsory expedited review by subsequent IRECs would resolve obstacles that individual IRECs face. IRECs must change their ethics approval processes to one that enhances facilitation of multi-centre research, which is now a normative process for health services.
Chaney et al. (2008) *Implement Sci*	While there are promising developments in the IRB community, it is incumbent upon implementation researchers to interact with IRBs in a manner that assists appropriate risk-benefit determinations and helps prevent the process from having a negative impact on efforts to reduce the lag in implementing best practices.
Gibson et al. (2008) *BMC Med Ethics*	REBs should participate in the creation of registries and biobanks and the eventual drafting of comprehensive legislation. As registries and biobanks expand, a critical analysis of suitable roles for REBs and subsequent guidance on such topics is needed.
Greene & Geiger (2006) *J Clin Epidemiol*	Policy-makers, researchers, and IRBs should convene to specifically discuss optimal approaches for multicenter review. However, until structural changes are implemented, observational researchers should develop and implement strategic plans for obtaining IRB approval in multicenter studies, including adopting models successfully employed by clinical trials.
Sherwood et al. (2006) *Otolaryngol Head Neck Surg*	For multicenter studies, investigators should seriously consider the establishment of cooperative authorisation agreements. On a simpler level, a standardised format for applications needs to be adopted nationwide.
Blustein et al. (2006) *Health Serv Res*	Engaging potential collaborators in planning for IRB review may help expedite and facilitate review, without compromising the fairness of the grant-making process or the integrity of human subjects protection.
Wolf et al. (2005) *J Pediatr*	Few IRBs present the kind of detailed guidance that investigators might need to ensure ethically designed protocols. IRBs should revise their web sites to ensure that they provide accurate, comprehensive, and sufficiently detailed guidance.
Rosenthal et al. (2005) *Intern Med J*	To develop a human research ethics committee (HREC) mutual acceptance (MA) model, based on the National Health and Medical Research Council's guidelines. The MA model aims to facilitate aspects of multicentre research and decrease the time taken to finalise the HREC review process. This (MA) model resulted in clear improvements in HREC processes and timelines. Stakeholder acceptance was high. This model provides a framework for a broader program of MA.
Shah et al. (2004) *JAMA*	To protect children from excessive risks while allowing appropriate research, IRB chairpersons need guidance on applying the federal risk and benefit categories and also need data on the risks children face in daily life and during routine physical or psychological tests.
Sengupta & Lo	IRB reform should include better training for non-scientist

(2003) *Acad Med*	and non-affiliated members so that they can have more active roles. In addition, measures are needed to strengthen the relationships between scientist and non-scientist and non-affiliated members.
Busby & Dolk (1998) *J R Coll Physicians Lond*	While new mechanisms including regional committees are being established, there is an urgent need for a standard application form to save time and resources for research. Continuing lack of consistency about the need for subject (parental) permission impedes the proper design and costing of research.
SECTION B: CENTRALISATION AS A REFORM STRATEGY	
Menikoff (2010) *New Engl J Med*	Recently, the Office for Human Research Protections put out for public comment a proposal to receive direct authority to take action against IRBs — as distinct from the institutions conducting the research — for noncompliance with regulations. The intent is to encourage greater reliance on outside (and central) IRBs by assuring the individual institutions participating in multi-site studies that they would not be blamed if an outside IRB were responsible for violations. Another approach to reducing the number of IRB reviews would be to have sponsors require the use of a central IRB as a condition for participating in a study.
Helfand et al. (2009) *J Urol*	The current system of local IRB review in the context of a multicenter surgical trial is inefficient in the review process and a central surgical IRB may be needed in multicenter trials.
Mansbach et al. (2007) *Acad Emerg Med*	There was substantial variation in IRB assessment of a standard protocol in this study. The burden of the application process contributed to some investigators not participating, but the majority of investigators remain enthusiastic about multicenter research. A national IRB may streamline the review process and facilitate multicenter clinical research.
Graham et al. (2006) *J Am Board Fam Med*	PBRN research often includes atypical, multi-site research activity, with practices simultaneously serving as research subjects and investigators. The high-risk nature of patient safety work further complicates this situation. Investigative work with the Office for Human Research Protections and the Agency for Healthcare Research and Quality to create a central IRB process could greatly facilitate work of this nature.
Green et al. (2006) *Health Serv Res*	Several features of the IRB system as currently configured impose costly burdens of administrative activity and delay on observational health services research studies, and paradoxically decrease protection of human subjects. Central review with local opt-out, cooperative review, or a system of peer review could reduce costs and improve protection of human subjects.
Gold & Dewa (2005) *Health Serv Res*	The increasing number of multi-site, health services research studies calls for a centralised system of ethics review. The local review model is simply not conducive to multi-site studies, and jeopardises the integrity of the research process. Centralised multi-site review boards, together with standardised documents and procedure, electronic access to documentation, and training for board

	members are all possible solutions. Changes to the current system are necessary not only to facilitate the conduct of multi-site research, but also to preserve the integrity of the ethics approval process in general.
Vick et al. (2005) *Am J Surg*	The IRB process for a multi-site observational study is expensive in both time and money. A VA national IRB for multi-site studies would significantly decrease the financial and temporal burden for observational studies.

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