Canadian Journal of Bioethics
Revue canadienne de bioéthique

Canadian Journal of Bioethics
Revue Canadienne de Bioéthique

Research Ethics Oversight for Multi-jurisdictional Clinical Trials in Canada: A Historical Perspective to Inform Future Direction

Brenda Lucas, Jaime Flamenbaum, Holly Longstaff, Srinivas Murthy et Brittney Schichter

Volume 7, numéro 2-3, 2024

Numéro hors-thème & Ateliers de la SCB
Open Issue & CBS Workshops

URI : https://id.erudit.org/iderudit/1112276ar
DOI : https://doi.org/10.7202/1112276ar

Aller au sommaire du numéro

Éditeur(s)

Programmes de bioéthique, École de santé publique de l'Université de Montréal

ISSN

2561-4665 (numérique)

Découvrir la revue

Citer cet article

Lucas, B., Flamenbaum, J., Longstaff, H., Murthy, S. & Schichter, B. (2024). Research Ethics Oversight for Multi-jurisdictional Clinical Trials in Canada: A Historical Perspective to Inform Future Direction. *Canadian Journal of Bioethics / Revue canadienne de bioéthique*, *7*(2-3), 23–32. https://doi.org/10.7202/1112276ar

Résumé de l'article

Comme condition de financement par les trois conseils canadienne, les chercheurs et les institutions doivent adhérer à *l'Énoncé de politique des trois Conseils : Éthique de la recherche avec des êtres humains* (EPTC) et les projets de recherche doivent être approuvés par un comité d'éthique de la recherche (CÉR). Pourtant, il existe un nombre limité de cadres et de normes pour guider la conduite et les décisions des CÉR au Canada, et ceux-ci sont le plus souvent volontaires. Les retards et l'augmentation des coûts résultant de l'absence d'une approche commune ou coordonnée de l'évaluation par les CÉR des essais cliniques multi juridictionnels constituent un problème de longue date dans l'environnement de la recherche au Canada. Dès 2006, des études et des recommandations officielles ont préconisé l'accréditation ou la qualification des CÉR, l'utilisation de formulaires et de modèles communs, ainsi que le leadership du gouvernement fédéral pour harmoniser les processus.

Canadian Journal of Bioethics
Revue Canadienne de Bioéthique

B Lucas, J Flamenbaum, H Longstaff, S Murthy, B Schichter
Can J Bioeth / Rev Can Bioeth. 2024;7(2-3):23-32

ARTICLE (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

Research Ethics Oversight for Multi-jurisdictional Clinical Trials in Canada: A Historical Perspective to Inform Future Direction

Brenda Lucas[a], Jaime Flamenbaum[b], Holly Longstaff[c,d], Srinivas Murthy[e], Brittney Schichter[c]

Résumé
Comme condition de financement par les trois conseils canadienne, les chercheurs et les institutions doivent adhérer à *l'Énoncé de politique des trois Conseils : Éthique de la recherche avec des êtres humains* (EPTC) et les projets de recherche doivent être approuvés par un comité d'éthique de la recherche (CÉR). Pourtant, il existe un nombre limité de cadres et de normes pour guider la conduite et les décisions des CÉR au Canada, et ceux-ci sont le plus souvent volontaires. Les retards et l'augmentation des coûts résultant de l'absence d'une approche commune ou coordonnée de l'évaluation par les CÉR des essais cliniques multi juridictionnels constituent un problème de longue date dans l'environnement de la recherche au Canada. Dès 2006, des études et des recommandations officielles ont préconisé l'accréditation ou la qualification des CÉR, l'utilisation de formulaires et de modèles communs, ainsi que le leadership du gouvernement fédéral pour harmoniser les processus.

Mots-clés
éthique de la recherche, pancanadien, harmonisation, essais cliniques

Abstract
As a condition of funding from the Canadian Tri-Agencies, researchers and institutions are expected to adhere to the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS) and research projects must obtain approval from a Research Ethics Board (REB). Yet there are a limited number of frameworks and standards to guide the conduct and decisions of REBs in Canada and these are most often voluntary. Delays and increased costs resulting from the lack of a common or coordinated approach to REB review for multi-jurisdictional clinical trials is a long-standing issue in the Canadian research environment. Formal reviews and recommendations as early as 2006 call for accreditation or qualification for REBs, use of common forms and templates, and federal leadership to harmonize processes.

Keywords
research ethics, pan-Canadian, harmonization, clinical trials

Affiliations
[a] Canadian Critical Care Trials Group and the Network of Clinical Trials Networks, Toronto, Canada
[b] Science Policy Branch, Canadian Institutes of Health Research, Ottawa, Canada
[c] Provincial Health Services Authority of BC, Vancouver, Canada
[d] Faculty of Health Sciences, Simon Fraser University, Vancouver, Canada
[e] Department of Pediatrics, BC Children's Hospital Research Institute, Vancouver, Canada

Correspondance / Correspondence: Brenda Lucas, brenda.lucas@sri.utoronto.ca

INTRODUCTION

In August 1998, the three science funding agencies of the Canadian federal government – the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council of Canada (SSHRC) – created the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS). It was, and still is, intended to set the minimum standard[1] for the safe and ethical conduct of research and the protection of participants. TCPS was amended most recently in 2022 and is now known as TCPS-2 (2022)[2] (1). To be eligible for funding by the three agencies, institutions must ensure that all projects that meet the TCPS definition of research under their auspices comply with TCPS. Many other bodies have voluntarily adopted it.

TCPS-2 (2022) requires institutions that follow TCPS to establish or appoint a Research Ethics Board (REB) to be accountable for research conducted under its auspices, with Article 6.1 stating "institutions shall establish or appoint an REB (or REBs) to review the ethical acceptability of all research involving humans conducted within their jurisdiction or under their auspices, that is, by their faculty, staff or students, regardless of where the research is conducted, in accordance with this Policy." (1, p.69) However, this requirement for REB oversight, and the various ways the requirement is interpreted by local institutions, becomes challenging to operationalize in practice when research projects are undertaken across multiple institutions and jurisdictions (each regulated by different provincial and territorial privacy laws), which is typically the case for clinical trials.

TCPS allows for coordination of reviews across multiple institutions or REBs through the optional adoption of "Alternative Review Models." (1, p.100). Under an alternative review model, an institution may authorize its REB to accept a review by an external REB, in some cases without a legal agreement (1). The guidance is clear that the "ultimate responsibility for approving

[1] Published Standards available at HRSO.
[2] Throughout this paper, the policy generally will be referred to as TCPS. Specific references to the current document will be cited as TCPS-2 (2022).

ISSN 2561-4665

alternative research ethics review models for potential use by REBs and researchers remains with their individual institutions." Yet, institutions that have a low tolerance for risk can make it difficult to implement alternative approaches.

Acknowledging this risk aversion, Townend et al. (including one Canadian author, Bartha M. Knoppers) looked at the challenges of international research and the tendency for local REBs to want to undertake their own reviews rather than delegating or accepting decisions of REBs from an external institution because of liability concerns (2). They described a "myth of liability" noting that there are actually fairly straightforward legal remedies to concerns that are raised, for example putting in place agreements to formalize responsibilities and indemnity between institutions and their REBs.

Despite the fact that Canada has a national policy for research ethics, there is no national framework for requirements of the conduct and decisions of REBs (3,4). Alas et al. (5) provide an excellent overview of the complex landscape created by the lack of clear requirements for the exercise of REB oversight, as compared to clear rules and requirements in other countries, including the United States and members of European Union, where legislation governs REBs or their equivalent. While noting that legislation alone may not fill the gaps, and that any federal effort to regulate would likely be seen as an intrusion into provincial jurisdiction, they suggest that "an entity with the authority to oversee REB operations while enforcing such policies and standards could promote the creation of a coordinated operational framework across Canada." (5) In addition, legislation of TCPS undermines the flexibility and nimbleness built into the policy and could lead to other unintended consequences.

It is the responsibility of the lead principal investigator (PI) of a study to navigate the approvals process through their local institution, in each applicable jurisdiction. Concerns have been identified about delays and increased costs as well as variability in decisions made by REBs (3,6). Investigators leading multi-jurisdictional studies must not only navigate different processes but also sometimes deal with conflicting requirements from different REBs. Further, a change required by one REB can necessitate changes to previous approvals from other REBs. This challenge is acknowledged by CIHR, including in a 2020 funding announcement which stated that:

> Investigators developing multi-site research studies in Canada often encounter challenges with gaining REB approval, in particular across more than one province. This can delay the research, increasing the costs and timelines of conducting projects that are often publicly funded. These challenges can discourage clinician-researchers from undertaking important child health research and reduces the ability of Canadian researchers to compete and participate in the international research arena. (7)

Given these unique challenges, this paper focuses on REB oversight for multi-jurisdictional clinical trials in Canada. We review REB harmonization and centralization initiatives and options for process changes and system changes that would be necessary to accomplish a single review and enable ethics approval to be recognized across Canada (a pan-Canadian approach to ethics review)[3]. Clinical research is also subject to regulation under Division 5 of the Food and Drugs Act; clinical trials for drugs and devices require approval by Health Canada and may be subject to provincial or territorial rules governing access, use and disclosure of personal health information (5). This paper does not address those approvals requirements.

PREVIOUS RECOMMENDATIONS

Less than a decade after establishing the TCPS, federal agencies were involved in undertaking reviews of ethics processes. The following is a brief summary of key recommendations (see Appendix for a timeline of reviews published from 1989 to date).

The 2003 review of the Severe Acute Respiratory Syndrome (SARS) outbreak, led by Dr. David Naylor, acknowledged the need to expedite ethics review processes during a pandemic. Recommendation 9.6 of the Naylor Report called for a Public Health Ethics Working Group and includes the following, without further explanation or context in the document, but crediting the Canadian Association of Medical Microbiologists for raising the concern: "the Work Group should […] develop templates for expedited ethics reviews of applied research protocols in the face of outbreaks and similar public health emergencies." (8) In 2012, the External Advisory Committee on Streamlining of Health Research Ethics Review (SHRER) was established by the Strategy on Patient-Oriented Research (SPOR) Working Group and SPOR National Steering Committee to provide advice on "processes, tools and strategies to improve the ethics review process for multi-site patient-oriented research in Canada, including but not limited to clinical trials."

The same year, the Senate Standing Committee on Social Affairs, Science and Technology issued a report that decried the long timeline for approvals of new drugs in Canada, noting that "while it is essential that trials be conducted thoroughly, the committee identified a factor that significantly impacts the time required to start up clinical trials in Canada – the absence of a standardized approach to research ethics review." (6, p.iii) The report focused on the need for standardization and accreditation of REBs and proposed the creation of a National Framework for Coordinating Clinical Trials.

[3] The views expressed herein are solely those of the authors and do not necessarily reflect those of Canadian Institutes of Health Research (CIHR) or Provincial Health Services Authority (PHSA).

Previous recommendations also had a strong emphasis on accreditation. The 2008 Expert Committee emphasized the need to replace the existing “fragmented” system of oversight with a “workable” and comprehensive REB accreditation system that would evolve over time, anticipating such a system would provide not only better protect research participants but also produce better quality research (9). But accreditation on its own has found little traction due to the resources required to set up and maintain such a system.

The 2008 Expert Committee suggested that accreditation may be a necessary but insufficient condition:

> It is important to acknowledge that accreditation, in and of itself, will not lead automatically to organizations accepting the reviews of other organizations in multi-site research. However, as Dr. G. Koski, the former Director of the US Office of Human Research Protections and currently Chair of the Advisory Board of World Health Organization’s Strategic Initiative for Developing Capacity for Ethical Review has stated, “Institutions and their REBs will relinquish autonomy only to the extent that they can trust others. Independent, private accreditation of Human Research Protection Programs and certification of individuals, especially investigators, are essential mechanisms for enabling collaboration and efficiency.” (9)

Clinical Trials Ontario (CTO) has been clear about “the necessity, value and impact of its REB Qualification Program to the success of its Streamlined Ethics Review System. Based on institution participation and stakeholder input, CTO asserts that it could not have implemented its Streamlined Ethics Review System without the REB Qualification Program.” (10)

Health Canada launched an initiative in 2007 to develop a national standard to assist REBs in enhancing harmonization of operations. The Canadian General Standards Board (CGSB) published research ethics oversight of biomedical clinical trials for REBs” (CGSB-191.1-2013), approved by the Standards Council of Canada in 2013 (11). However, the standard was withdrawn in 2018, citing that “there may be other documents available for use in this subject area.” (12) The standard was apparently not used, suggesting that a formal (but voluntary) standard was considered unnecessary or redundant.

Some reports also focus on the development of standard tools or templates that can be used to ensure consistency in the application process and reviews. The two key elements targeted for standardization are the form used to obtain participant consent (a major component of each ethics application) and the legal contract agreement between a host institution and participating sites. The legal contract is perceived to be the larger impediment to starting a trial, and evidence is emerging to support this concern (13). The 2012 Senate report notes that there has been some work to create a common consent form, but also notes the challenges of provincial privacy legislation as a barrier to adoption (6). The report “commends CIHR’s stated efforts to develop, in partnership with Association of Canadian Academic Healthcare Organizations (ACAHO) and Innovative Medicines Canada (formerly Rx&D), a standard clinical trial agreement as a significant step in streamlining the system.” The groups hosted a Clinical Trials Summit, and the 2012 report from that Summit went further, offering detailed recommendations that included developing a common application form, consent form template, elements of an accreditation system, information sharing mechanisms for ethics reviews and establishing a model Clinical Trials Agreement (mCTA) (15).

An organization called the Canadian Clinical Trials Coordinating Centre (CCTCC) was tasked with developing the mCTA. After multiple iterations, this model – focused primarily on industry-led clinical trials – was released in 2017 (10). The CCTCC appears to have been disbanded.

In addition to standardization and accreditation, the past two decades of reports call for more federal leadership. The Senate Standing Committee recommended “that the federal government assume a leadership role in facilitating, coordinating and encouraging a comprehensive clinical trials infrastructure.” (6)

The most recent comprehensive review and recommendations was undertaken by a Research Ethics Board Accreditation Working Group that was created jointly by CCTCC and Health Canada in 2015. Its final recommendations, published in 2017, recommended the creation of a national strategic leadership forum (10). The report also noted that effective streamlining or coordination, like CTO’s approach, is dependent upon a common online documentation system and standardization requirements. It supported such a comprehensive national online documentation system. But the authors also suggest a less comprehensive approach were this not to be practical, i.e., creating a national database of REB reviews so that REBs can access the decisions of other REBs.

The report goes into some detail of the CTO process, and notes that Ontario Cancer Research Ethics Board (OCREB) was the first REB to be designated under CTO and supports the CTO qualification process. OCREB was established before the CTO qualification; it is noted that it took years to gain the trust of REBs to delegate to the OCREB. The report also urged Health Canada to issue a public notice (as an interim measure) “that it strongly encourages REBs overseeing clinical trials to submit attestation forms that certify to sponsors that they meet accreditation, qualification or designation standards under an existing system in Canada. This in effect would mean that all REBs that review regulated clinical trials would need to demonstrate equivalency with one of the established standards: Association for the Accreditation of Human Research Protections Program (AAHRPP) accreditation, CTO REB Qualification, or Ministère de la santé et des services sociaux (MSSS) designation.” (10, p.20)

The joint HC/CCTCC response to the recommendation regarding sharing of reviews among REBs states:

> This topic has been extensively studied and is well understood. Provincial bodies have already done considerable work to harmonize the REB review process and there already are agreements to this end in place. In some cases, there are some issues to be resolved, e.g., compatibility of different online systems. Therefore, the ongoing efforts on sharing REB reviews of multicentre research should *be promoted*. Further sharing of REB reviews of multicentre research should be *encouraged and enabled*, and additional collaboration where possible should be *established*. (10, emphasis added)

The joint HC/CCTCC response to the report's recommendation to establish a national strategic leadership forum was that "Health Canada and CCTCC will work in 2017 to further consider the feasibility of this recommendation." (10) As of 2024, no leadership forum has yet been created.

EVOLVING PROVINCIAL ROLE

In the past decade, provinces have filled the gap in national leadership with their own efforts to streamline or centralize and, in some cases, regulate requirements within their own jurisdictions. While this has clarified the ethics oversight process in those provinces, it has reinforced the patchwork of ethics review across the country.

As part of its Life Sciences Commercialization Strategy, Ontario's Ministry of Research and Innovation (as it was named at the time) committed to streamlining approvals for clinical trials. It established Clinical Trials Ontario (CTO) in 2012 as an independent not-for-profit organization and continues to fund its operation (new funding of $6m was announced in January 2022) (15). In 2014 CTO implemented its REB Qualification Program and in 2014 officially launched its Streamlined Research Ethics Review System (SRERS). Institutions must sign a Participation Agreement with CTO to use the system (it is voluntary). Lead sites for a study submit an application and receive approval from a designated REB (REB of record) that is a qualified REB. Other sites then apply to obtain approval to join the study, under a single ethics review. CTO currently has 116 participating institutions and 19 qualified boards of record (16).

Under the auspices of a provincial organization called Michael Smith Health Research BC, the Provincial Research Ethics Platform (PREP) was launched in 2018 to enable multi-jurisdictional review of research ethics applications in a single online system in British Columbia (BC). The BC system's harmonization model selects a REB of record which then coordinates a full board review with at least one representative from each participating REB with the exception of the BC Cancer and in some cases Children's & Women's REBs, which are considered provincial specialized UBC REBs that conduct centralized ethics and privacy reviews (17). More recently, however, the province has launched a transformative new project in 2023: The Research Approvals Processes Project (RAPP) (18). As stated on the program website, "RAPP has received support from the Leadership Council, a council of Health Authority Chief Executive Officers, and Ministry of Health leadership. Recognizing the pivotal role of health research in fostering a high-quality and efficient health system, Leadership Council has indicated strong support for the streamlining efforts proposed by RAPP, which encompass ethics, privacy, data access and sharing, contracts, and operational approvals." Ultimately the project aims to "provincially coordinate and standardize research approval processes (ethics, privacy, data access, operational review and contracts and agreements) for multi-site studies crossing more than one Health Authority."

In Saskatchewan, a reciprocity agreement is in place to allow for a single provincial review by one of the following three REBs, at the University of Saskatchewan, the University of Regina or the Saskatchewan Health Authority (19).

Some provinces have enacted legislation to set requirements for ethics review. For example, Newfoundland and Labrador established the Health Research Ethics Authority, a not-for-profit corporation (NFP) and a provincial Health Research Ethics Board in 2011 when the Health Research Ethics Authority Act (2006) was proclaimed. All health research conducted in the province must be approved by the HREB. In Quebec, the Ministère de la santé et des services sociaux (MSSS) implemented changes to the 2014 MSSS Multi-Centre Research Ethics Review Mechanism in 2015 to require that multi-site studies be subject to single ethics review for all sites, conducted by the REB of record with site specific assessment and research authorization by a mandated person at each site. And in Manitoba, Research Improvements Through Harmonization in Manitoba (RITHIM) is moving the province toward a system that will harmonize ethics, privacy and other processes to streamline health research reviews. Recent amendments to the Personal Health Information Act require the Minister to create a provincial research review committee that will take the place of institutional committees (20).

The approach taken to require a single ethics review in some provinces imposes a legal requirement that the review be done within the province in question but often does not capture all research conducted within that jurisdiction. While effective in creating a streamlined process for that province for some research, it could be perceived as a legal barrier to national harmonization. Quebec, for example, cannot legally accept the decision of another provincial REB. Any serious effort at national harmonization will require that these legal barriers be addressed. Some groups are calling for a single ethics review process (as opposed to a single REB decision) that might involve a multi-jurisdictional panel for decision-making on behalf of the provincial REBs, which would effectively create a model in Canada for centralized review for some studies at the provincial and territorial level and a harmonized review at the national level (21,22).

RECENT DEVELOPMENTS

In the absence of clear mandatory federal procedures, and with the emergence of different provincial processes and requirements, navigating multi-site trials that cross provincial boundaries remain a complex challenge. Two significant efforts have been developing to navigate this compliance landscape, both led by non-government organizations and focused on a particular discipline: cancer and pediatrics.

For some years, cancer-focused research, with well-funded and well-established leadership of NFP organizations, has been charting its own path. In 2013, the Ontario Institute for Cancer Research (OICR) established the OCREB to provide a single REB review for oncology clinical trials (23). OCREB is currently working with Manitoba on a Pilot REB Streamlining Project that is intended to "provide the foundation for a larger scale project aimed at determining the feasibility of a pan-Canadian approach to REB review, and a model or models acceptable to each province." (24) The pilot project, based on a plan called a pan-Canadian Approach to Research Ethics Review (CARE), will begin with facilitated review, that is, providing access to the reviews of other REBs to expedite subsequent reviews. The aim is to enable reciprocal review (under a reciprocity agreement) with initial REB review and subsequent delegated reviews for local consideration.

CTO is also leading initiatives to expand its successful programs nationally, with an initial focus on pediatric clinical trials research (there are 17 pediatric teaching hospitals in Canada). In 2020, CTO and the Maternal Infant Child & Youth Research Network (MICYRN) launched the Canadian Collaboration for Child Health: Efficiency and Excellence in the Ethics Review of Research (CHEER) to a create a cross-province streamlined ethics review process for multi-site studies that would permit a single ethics review for child health studies in Canada. The project was awarded $2.5m through a 2019 CIHR Operating Grant competition launched specifically to identify and fund a national Pediatric REB Initiative (25). The CHEER project is expected to develop a cross-province streamlined research ethics review platform customized to support the needs of the child health research community and create a Canada-wide Research Ethics Board (REB) assessment program to ensure quality and engender trust across Canada's REB and institutional communities (25).

These two projects demonstrate the evolution of ethics oversight, and what is emerging is a move toward establishing robust, coordinated and harmonized provincial and territorial systems. These projects also illustrate the risk that, like health administrative data, we will see the development of distinct and potentially incompatible information systems across the country without national coordination and federal leadership – either by jurisdiction or discipline.

APPLYING THE "REB OF RECORD" ACROSS JURISDICTIONS

As noted above, provincial systems are attempting to streamline processes through the development of central or coordinated administrative systems, qualification of individual REBs, and recognition of single REB of record decisions. In theory, the decision of an REB of record in one jurisdiction could be recognized in other jurisdictions, as the OCREB and CHEER examples above are demonstrating.

In a 2021 public consultation, the federal government's Panel on Research Ethics proposed guidance changes to the TCPS for multi-jurisdictional studies. The guidance proposed a new mandatory requirement for approval from a single REB that would be accepted by other jurisdictions for "minimal risk" studies (26). It noted the need to move "from the model of multiple single-site reviews of multi-jurisdictional studies toward a model of single review for multiple sites, unless local circumstances merit additional scrutiny."

The proposed mandatory approach was not included in the final guidance, even for "minimal risk" studies. Instead "institutions are strongly encouraged to establish mechanisms for streamlining the ethics review process using one or more, or a mix of models for research ethics review" including the option for "an REB to recognize research ethics review decisions made by another REB." (1) While "strong encouragement" is welcome, it falls far short of mandating a single approval for multi-jurisdictional "minimal risk" studies. Even the draft guidance was not prescriptive in the mechanism for achieving a single approval nor navigating the potential challenges of different jurisdictional requirements. In fact, provincial statutory requirements were listed in the proposed draft guidance as one of the "local circumstances" that could be raised that would lead to local REB conducting its own review rather than acknowledging the decision of the REB of record. The proposed process allowing for consideration of "local considerations" in the acknowledgement of local REBs makes sense in principle, but multiple responses to the public consultation on the proposed guidance pointed out that this would in fact have introduced new uncertainty and inconsistency where it doesn't currently exist (27). Once again, the research community is left with a patchwork of voluntary systems for REB coordination and reciprocity, not unlike the "Alternative Review Models" mechanism that has enabled the provinces to develop their own unique systems.

Beyond the amendments and guidance offered through TCPS, there are no requirements in place for how REB oversight is to be conducted. While the latest set of TCPS Interpretations refer to other research ethics norms such as the HRSO standard for Ethical Review and Oversight of Human Research (CAN/HRSO-200.01-2021), they are also clear that the TCPS does not require their adoption (28). Despite multiple calls for leadership at the federal level, there has been no official direction or coordination of the tools, processes or procedures to be used by institutions across the country. Over the past decade, provinces and specific research communities have stepped in to address this gap by clarifying and streamlining review in their

own jurisdictions. And a handful of non-government organizations have spearheaded attempts to harmonize across jurisdictions.

There is a clear federal stake: in addition to protecting the health of all people living in Canada and supporting the broader economic benefits of having a transparent and efficient process – the Canadian research and development pharmaceutical sector contributed $15 billion to GDP in 2018) (29) – there is also a huge direct investment by the federal government that is potentially affected by delays. CIHR invested over $1.2 billion in grants and awards for health research in 2020/21 including $630 million for investigator-initiated research (26); and the administrative burden on investigators and institutions is both significant and costly (7).

There is no sound ethics reason for there to be substantial differences in the reviews of particular protocols under TCPS, yet they persist.

OPTIONS GOING FORWARD

There are two pathways to reform that are complementary: fundamental system changes to enable a single centralized REB review or harmonized review and developing common templates to harmonize and streamline the review process.

System Changes

Establish a single federal REB

As suggested by the Naylor report, the federal government could create a distinct new mechanism for a single REB for multi-site, multi-jurisdictional clinical trials; a national REB available to publicly funded, investigator-led trials. It could be optional (as opposed to mandatory) with opt-in via legal agreement by institution or by province/territory.

Health Canada and Public Health Agency of Canada (PHAC) currently operate an REB for research involving human participants. However, the mandate of this REB is limited to studies conducted by (or in collaboration with) Health Canada or PHAC or done under contract to one of those agencies (1). In 2019/20 it reviewed 43 studies (30 to the full board, 13 delegated reviews) (30). In comparison, the same year, CTO received 3,600 applications for research ethics approval (31). Thus, the legal mechanisms and framework exist for a federal government REB, but the capacity, resources, and training to undertake ethics reviews of clinical trials would have to be built and sustained, requiring significant investment. In 2006, the cost to establish such a body was estimated by CIHR to be $6 million. This would be considerably higher today, with annual operating costs as well. The question of an appropriate federal body for oversight is among the legal and operational questions that have not been addressed.

Moreover, there would likely be significant resistance to this approach from provinces that have provided significant financial investments in their own streamlined provincial processes, where it could be seen as duplication. It would also require legislative change (or a change to how these laws are interpreted) in those provinces that mandate reviews by their own provincial REBs. But, if these issues could be addressed, it would allow for a single REB approval, thereby providing clarity and consistency and easing the burden on investigators (although confusion around institutional approvals and other local permissions would persist).

Formal harmonization of provincial/territorial systems in a pan-Canadian framework

The other approach would be for the federal government to work with the provinces and territories to ensure that there are efficient and streamlined systems in place in each jurisdiction, based on harmonized processes and standards for REB qualification, and development of a common portal (capable of connecting with existing systems) for submission of applications with common templates. Along with a coordinated, streamlined system within each province and territory, a process for harmonizing ethics review across multiple jurisdictions would also be necessary.

There are essentially two mechanisms for this: 1) acceptance of a single REB of record across jurisdictions or 2) a coordinated review process that happens in each jurisdiction simultaneously. Both mechanisms have emerged in the models for streamlined ethics review provincially, described by Nichols et al. as i) Centralized Review with Alternating board of record, ii) Centralized Review with Single board of record, and iii) Collaborative Review (1). To be implemented nationally, clear requirements would have to be established for how multi-jurisdictional approvals are managed, but a coordinated process has fewer legal barriers and could be led by the provinces and territories, provided that jurisdictions already have streamlined processes in place that work well. Those that do not have such structures could be end up being less competitive in the clinical research environment and so less likely to attract and set up clinical studies for their local populations.

To advance a single REB of record, a legal review of the requirements in place in each jurisdiction would need to be conducted, and master agreements implemented (or changes to provincial regulation if required) to enable acceptance of a decision by another qualified provincial or territorial REB. The process would require a mechanism for provincial/territorial or local acknowledgement (for considerations within a well-defined scope) but would allow a delegated or expedited review after a trial was approved by one qualified provincial REB. Unfortunately, the recent changes to TCPS-2 (2022) and lack of mandatory requirement for streamlining even minimal risk studies suggest that a strong federal push for this is unlikely.

A coordinated “collaborative” review process would not require any jurisdiction to accept another jurisdiction’s review. It would prioritize continued provincial and territorial autonomy. This could be implemented today without significant change, building on what is already working. Coordination could be enhanced through federal investments such as a common data system and application portal developed in partnership with the provinces and territories and managed by them. However, without a formal pan-Canadian mechanism for coordination and harmonization with reciprocal acceptance of REB approvals, we are unlikely to realize a durable and predictable approach that would ease the burden on investigators initiating new clinical trials and enable a quicker response and start-up for critical studies once fully implemented. Federal government intervention may also be required to address insurance and indemnification, which is another major impediment to inter-provincial collaboration. Not all hospitals can indemnify another party. In some cases, the insurance of an institution or REB will not indemnify them for reviewing on behalf of institutions outside of their province. A federally funded insurance program to cover this low-risk activity would alleviate the problem, particularly if accompanied by a common legal agreement to allow REB oversight activities to be delegated to a REB outside of the participating institution (even in a different province).

Federal leadership to drive formal harmonization could provide benefit to provinces and territories through the establishment of effective systems to streamline reviews (where these are lacking), financial investment in data systems that could lead to cost efficiencies and reducing a costly burden on researchers and REBs by removing duplication of reviews for studies already rigorously reviewed and approved elsewhere.

Procedural Changes

In parallel to any system changes, there are steps that can be taken that would have immediate impact on streamlining ethics approvals for multi-centre clinical trials. In jurisdictions where there is a streamlined process for ethics review, common application formats including templates for consent forms have emerged (e.g., Clinical Trials Ontario and Quebec). Despite calls for this in 2012 by the Canadian Senate (6), we still lack a common application form or consent form template that is accepted across jurisdictions. This would be a significant improvement. Investigators leading multi-centre trials in Canada have long documented the practical challenges and inconsistencies of REB decisions for multi-centre clinical trials (30,31). Matheson et al. (2012) evaluated the REB decision-making process for a single large multi-centre clinical trial in pediatric rheumatology and found that application forms were very similar in content, but with differences in format and number of copies. Despite having a central coordinating centre to manage the reviews at all 12 REBs involved, “the most inefficient part of the ethics process was the preparation of the documentation” (32) leading the authors to suggest standardizing the application would be more constructive than creating a centralized REB.

A recent exercise to create a “core consent guideline” for research in human genomics provides a good example of how this might be accomplished. The guideline is the result of a process led by CIHR’s Ethics Office with the Institute of Genetics, to create a core set of elements for documents used to obtain participant consent for human genomics research in Canada (34). The Ethics Office is currently working with the Canadian Critical Care Trials Group (CCCTG) to apply a similar method to informed consent for health studies in Canada. The project will compile the requirements that apply to informed consent, from TCPS-2 (2022), Health Canada regulations and guidance, but also USFDA and the International Council for Harmonization – essentially any elements that a TCPS compliant REB may be expected to require as part of an informed consent form. This analysis will then be used first to conduct a gap analysis of the legal and policy requirements of existing publicly available templates provided by Canadian REBs, and second to build a template for a standard set of requirements that should be included in any consent form that is short and concise, including only the information that is relevant to a participant’s decision-making. The expectation is that having a common approach to the “core” required elements of consent would provide a standard approach that can be consistently applied, streamlining the process for investigators and setting an expectation for short, understandable consent forms. The approach would allow for small additions to meet local compliance or policy requirements and would encourage researchers to present information in a format that best supports a participant’s full understanding of the research for which they are consenting to participate.

Development of common consent form templates or other elements of the application processes, if fully supported or led by REBs, could be implemented immediately. There would be no legal or jurisdictional barriers and it would be very low cost. It would also be complementary to broader reform or system harmonization that will require common application processes.

CONCLUSIONS

Most provinces and territories are putting in place streamlined processes within their jurisdiction, so gradually the requirement to separately obtain REB approval in each province could become less burdensome on investigators. But this will take time, and it doesn’t eliminate the duplication or the potential inconsistencies in decisions across provinces and territories. The current system is not resilient and is vulnerable to “breakdowns and unclear accountability” (35). It also leads to the evolution of potentially very different systems and processes in each province and territory that are difficult to harmonize.

The Canadian Government, in describing the “Clinical Trials Environment in Canada”, includes a short list of “major initiatives and supports” that comprise “national and regional efforts to make Research Ethics Boards more efficient, including through the development of a national standard in this area.” (36) Developing a national standard (which has already been done and discontinued) is not likely to create efficiency nor lead to harmonization. But the indication that the federal government is poised to seriously engage on the issue of harmonizing REBs is encouraging. This potential for a renewed commitment is also

evidenced in the recent $39 million CIHR investment to establish the Accelerating Clinical Trials (ACT) Canada Consortium with a mandate to “accelerate, optimize, and facilitate the conduct, implementation, and results translation from high-quality, high-impact randomized controlled trials.” Streamlining ethics review is one of ACT’s priorities.

Commitment by the federal government to work with the provinces and territories to implement a strong pan-Canadian process for streamlined multi-jurisdictional approval is needed. Such a process would also need to respect existing and forthcoming efforts from Indigenous communities, organizations, and scholars to ensure that Indigenous data sovereignty, ethical norms, and processes are respected and upheld. Working with this new national consortium, established provincial and territorial REBs are well-positioned to lead harmonization, with templates and processes (including qualification) that are already working and will ensure the support of participating TCPS compliant institutions in streamlining the review of multi-jurisdictional clinical trials and studies in Canada.

Reçu/Received: 01/09/2023
Publié/Published: 21/06/2024

Remerciements
B. Lucas souhaite remercier Samantha Buttemer et Warren Mabee de la School of Policy Studies de l’Université Queen’s pour leurs commentaires sur un document de cours pour le Master of Public Administration qui a servi de base à ce manuscrit. Les auteurs souhaitent également remercier Robert Fowler, Kusum Menon et Mary-Ellen Rayner pour leurs commentaires sur une version antérieure, ainsi que Kim McGrail, Susan Marlin et deux relecteurs pour leurs commentaires sur ce manuscrit.

Acknowledgements
B. Lucas would like to thank Samantha Buttemer and Warren Mabee of the School of Policy Studies at Queen’s University for input to a course paper for the Master of Public Administration that informed this manuscript. The authors also wish to thank Robert Fowler, Kusum Menon, and Mary-Ellen Rayner for comments on an earlier version, and Kim McGrail, Susan Marlin and two reviewers for comments on this manuscript.

Conflits d’intérêts
Aucun à déclarer

Conflicts of Interest
None to declare

Édition/Editors: Aliya Affdal

Les éditeurs suivent les recommandations et les procédures décrites dans le Code of Conduct and Best Practice Guidelines for Journal Editors de COPE. Plus précisément, ils travaillent pour s’assurer des plus hautes normes éthiques de la publication, y compris l’identification et la gestion des conflits d’intérêts (pour les éditeurs et pour les auteurs), la juste évaluation des manuscrits et la publication de manuscrits qui répondent aux normes d’excellence de la revue.

The editors follow the recommendations and procedures outlined in the COPE Code of Conduct and Best Practice Guidelines for Journal Editors. Specifically, the editors will work to ensure the highest ethical standards of publication, including: the identification and management of conflicts of interest (for editors and for authors), the fair evaluation of manuscripts, and the publication of manuscripts that meet the journal’s standards of excellence.

Évaluation/Peer-Review: Cory Goldstein & Ruby Shanker

Les recommandations des évaluateurs externes sont prises en considération de façon sérieuse par les éditeurs et les auteurs dans la préparation des manuscrits pour publication. Toutefois, être nommé comme évaluateurs n’indique pas nécessairement l’approbation de ce manuscrit. Les éditeurs de la *Revue canadienne de bioéthique* assument la responsabilité entière de l’acceptation finale et de la publication d’un article.

Reviewer evaluations are given serious consideration by the editors and authors in the preparation of manuscripts for publication. Nonetheless, being named as a reviewer does not necessarily denote approval of a manuscript; the editors of *Canadian Journal of Bioethics* take full responsibility for final acceptance and publication of an article.

REFERENCES

1. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2 (2022). 2022.
2. Townend D, Dove ES, Nicol D, Bovenberg J, Knoppers BM. Streamlining ethical review of data intensive research. BMJ. 2016;354:i4181.
3. Nicholls SG, Morin K, Evans L, and Longstaff H. Call for a pan-Canadian approach to ethics review in Canada. CMAJ 2018;190(18)E553-55
4. Kelly LE, Richer L, Ali S, et al. 2019. Innovative approaches to investigator initiated, multi-centre paediatric clinical trials in Canada. BMJ Open. 2019;9(6):e029024.
5. Alas JK, Josmar K, Godlovitch G, Mohan CM, Jelinski SA, Khan AA. Regulatory framework for conducting clinical research in Canada. Canadian Journal of Neurological Sciences. 2017;44(5):469-74.
6. Senate Standing Senate Committee on Social Affairs, Science and Technology. Canada’s Clinical Trials Infrastructure: A prescription for Improved Access to New Medicines. Ottawa; Nov 2012.
7. Canadian Institutes of Health Research. Promoting child health through a streamlined ethics review. Health Research in Action. 5 May 2020.
8. National Advisory Committee on SARS and Public Health. Learning from SARS: Renewal of Public Health in Canada. Ottawa: Health Canada; Oct 2003.
9. Experts Committee for Human Research Participant Protection in Canada. Moving Ahead: Final Report. Ottawa; 15 Jun 2008.

10. CAREB-ACCER. CCTCC Research Ethics Board Accreditation Working Group Final Recommendations. 10 Feb 2017.
11. Standards Council of Canada. Research ethics oversight of biomedical clinical trials. 2013
12. Government of Canada. Research ethics oversight of biomedical clinical trials / prepared by the Canadian General Standards Board; approved by the Standards Council of Canada. 2018.
13. Teo K, Fowler RA, Adhikari NKJ, et al. Time required to initiate a clinical trial in Canada at the onset of the COVID-19 pandemic: an observational research-in-motion study. CMAJ Open. 2023;11(4)E615-20.
14. Rx&D, CIHR, ACAHO. To Your Health & Prosperity...An Action Plan to Help Attract More Clinical Trials to Canada. 30 Mar 2012.
15. Ontario Government. Ontario Strengthening Province's Research and Innovation Sector. 14 Jan 2022
16. Clinical Trials Ontario. 2022 Annual Report. 2023.
17. Research Ethics BC. Participatory Partnerships and Harmonization in BC: Developing the Provincial Research Ethics Platform (PREP). 2022.
18. Michael Smith Health Research BC. Research Approvals Processes Project (RAPP). 2024
19. Saskatchewan Health Authority. Research Ethics Board. (n.d.)
20. The Legislative Assembly of Manitoba. Bill 54, The Personal Health Information Amendment Act. 3rd Sess., 42nd Legislature, 2022.
21. Health Data Research Network Canada. TCPS2 (2018) Proposed Revision 2021 – Consultation Response. 2021.
22. UBC Affiliated Research Ethics Board. Comments from Research Ethics BC and UBC Panel on Research Ethics Proposed Revised Guidance. 2021.
23. OCREB. Ontario Cancer Research Ethics Board. 2022.
24. OCREB. Annual Report 2019/2020. 2020.
25. CHEER (n.d.)
26. Panel on Research Ethics. Ethics Review of Multijurisdictional Research – Proposed Revised Guidance. 2021.
27. Panel on Research Ethics. Consultations: Public Comments on the Proposed Guidance to TCPS 2 (2018). 2021
28. Panel on Research Ethics. TCPS 2022 Interpretations. May 2024.
29. Statistics Canada. The Canadian Research and Development Pharmaceutical Sector. 7 May2021.
30. Health Canada-PHAC REB. Annual Report 2019 – 2020. 2021.
31. Clinical Trials Ontario. 2019/20 Annual Report. 2020.
32. Matheson LA, Huber AM, Warner A, Rosenberg AM. Ethics application protocols for multicentre clinical studies in Canada: A paediatric rheumatology experience. Paediatrics & Child Health. 2012;17(6):313-16.
33. Needham AC, Kapadia MZ, Offringa M. Ethics review of pediatric multi-center drug trials. Pediatric Drugs. 2015;17(1):23-30
34. Longstaff H, Flamenbaum J, Richer E, Egar J, McMaster CR, Zawati MH. Core elements of participant consent documents for Canadian human genomics research and the National Human Genome Library: guidance for policy. CMAJ. 2022;194(44):E1500-8.
35. Flood CMM, Thomas BP, Lahey W. Federalism and health care in Canada: a troubled romance. Working Papers, Dalhousie University Schulich Law School, 2017.
36. Government of Canada. Clinical Trials Environment in Canada. 2022

APPENDIX: TIMELINE OF HUMAN RESEARCH ETHICS REVIEW IN CANADA

1989	National Council on Ethics in Human Research (**NCEHR**) is established as a non-governmental organization (incorporated in 2003). NCEHR is sponsored by: Canadian Institutes of Health Research (**CIHR**), Health Canada, Interagency Advisory Panel on Research Ethics and the Royal College of Physicians and Surgeons of Canada. Dissolved in 2016.
1998	Tri-Council Policy Statement: Ethical Conduct of Research (**TCPS**) is created as the official human research ethics policy of the Agencies: CIHR, the Natural Sciences and Engineering Research Council of Canada (**NSERC**), and the Social Sciences and Humanities Research Council of Canada (**SSHRC**). Amended most recently in 2018.
2000	Canadian Association of Research Ethics Boards (**CAREB**) established.
2001	CIHR, NSERC and SSHRC jointly create the Interagency Advisory Panel on Research Ethics (**PRE**).
2006	NCEHR Task Force Report supports accreditation, recommends that the primary focus of an accreditation process should be Programs for Ensuring Ethical Research with Humans (**PEERH**). Experts Committee for Human Research Participant Protection in Canada formed by a large group of "Sponsors" including Health Canada, CIHR and SSHRC, NSERC, Association of Universities and Colleges of Canada, Royal College of Physicians and Surgeons of Canada and others.
2008	Moving Ahead: Final Report of the Experts Committee for Human Research Participant Protection in Canada released. Proposes creation of "Canadian Council for the Protection of Human Research Participants (**CCPHRP**)" as an independent corporation to implement all aspects (accreditation, policy and education) of a new system for ethics oversight. Endorses PEERH as primary focus and would build on the standards developed by NCHER.
2011	Clinical Trials Summit hosted by CIHR, Association of Canadian Academic Healthcare Organizations (**ACAHO)** and Canada's Research-Based Pharmaceutical Companies (**Rx&D**). Newfoundland and Labrador Health Research Ethics Authority (a NFP corporation) and Health Research Ethics Board are established when the Health Research Ethics Authority Act (2006) is proclaimed. All health research conducted in the province must be approved by the HREB.
2012	Senate Standing Committee of Social Affairs, Science and Technology issues report, Canada's Clinical Trial Infrastructure: A prescription for improved access to new medicines. External Advisory Committee on Streamlining of Health Research Ethics Review (**SHRER**) established to advise the Strategy on Patient-Oriented Research (**SPOR**) Working Group and SPOR National Steering Committee on processes, tools and strategies to improve the ethics review process for multi-site patient-oriented research in Canada, including but not limited to clinical trials. Rx&D, CIHR, and ACAHO Action Plan released (report of the 2011 Clinical Trials Summit) Clinical Trials Ontario (**CTO**) established as an independent NFP organization, with support from the Ontario Government (this was an initiative of the province's Life Sciences Commercialization Strategy led by Ministry of Research and Innovation).
2013	SPOR / SHRER External Advisory Committee Report for Discussion released
2014	Canadian Clinical Trials Coordinating Centre (**CCTCC**) created by CIHR, Canada's Research-Based Pharmaceutical Companies (Rx&D – later Innovative Medicines Canada), and the merged organizations of the Association of Canadian Academic Healthcare Organizations and the Canadian Healthcare Association (ACAHO/CHA – later HealthCareCAN) as response to the 2012 Action Plan.
2015	CTO officially launches Streamlined Research Ethics Review System (SRERS) building on 2014 implementation of CTO REB Qualification Program. Quebec Ministry of Health and Social Services (MSSS) implements changes to the 2014 MSSS Multi-Centre Research Ethics Review Mechanism to require that multi-site studies will be subject to single ethics review for all sites conducted by the REB of record with site specific assessment at each site and research authorization by a mandated person at each site.
2016	NCEHR legally dissolved (no filing since 2010)
2017	**CCTCC REB Accreditation Working Group** Final Recommendations and joint response by the CCTCC and Health Canada released (January)
2018	Research Ethics BC (REBC) and the University of British Columbia (UBC) launch the Provincial Research Ethics Platform (**PREP**) to enable multi-jurisdictional review of research ethics applications in a single online system.
2019	Alberta implements requirement for investigators submitting to any of the Health Research Ethics Board of Alberta (HREBA) committees (Clinical Trials, Cancer, Community Health) to have an official agreement appointing HREBA as their Board of Record. Uses common online workflow, the Institutional Research Information Services Solution (IRISS).
2020	Canadian Collaboration for Child Health: Efficiency and Excellence in the Ethics Review of Research (**CHEER**) is launched by CTO and the Maternal Infant Child & Youth Research Network (MICYRN), to a create a cross-province streamlined ethics review process for multi-site studies to achieve a single ethics review for child health studies in Canada (awarded $1.5m through a 2019 CIHR competition for Operating Grant: Pediatric REB Initiative). Health Canada's 2020 Interim Order Respecting Clinical Trials for Medical Devices and Drugs Related to COVID-19 expedites Department review (no effect on ethics review).
2021	Panel on Research Ethics (PRE) and the Secretariat on Responsible Conduct of Research (SRCR) public consultation on new proposed guidance to inform broad consent and enable multi-site ethics approvals. Includes proposal for mandatory single REB of record for multi-site ethics approvals that are minimal risk.
2022	Research Improvements Through Harmonization In Manitoba (RITHIM) established harmonize ethics, privacy and institutional impact review processes.
2023	TCPS 2 (2022) finalized. Chapter 8 "streamlining multi-jurisdictional research ethics review of minimal risk research" "encourages streamlining multi-jurisdictional ethics review of minimal risk research without a requirement for official agreements amongst institutions." It also "strongly encourages institutions to streamline ethics review and asserts that duplication of ethics review that is not anticipated to provide additional protections for research participants can rarely be justified for research of all risk levels, and particularly for minimal risk multi-jurisdictional research." BC launches Research Approvals Processes Project (**RAPP**).