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COMMUNICATIONS

Streamlining review of research involving humans: Canadian models

INTRODUCTION

Biomedical research post sequencing of the first human genome is increasingly eroding a traditional ecology of individualist science. It is, furthermore, normalising collective innovation and shared scientific discovery.[1 2] Achieving sound statistical power in a genome-wide association study, for example, can often be well beyond the scope of any one researcher's capacity. For this reason and others, the scientific imperative of research collaboration can be more pronounced in the 'omics' disciplines,[3] where millions of data points are needed to make global inferences about links between the human genome and disease.[4] From the scientific necessity to adequately power a study through research collaborations is also born an ethical imperative to do so. That is, the anticipated benefits and harms of a particular study are justified based on the researchers' sound predictions about potential outcomes and contributions to knowledge. Either underestimating or overestimating translational possibilities can disturb the benefit–harm balance due largely to insufficient statistical power.[5]

Two important milestones, therefore, rest on this bench-to-bedside continuum for 'omics' research, and are essential for any clinical translation endeavour: research ethics and data-access reviews. The former ensures appropriate ongoing ethical oversight and participant protections, while the latter enables research collaboration by providing researchers with access to data. Debates surrounding traditional issues facing such reviews are ubiquitous in the literature, yet little attention has been paid to how these issues are exacerbated when studies span across multiple jurisdictions. This is particularly true for research typified in the 'omics' disciplines, where international collaboration is the norm rather than the exception.

Here, a distinction between multi-site and multi-jurisdictional research should be emphasised. While multi-site research implies that the project takes place across many individual sites, multi-jurisdictional research involves sites in different legal jurisdictions. Multi-jurisdictional research along with the ethics review processes required to approve it adds to the procedural complexity of multi-site studies in that researchers must consider the regulatory as well as legal differences among all participating sites. Each jurisdiction housing the participating research sites comes equipped with its own regulatory mechanisms, procedures and bureaucracies. This can pose a number of practical and interpretive challenges[6 7] to ensuring an equally high standard of participant protections across all research sites, not the least of which can include reconciling data privacy and security statutes, ensuring specific protections for research with vulnerable populations and navigating issues of broad consent in using biobanked samples. Where policies regulating health research are not federalised, multi-jurisdictional ethics review can complicate abilities to collaborate and, ultimately, limit clinical translation possibilities. These policies must, therefore, be able to respond to the multi-jurisdictionality that such research collaborations invite.[8]

It does not come as a surprise that current evidence of procedural inefficiencies and bureaucratic delays in research ethics review substantiate acute needs for reform. Likewise, redundant and, at times, contradictory mechanisms for data-access review of multi-jurisdictional studies impede data sharing that is necessary to achieve the statistically significant findings mentioned earlier. Both data-access and research-review mechanisms can, therefore, lead to fragmented systems of governance, and more importantly is not translating into improved protections for research participants.[9 10]

This paper will focus on the contemporary issues arising from two types of multi-jurisdictional reviews: those conducted by research ethics boards (REBs) (ethics) and those performed by expert committees evaluating data-access requests (data access). It presents two innovative approaches from projects in Canada, which have set their sights on streamlining ethics and data-access procedures. These approaches can, furthermore, serve to guide other researchers and review committees facing similar multi-jurisdictional challenges in Canada and internationally.

MULTI-JURISDICTIONAL RESEARCH ETHICS REVIEW: MATERNAL INFANT CHILD AND YOUTH RESEARCH NETWORK

Independent research ethics review has been criticised for its lack of central coordination,[11] inconsistencies,[12] as well as its inability to ensure participant protections in some research domains.[13] REBs are beginning to harmonise documents required for submission for studies across multiple sites to address these issues. Policy and document harmonisation reduces delays, among other benefits, commonly associated with researcher's underpreparedness in the multi-site review process.[14] Some international[15] as well as Canadian jurisdictions[16 17] are consolidating their procedures for multi-site ethics review in response. While such efforts towards streamlining multi-*site* procedures should be lauded, few specifically pertain to multi-*jurisdictional* projects.[18]

Research ethics review is subsumed under the healthcare and health policy purviews of the individual provinces in Canada;[19] each its own legal and regulatory jurisdiction. Developing an efficient, yet ethically rigorous method of conducting ethics review for projects across multiple provinces, therefore, presents a formidable challenge. To this end, the *Tri-Council Policy Statement (TCPS2-2014)*[20]—a pan-Canadian ethics document binding researchers and institutions funded by the three federal funding agencies—puts forth three alternative models for research ethics review: (1) independent ethics review with heightened communication between REBs, (2) delegated review and (3) reciprocal REB review (see table 1 for detailed characteristics).

The Maternal Infant Child and Youth Research Network (MICYRN) is one Canadian organisation that is developing innovative approaches to building an ethics model that draws from the strengths of both the independent and delegated review models. A federal not-for-profit society bringing together 20 maternal and child health research institutions across Canada, MICYRN facilitates reproductive and child health research by improving the quality of REB decision-making specific to research in this field. Indeed, many Canadian maternal and child health research studies often involve more than 20 sites across the country. Under the current independent ethics review model—that is, an institution-by-institution approach—the network estimates that it can take upwards of 2 years for a study to be approved at all sites (provided that researchers plan ahead and anticipate the respective requirements of all the participating REBs). Alternatively, MICYRN provides affiliated researchers and REB committees with 'an integrated infrastructure underpinned by a coordinating center and overseen by a common governance structure, that removes barriers and builds capacity for high quality health research...'.[21] Hence, MICYRN acts as a 'one-stop shop' for multi-jurisdictional reviews.

Acting in concert and without a legal mandate via inter-institutional agreements (reciprocal recognitions), the national

Table 1 TCPS2 descriptions of independent, delegated and reciprocal research ethics review models

Alternative model	TCPS2 description (Chapter 8)[11]
Independent ethics review by several REBs	'The REBs involved at each participating institution conduct an independent research ethics review and provide their separate decisions, either concurrently or sequentially. The level of ethics review for research that involves multiple REBs and/or institutions shall be proportionate to the risk involved in the research (see Article 6.12). […] When multiple REBs are involved, the principal investigators should work with their REBs to formulate a strategy to address procedural inconsistencies or substantive disagreements that may arise among the participating REBs'
Research ethics review delegated to an external, specialised or multi-institutional REB	'Institutions may allow research on specialized content or research methods to be reviewed by an external, specialized or multi-institutional REB, where such a body exists. External, specialized or multi-institutional REBs may be established regionally, provincially/territorially or nationally, as necessary. Two or more institutions may choose to create a single joint REB, or to appoint an external REB, to which they delegate research ethics review. This delegation of review may be based on geographical proximity or other considerations such as resources, volume of reviews or shared expertise. […] In the official agreement between the selected REB and the institutions submitting research for ethics review, the external, specialized, or multi-institutional REB shall agree to adhere to this Policy'
Reciprocal REB review	'Multiple institutions may enter into official agreements under which they will accept, with an agreed level of oversight, the research ethics reviews of each other's REBs. This might involve specific agreements between institutions for sharing their workload. Alternatively, institutions may decide that reciprocity agreements should be established for the ethics review of each relevant research proposal on a case-by-case basis. In either case, researchers shall ensure that the reviewing REB is provided with any relevant information about the local populations and circumstances that would ordinarily be available to the local REB, and that may have a bearing on its review. The reviewing REB might call upon local REBs to provide information in addition to that provided by the researchers'

REB, research ethics board; TCPS2, Tri-Council Policy Statement.

MICYRN Ethics Board brings together the chairs and one representative of each member institution's committee to review multi-site protocols. Such a comprehensive review allows the membership to share input and discuss the submitted documentation at one time. Local REBs from participating institutions make their final decisions upon receiving MICYRN's review. Given the institutional representation on the MICYRN Committee, the final review at the local level is as streamlined as possible. This approach is particularly important in paediatric research where provincial variations in the special legal protections afforded to minors often contribute to inconsistent ethics review. Representation from each of the MICYRN member sites allows for discussion and resolution of jurisdiction-specific issues, and ensures that future decisions are applicable to all participating sites. The advantage of this delegated approach is the representative function afforded to researchers and REBs across multiple jurisdictions, and the enhanced communication and cooperation it promotes among them. The delegated approach facilitates the harmonisation of ethics policies and documents (such as consent) and draws attention to regional differences in the interpretation of such policies (such as age of consent).

MULTI-JURISDICTIONAL REVIEW OF ACCESS REQUESTS: CANADIAN PARTNERSHIP FOR TOMORROW PROJECT

To achieve the statistical significance in genomic research, large numbers of samples and data are required.[22] Providing access to data and samples is seen as a scientific necessity and also an ethical one, supported by international and Canadian policy.[23] Participant altruism, public trust and accountability of medical researchers underpin the position that data and samples should be openly shared with the research community to facilitate high-quality science and maximise benefits. Determining the degree of appropriate ethical oversight for such collaborative projects has proven more challenging. For instance, should a biobank project that includes cohorts in different jurisdictions require interested researchers to apply to numerous regional committees for access to its data/samples? Or is it possible to create a national process whereby applications are centralised and arrangements harmonised?[24] Here, lessons can be learned from the Canadian Partnership for Tomorrow Project (CPTP).

CPTP is comprised of five participating cohorts (BC Generations Project, Alberta Tomorrow Project, Ontario Health Study, Quebec's CARTaGENE and Atlantic PATH). Together, the cohorts have enrolled over 300 000 Canadians between the ages of 35 and 69 years who are followed throughout their adult lifetimes. The goal of CPTP is to explore how genetics, environment, lifestyle and behaviour interact and contribute to the development of cancer and other chronic diseases.[25] To this end, the study collects health, lifestyle and environmental information from participants over several decades. Researchers also collect biological samples as well as physical measurements. Through partnership, the cohorts have created a federated CPTP infrastructure with a common operating framework. The framework recognises the nuances and local specificities of each cohort while still facilitating their integration in the collaborative project. To achieve this, harmonisation of approaches and tools has been the key.

Consent forms for the five participating studies all provide access to their data and samples to Canadian and international researchers, but with certain conditions (eg, necessary approvals).[14] CPTP proposes a national access system that allows researchers applying for access to data from two or more cohorts to benefit from a one-stop-shop process to reduce delays and inconsistencies. This avoids a laborious and inefficient submission mechanism to multiple bodies across the country. Under the current proposal, applicants who have obtained prior ethics approval from their institution can submit their access requests to CPTP's Access Office. This Office will then assess it for consistency with CPTP's mission as well as for completeness in collaboration with a centralised access coordination centre. Recommendations along with a feasibility review will be sent to a national access oversight committee (AOC), which makes a decision on the application. The AOC is formed of representatives from the access committees of each participating cohort. This allows for representation from each region and upholds the terms of the consent forms signed by the research participants. While this is not an ethics

review, this mechanism is inspired by the delegated approach outlined in the TCPS2-2014. CPTP's streamlined access model will reduce delays and redundancies in the evaluations, hence encouraging more researchers to apply.

HOW DO THE CANADIAN MODELS FIT INTERNATIONALLY?

As sequencing has become the preferred scientific tool for biomedical research in the 'omics' disciplines, so too have issues of data custodianship, security and analysis emerged as immediate areas for further discussion and collaboration.[26] Scholars term this the era of Big Data in research, and others call for a parallel initiative to promote big collaboration.[27] The recent Framework for Responsible Sharing of Genomic and Health-Related Data[28] exemplifies this. Like many large-scale research projects, Big Data research falls victim to the inefficiencies of the independent multi-jurisdictional reviews. Ethics must, therefore, be negotiated at all levels of Big Data, from collection, to storage, sharing and even publication, domains that largely fall under the remit of jurisdictional policies and laws. The diversity of legal structures among collaborating institutions is well recognised, but achieving a common denominator of ethics values and protections in the context of Big Data remains less intuitive.

The Canadian models proposed here break the current status quo of research ethics review, and represent a microcosm of the ethical issues and Big Data management strategies for multi-jurisdictional review unfolding on the global stage. Efficient ethics review, open data-sharing practices and harmonised data-access agreements are universal considerations for multi-jurisdictional review processes, irrespective of the specific jurisdictions implicated. In addition to MICYRN and CPTP, international approaches to multi-jurisdictional review can also look to the conceptual models and experiences proposed by the Ethics Review Safe Harbor, the Global Alliance for Genomics and Health (GA4GH) and the International Cancer Genome Consortium (ICGC).

Pursuant to the ideals of an efficient yet rigorous review process, the Ethics Review Safe Harbor[29] prioritises mutualism with respect to data-access agreements and ethics review across jurisdictions. Its goal is to create an ethics governance mechanism adapted specifically for international data-driven genomics research projects. Much like MICYRN's model—but on an international scale—the Safe-Harbor concept proposes a central ethics review body that doubles as a 'forum for review and follow-up of policies concerning ethics norms'[19] for international genomics research.

Open data-sharing practices and the harmonisation of international data-access agreements are sister initiatives that together help to build health research collaboration. GA4GH expands the scope and practicality of international collaboration in genomics through optimising models of data sharing.[30] To GA4GH, data sharing is the key to progress in the data-driven world of biomedical research. A right of all citizens to benefit from advances in science and the right of scientists to be recognised for their contributions ground the foundational principles of GA4GH within a human rights framework.[31] Other principles include respect for families, communities and individuals; advance research and scientific knowledge; promote health, well-being and the fair distribution of benefits; and finally to foster trust, integrity and reciprocity.[18]

In turn, ICGC is a proof of concept that an organised, tiered body for data access can operationalise principles of solidarity and universality. It does so, in part, by easing current barriers to data access[32] without compromising privacy or security.[33] The controlled data-access strategy that both ICGC and CPTP endorse supports the data demands of international research projects, and addresses privacy concerns research participants frequently cite as a primary reason for limiting consent to share their data.[34]

Taken together, the projects presented in this article highlight how the spirit of interoperability and harmonisation of ethics norms in Big Data research transcend jurisdictional boundaries. They bring together Canadian and international researchers alike under the auspices of research collaboration for the betterment of population health globally. The successes of multi-jurisdictional projects will increasingly rely on coordinated, streamlined ethics review process coupled with ethical, efficient and economical data-access systems.

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