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A Systems Approach to Human Research Protection: Innovation in Healthcare

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Abstract: Canada has a fragmented regulatory and governance approach to research involving humans. This complex regulatory environment makes it difficult for research institutions to adequately oversee the conduct of research involving humans. The University Health Network (UHN) in Toronto has implemented a systems approach as a mechanism of establishing more effective oversight for all research involving humans. An Institutional Authorization model promotes a safety culture and provides the institution with a mechanism to monitor and provide feedback to the leadership about system processes. This model allows research institutions to minimize risk and identify opportunities to generate efficiencies which may be applied to other sectors. The development of national standards is an innovative approach in healthcare which ensures that organizations conducting human research in Canada have appropriate procedures and structures to maintain oversight of human research, and promote a culture of research safety and quality through the creation of a trust framework.

Keywords: Research ethics; human research; research ethics board; research ethics committee; institutional review board; human research protection program; institutional authorization; accreditation; standards development.

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1 Introduction

Canada has a fragmented regulatory and governance approach to research involving humans. There are federal guidelines for institutions receiving federal funds issued by the Interagency Advisory Panel on Research Ethics (PRE), and federal guidelines on research integrity and conflict of interest issued by the Interagency Advisory Panel on Responsible Conduct of Research (PRCR) (Alas et al., 2017). Canada has federal regulations for human research involving investigational drugs, medical devices and natural health products issued by Health Canada, and it also has varying federal (PIPEDA) and provincial (PHIPA in Ontario) regulations relating to the privacy of personal health information. In addition, there are federal regulations for radiation safety, transportation of dangerous goods, the use of controlled goods, and provincial regulations on biosafety (Lamontagne et al., 2021).

This complex regulatory environment makes it difficult for research institutions to adequately oversee the conduct of research involving humans that may involve some or all of these regulations and guidelines. Research Ethics Boards (REBs)/Research Ethics Committees (RECs)/Institutional Review Boards (IRBs) have been the main regulatory bodies to assuming the responsibility for the oversight of research involving humans even though their mandate and focus is to ensure the ethical feasibility and appropriateness of research projects (National Research Service Award Act, 1974; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978; Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, 2014). Owing to this complexity, the REB is conventionally regarded as the main gatekeeper controlling access to research activities (Legand, 2010; Owen et al., 2009).

2 Research Ethics Board Review Ethics Creep

Over time, the REB had become responsible for ensuring that all other regulatory, compliance, service provision, and impact assessment activities would be reviewed prior to granting its approval. For researchers, this had several disadvantages as they would need to be aware of all of the approvals required in addition to that of the REB (if the REB was not coordinating and overseeing this process). In many cases, this involved completing multiple applications to these relevant departments which duplicated effort, generated multiple reference numbers and also repeated similar information entered into all of the application forms. This did not ensure that all required approvals were, in fact, obtained and that no review processes and approvals were missed by the researcher that would potentially create delays in the initiation of the study.

The rapid increase in the size and complexity of the research enterprise also meant that the REB would need to take on areas not traditionally associated with ethical feasibility and appropriateness such as privacy, conflicts of interest, and other aspects of research integrity, often including the responsible conduct of research (Friesen et al., 2018; Nuttgens, 2021). This is commonly referred to as ethics or mission creep (Robson and Maier, 2018). The REB's responsibilities were expanding in a framework where REB members were, in most cases, completing these tasks on a voluntary basis or as

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"community service" not always formally recognized by research and academic institutions for promotion and tenure evaluation purposes.

In institutions with a lower volume of studies or with a more centralized research infrastructure, this type of coordination and oversight was manageable. However, in research organizations with a higher volume of studies or a more specialized or decentralized infrastructure, this oversight could become more challenging. Furthermore, in most cases, it was more difficult for the institution to cross-reference these multiple applications in a way to ensure that all of the required approvals were obtained. Therefore, institutions could not be sure that their regulatory oversight was indeed complete. It was also more problematic for research institutions to be able to track the progress of studies and later report on all research activities occurring under their auspices. However, the major disadvantage for an institution was the ability to suspend a research study on grounds unrelated to ethical feasibility and appropriateness. In these situations, the institution would try to make a case to the REB to withdraw their approval while understanding that their mandate may not be able to accommodate this type of request.

3 The Conception of the Human Research Protection Program

The notion of a Human Research Protection Program (HRPP) seems to have been conceived in 1995 in the Canadian "Deschamps Report" (Deschamps et al., 1995). The term itself seems to have originated in two major initiatives in the United States to create standards for accreditation of human research. The first was an initiative by Public Responsibility in Medicine and Research (PRIM&R) and another as a result of a collaboration between the National Committee for Quality Assurance (NCQA) and the Veterans Administration (VA). Both initiatives involved the development of standards for human research accreditation and prompted the Secretary of the US Department of Health & Human Services (HHS) and the Institute of Medicine (IOM) to conduct a study on the protection of human research subjects. These initiatives eventually identified the HRPP as the system of oversight that was recommended as the optimal method to oversee research involving humans (Institute of Medicine, 2001).

A Human Research Protection Program (alternately known as a Human Research Participant Protection Program) is an organizational-wide program composed of all entities involved in human research protection where the responsibility for research participant protection is shared among these entities within the organization under a unified leadership with financial and operational control over all the aspects of the program.

Americans were quick to establish an accreditation program for human research and the Association for the Accreditation of Human Research Protection Programs (AAHRPP) was founded in 2001 with the first organizations accredited in 2003. Currently, there are hundreds of accredited HRPPs around the world, the majority of which are represented by American academic health centres such as Johns Hopkins Medicine, Harvard University Faculty of Medicine, the Mayo Clinic, among other prestigious entities (Association for the Accreditation of Human Research Protection Programs, 2018).

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In Canada, after the release of the Deschamps Report in 1995, the National Council on Ethics in Human Research (NCEHR) began an initiative towards accreditation (Owen and Davey, 2006) which was followed up by convening The Experts Committee for Human Research Participant Protection in Canada (2008). Issues related to funding, governance structure and oversight jurisdiction of the eventual accreditation body led to continued discussions over the next 10 years by various consortia and committees without a consensus ever being achieved (Canadian Clinical Trials Coordinating Centre, 2016; 2018). However, there were no standards for human research in Canada on which an accreditation program could be based.

Few Canadian research organizations opted for voluntary accreditation by AAHRPP, largely due to the focus by AAHRPP on US normative documents and the significant cost and effort to successfully complete the accreditation program. Without the establishment of a human research accreditation program in Canada, most Canadian organizations have chosen not to create HRPPs. In fact, as of 2021, to our knowledge, only Sunnybrook Health Sciences Centre in Toronto, and the Horizon Health Network (one of two regional health authorities serving New Brunswick) have formally established HRPPs. Horizon Health Network established an HRPP as a systematic approach to ensuring adherence to ethical, methodological and regulatory guidelines relevant to human research participant protections and to facilitate the responsible conduct of research throughout the Horizon network. Horizon Health Network's became the first regional health authority in Canada to have its HRPP accredited in 2020 by a human research accreditation body established in Canada (McKinnon, 2020).

4 REB Local Review versus the "Single REB Review for Multisite Research" Model

REB ethical review has traditionally been conceived of as a local review occurring at each site where research activities are proposed to be conducted. This was rooted in the belief that the expertise and constitution of the REB will be made with members from the institution and representing its surrounding communities. This was to reflect that local norms and perspectives should be taken into account when making decisions on the ethical feasibility and appropriateness of the research being proposed in that organization or community (Klitzman et al., 2019).

At the same time however, when human research has to be conducted at multiple sites, researchers found the review undertaken at these multiple sites, whether in the same country or internationally, yielded different and sometimes inconsistent results for the same study (Klitzman et al., 2019). This would extend the time taken for the ethical reviews to be completed across multiple sites and would occasionally result in different REBs mandating varying requirements of the research team that were at times in conflict with decisions rendered elsewhere. This could result in some REBs asking for requirements which may not agree with the recommendations of others, which may then require additional iterations between the researchers and these dissenting REBs, thus lengthening the process even more. Human research requiring reviews by multiple REBs could therefore be a lengthy and unpredictable process.

As the research enterprise has grown in scope and complexity, including studies and trials spanning multiple sites and, in many cases, many countries, a model of "single REB

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review for multisite research" has evolved (Petrova and Barclay, 2019). This involves one REB (the "REB of Record" or "Board of Record") designated to review research activities proposed to occur at multiple sites (Diamond et al., 2019). In the past, the REB at each site would be required to review these ethics submissions and it was deemed an ineffective use of resources that took an inordinate amount of time and a duplication of resources and efforts. However, if the REB were required to coordinate the review of all required approvals at each individual institution, this would be challenging without including each individual REB in the "single REB review for multisite research" model (Klitzman et al., 2019). This reinforces the need for an HRPP to be in place at each institution so that the non-ethical reviews can occur even when the institutional REB is not reviewing a study (Lidz et al., 2018; Taylor et al., 2019).

In Ontario, first with the development of regional disease-specific research ethics boards like the Ontario Cancer Research Ethics Board (OCREB) (Chaddah, 2008) and later with the implementation of a provincial Board of Record process for multisite research coordinated by Clinical Trials Ontario (CTO), there was an understanding that when the ethical review was undertaken by an external Board of Record (Alas et al., 2017), it would be more challenging for site specific oversight activities to continue to be coordinated by the REB at each institution. Indeed, these site specific oversight activities needed to be undertaken by processes at the site institutions. The Board of Record would be unable to undertake these activities at the other institutions involved in multisite research. Therefore, a program needed to be in place at each institution to ensure oversight of the non-ethical reviews when the ethical review is conducted by a Board of Record external to the organization. This HRPP would be complementary to the single site review model for multisite research whether using a Board of Record process based on institutional, disease-specific, population-specific REBs or a combination of these.

5 The Evolution of the Institutional Authorization Model

In 2011, the University Health Network (UHN) in Toronto was one of the first organizations in Canada to implement an Institutional Authorization (IA) model for research involving humans. This introduced a systems approach as a way of establishing improved oversight for all research involving humans. Such a systems approach includes the REB as well as other important stakeholders in the conduct of research and research integrity (Fontanesi et al., 2018). For example, other compliance and regulatory stakeholders such as the Pharmacy, Biosafety, Radiation Safety, Research Integrity, Responsible Conduct of Research, Privacy and Conflict of Interest groups would review research proposals for their feasibility and appropriateness (Trace and Kolstoe, 2018). Indeed, other service providers and impact assessment groups would also need to review proposed research before the start of research activities: Contracts, Laboratories, Imaging, etc. (Desai et al., 2017)

This innovative approach allows the REB to focus on the review of ethical feasibility and appropriateness without their resources being stretched to review additional institutional responsibilities (Friesen et al., 2021). In addition, it allows the research institution to reduce risk in other domains unrelated to ethics such as research integrity, responsible conduct of research, contractual agreements, privacy and conflicts of interest. The IA model provides the research institution with the discretion to suspend and

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terminate research even if ethical appropriateness was not at issue. An IA model would also support the recent implementation of the "single REB review for multisite research" model where all non-ethical approvals could take place even if an institutional REB is not involved in reviewing that submission.

IA is based on similar components that make up an HRPP such as resources, procedures, auditing, training, funding, and leadership. The initial implementation of IA at UHN involved the development and enactment of an Institutional Authorization Policy for research involving humans. This policy establishes the new IA status as the requirement to initiate research activities at UHN. This institutional requirement will now become the standard at UHN to conduct research involving humans even though the regulatory requirement is still based on REB approval as per human research guidelines and regulations. The institution reduces risk in all regulatory and compliance domains and therefore can comply with all related regulations and guidelines stated at the outset of this case study (responsible conduct of research, research integrity, privacy, radiation safety, controlled goods and biosafety).

These activities could be categorized as three different activities: compliance and regulatory; service provision; or impact assessment. Compliance and regulatory activities might include adherence to local, provincial or state as well as national and international requirements (such as privacy, occupational health and safety, biosafety, radiation, training, and good clinical practice (GCP)). Service provision might include laboratory, imaging and other clinical or research services. Impact assessment might include the impact on health professions, clinical resources, or patient and research participant populations.

6 Institutional Authorization as a Pathway to the Human Research Protection Program

IA is based on the foundational framework of an HRPP but may not meet all of the stated objectives of an HRPP such as unified leadership and control of all resources under one program. It is, however, a major improvement over the current model that is based on the REB ensuring that all approvals and requirements are met on behalf of the institution. IA does have a distinct advantage in that it is founded on an institutional policy model that establishes a new requirement to begin all activities associated with research involving humans. More importantly, IA allows the institution to suspend or terminate a study without having to make a case to the REB, an independent, arm's length group, in order to withdraw their approval.

The systems approach to human research oversight allows for all of the components required to review and oversee research involving humans to be part of the authorization process (Deschamps, 2011). It ensures that the adequate resources are applied to the system, that these staff are properly trained, that the system is funded appropriately, and that the quality of the system is monitored with feedback going to the leadership. The leadership can then use the feedback to continually review the operation of the system and ensure that the resources, procedures, training and funding can be maintained and are adjusted as necessary. Such a systems approach maintains the efficiency of the system and can lend itself to continual assessment and improvement (Fontanesi et al., 2018)

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where many of the system components used to function in operational silos within the institution.

An IA model promotes a safety culture and provides the institution with a mechanism to monitor and provide feedback to the leadership about system processes. This model allows for the management of its people, processes and tools to more effectively minimize risk and identify opportunities to improve efficiencies. For example, the airline (Levitin, 2008) and nuclear power sectors (British American Security Information Council, 2016) have also successfully implemented systems approaches to improve safety which may be considered and applied by other sectors and industries.

7 Evaluation of the Human Research Protection Program

There has been little evidence in the literature about the effectiveness of HRPPs, and for that matter that of REBs, even though there have been over fifteen years of experience and data collection in the United States (Tsan, 2018). Researchers and industry sponsors have focused on reducing the time of the approval process while human research administrators and institutions have been more concerned with improving the quality of the review process. AAHRPP gathers self-reported data on their accredited organizations and there is anecdotal evidence that both the REB's time to approval and the number of audit findings seem to decline over time (Association for the Accreditation of Human Research Protection Programs, 2018). These are positive indicators, however, there has been renewed interest in establishing reliable and evidence based metrics for the effectiveness of HRPP quality and performance. An IA model would enable better tracking of the entire authorization process (the so-called "Time to Institutional Authorization (IA)") rather than basing solely on the REB approval process.

The launch in 2018 of a Canadian human research accreditation body, Human Research Accreditation Canada, has confirmed the AAHRPP findings for the small number of Canadian accredited organizations and has committed to establishing robust metrics of HRPP evaluation (Parente, 2018). An IA model will assist in this regard, as all components of the HRPP will need to be tracked and monitored, not just the time to approval by the REB.

8 Developing National Standards to Promote a Culture of Research Quality

National standards frame, guide, and normalize almost every aspect of our lives, promoting best industry and safety practices, and ensuring the interoperability of such practices. Canada has national standards for health care, information technology, accounting, agriculture, plumbing, electricity, and numerous other sectors of our society (Benefits of applying standards, 2021; Sarna, 2017). However, although we have had standards for healthcare for about one hundred years and standards for animal research for about fifty years, there have been no Canadian standards for human research (Hayes, 2020). The development of national standards for human research promotes uniform conduct and oversight of human research from one organization to another, from one province to another, and indeed from one country to another (Hebert and Saginur, 2006; Legand, 2010). Standards are based on requirements that clarify and focus the

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interpretation of policies and regulations when institutions create their procedures, specifically around mitigating disruptions (Benefits of applying standards, 2021). When an institution follows procedures in compliance with national standards, it raises the level of quality of the research they conduct, and increases the protections of the research participants enrolled in their research (Kizer, 2001). And when all Canadian institutions do the same, it breaks down barriers to interoperability leading to harmonization, collaboration and partnership between organizations in Canada and worldwide (Alas et al., 2017).

The organizational structures recommended by national standards will be responsible for the way education is designed and delivered to stakeholders and will be critical to creating and promoting a culture of research safety and quality, and enhance education for researchers and healthcare professionals in those institutions. If organizations choose to undertake conformity assessment of their procedures against the established national standards, through human research accreditation, then when these organizations collaborate with other accredited organizations, they will become part of a "trust framework" not only nationally but internationally. This term is normally used to describe the technologies and policies to enable and support a framework for secure digital transactions (Schultz, 2006), but the concept would also be applicable and appropriate to describe and characterize the trust established between organizations that have been accredited against national standards for human research.

The development of national standards will allow for the establishment of a "trust framework" for the conduct and oversight of research involving humans in Canada (DIACC Trust Framework Expert Committee, 2016). As a leader in the establishment of standards in many sectors, Canada will now benefit from having national standards for human research which will greatly influence healthcare education: a course of action that is optimal for transforming our hospitals into learning healthcare institutions (Asch et al., 2020).

9 Conclusion

This IA model creates a more effective systems approach to protect the safety of human research participants and establishes a framework for developing an HRPP. It improves upon the currently, widely used model where the REB coordinates all reviews on behalf of each institution. The IA model enables the more effective application of the "single REB review for multisite research" model now being implemented in North America and internationally.

The IA systems approach also lends itself to improved monitoring and development of metrics and key performance indicators, and would therefore be readily appropriate for the evaluation of HRPP quality and performance assessments that are part of human research accreditation processes. Other independent groups have proposed evaluation initiatives including the Canadian Clinical Trials Coordinating Centre (CCTCC) in Canada (Canadian Clinical Trials Coordinating Centre, 2018) and The Consortium to Advance Effective Research Ethics Oversight (AEREO) in the United States (Lynch et al., 2018).

Human research standards development engages experts from across the country to propose national standards of relevance to Canadians conducting, overseeing, and

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participating in human research (McClintock, 1997). National standards ensure that all organizations conducting human research in Canada have appropriate procedures and structures to initiate and maintain oversight of human research and promote a culture of research safety and quality through regulatory compliance and education (Benefits of applying standards, 2021). By applying a systems approach, relevant institutional stakeholders are engaged and participate in ensuring compliance and education with leadership support to promote the protection of human research participants (Colchester, 2018).

Despite the gap in the literature with respect to the evaluation of HRPP and more broadly REB quality and performance assessments, there has recently been an interest in a more effective approach to protect the safety of human research participants and highlighted the need for human research standards (Koski et al., 2018). This systems approach establishes a trust framework for developing an HRPP that lends itself to accreditation consistent with what is currently in place for animal research and patient care in Canada, and ultimately allows more effective knowledge translation from research to society (Legand, 2010).

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