

Research Ethics Broadly Writ: Beyond REB Review

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*"...no aspect of research, from formulation of initial hypothesis down to final clinical acceptance, is devoid of ethical significance."*¹

In Canada, as well as elsewhere, governments, sponsors, institutions, and researchers tend to view research ethics almost entirely through the lens of research ethics board (REB) review. According to these stakeholders, research ethics *is* REB review. In this paper, we aim to show that there is much more to research ethics; health research is a multi-stage process and each stage has unique ethical implications that may or may not fall under the mandate of the REB. We also aim to show that our current governance system fails to address those ethical issues lying outside of the mandate of the REB. Finally, we consider two possible explanations for this state of affairs: (1) the presumption that REBs can handle all of these issues; or (2) failure to recognize of the broader ethical issues associated with research involving human subjects. Ultimately, we reject both of these explanations in favour of a third: key stakeholders lack the foresight and political will to make the necessary changes.

We begin by providing a moral geography of research involving human subjects. We describe the various stages involved in the planning and execution of research involving human subjects, and identify some of the ethical issues arising at each stage. We then explore the role of the REB within the process as a whole, contrasting the *de jure* role of the REB (as specified in the *Tri-Council Policy Statement*) with its *de facto* role in the current system. We conclude by calling for systematic

efforts to redress the gaps in our current governance system.

We note, however, that though many of our points apply to all research involving human subjects, some are clearly more relevant to the conduct of health research in general and clinical research in particular. This is partly an artefact of the authors' expertise and partly because our Network is centred on health research. But the focus on health research also allows us to simplify our remarks since taking into account the sometimes significant variances within different types of research involving human subjects would be very difficult within the ambit of a single paper.

The problem: ethical tunnel vision

Ten years ago, one of us concluded a report on the governance of research involving human subjects for the Law Commission of Canada with the following observations (among others):

[W]ith respect to ethical conduct of HRIHS [health research involving human subjects] there [are] three central ethical objectives:

- a. The **promotion** of socially beneficial research
- b. The **protection** of research participants
- c. As an overarching aim, the maintenance of **trust** between the research community and society as a whole.



These objectives enjoy broad social endorsement and are represented in the numerous international, national and professional codes and [sic] aimed at the conduct of ethical research involving humans. But when we compare these three objectives with what actually takes place in the name of ethical research, we find a narrowing of concerns that could aptly be described as **ethical tunnel vision**, in which the three ethical objectives are given the most minimal instantiation. In effect, our current governance processes for HRIHS reduce research ethics to a dangerously simplistic concern for REB approval that is often functionally an approval of consent forms. The result is that the REB approval process and informed consent bear far more moral weight than they can possibly sustain.²

Though there has been some progress toward improving this situation over the last decade, these remarks remain all too true today. For the most part, governments, sponsors, institutions, and researchers continue to view research ethics almost entirely through the lens of REB review.

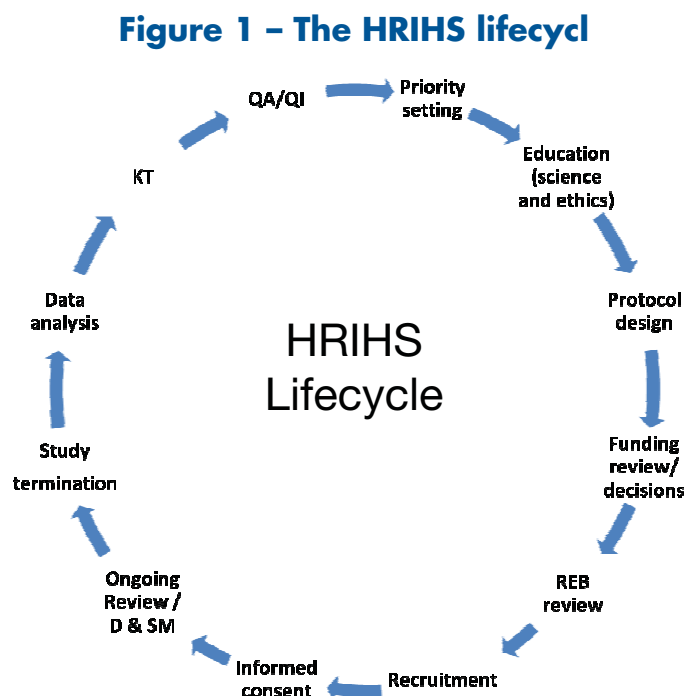
This situation is problematic for a number of reasons. First, even in ideal circumstances the REB system cannot meet the above stated ethical objectives on its own. Second, current circumstances are far from ideal. REB function is hampered by a chronic lack of commitment and resources at the macro (societal), meso (institutional), and micro (individual, i.e., project or researcher) levels.

The narrow vision of research ethics as REB review, combined with the *de facto* limitations of the REB system, creates conditions ripe for institutional failure. First, tensions between REBs and researchers are exacerbated: REBs are overburdened by obligations (ethical and administrative) that should be borne by other stakeholders (e.g., governments, sponsors, institutions, and researchers); and the offloading of ethics onto the REB reinforces both the impression of REBs as the “ethics police” and the supposition that ethics is “somebody else’s problem” (i.e., the REBs). Institutional failure, finally, threatens to undermine the trust between research community and society that is required for the on-going support and conduct of socially

beneficial research. Recognizing the shortcomings in our ethics governance system is a first step toward managing the substantial risks involved.

The Health Research Involving Human Subjects lifecycle

In order to better understand the limitations of our current governance system, we need a clear picture of the process the system is supposed to govern; the process of, or various processes involved in, conducting health research involving human subjects (HRIHS). We call this the ‘HRIHS lifecycle’ (see Figure 1). The lifecycle includes twelve elements. Each element comprises an essential stage in the conduct of HRIHS, and each occurs at one or more levels (macro, meso, or micro). Furthermore, the ethical issues arising at each stage are themselves macro, meso, micro, or some combination thereof. It is important to distinguish the level of the element from the level at which the ethical issue(s) arise because, in some cases, the level of the issue does not correspond to the level of the element. For example, though data analysis typically occurs at the micro level because it is the responsibility of the researcher(s), it raises important ethical issues at the micro, meso, and macro levels. The elements comprising the HRIHS lifecycle are: (1) priority setting; (2) education – scientific and ethical; (3) protocol design; (4) funding review/decisions; (5) REB review; (6) recruitment; (7) informed consent; (8) ongoing review/D & SM; (9) study termination; (10) data analysis; (11) knowledge translation (KT); and (12) QA/QI.



review; (5) ethics review; (6) recruitment; (7) informed consent; (8) monitoring; (9) study termination; (10) data analysis; (11) knowledge transfer (KT); and, (12) quality assurance and quality improvement (QA/QI) – of all relevant processes.

For the most part, the elements themselves are self-explanatory. However, our decision to focus on these particular elements and to represent them in this manner is not. Clearly the HRIHS lifecycle could include more or less elements, with corresponding levels of detail. Furthermore, the process as a whole could be represented differently. For example, we could have represented the elements non-sequentially or linearly as

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opposed to cyclically. We hope that the HRIHS lifecycle – as represented here – strikes an effective balance between comprehensiveness and economy, but our primary aim is to bring out the procedural and ultimately ethical complexity of HRIHS. We have represented the whole process cyclically instead of linearly in order to emphasize the importance of continuous learning in the HRIHS enterprise; the results of today’s research should inform the research of tomorrow. But we recognize that this picture is highly idealized. In reality, the elements are not always sequential (e.g., recruitment and consent can occur after ongoing review by a data and safety monitoring board (DSMB) has begun; and opportunities for KT arise at multiple points in the lifecycle). We also acknowledge that in some cases it may be misleading to represent some elements as discrete steps (e.g., REBs are responsible for reviewing protocol design, and the responsibilities of a DSMB include recommending study termination). Furthermore, it is far from clear that the real world of HRIHS is accurately represented as a closed feedback loop given the fragmentary character of the enterprise and the lack of a systematic outcomes

measurement or QA.³ Finally, as noted above, life cycles for different areas of health research (e.g., research in population health, health behaviour, and infectious disease) would require somewhat different diagrams even though they would share many common elements with those indicated in Figure 1. Hence, Figure 1 should be viewed as an idealized picture of the HRIHS lifecycle, not a literal description.

The elements and the ethical issues

The crucial goal, for present purposes, is the illumination of the ethical complexity and richness of HRIHS. One of the things that the HRIHS lifecycle makes clear is that ethics review comprises but one of the twelve elements involved in the conduct of HRIHS. The other eleven elements are both procedurally and ethically distinct, raising unique challenges of their own. Since we will discuss the role of the REB in detail in later sections, we focus here on the other eleven elements in the HRIHS lifecycle. Assuming the above stated ethical objectives of research governance (i.e., the promotion of socially beneficial research, the protection of research participants, and the maintenance of trust) we highlight key macro, meso, and micro ethical issues arising at each step. We also indicate the level at which each element occurs. The results of this analysis are summarized in Table 1.

Priority setting

Level: Priority setting generally occurs at the macro and meso levels.

Ethical issues: Health research requires funding and, though the private sector funds an increasingly large share of health research, the public sector remains a significant source of financial support, particularly for “curiosity-driven” research. Funding priorities include not only direct support of research, but also support of research infra-structure including institutional funding, oversight, and training and education for new and established researchers. It also includes the funding of research institutions including positions for researchers, research workers, and trainees. Thus, even if explicit priority setting does not occur in the same way in the private sector (priorities there are generally determined by market demand as well as other criteria), fair and socially beneficial priority setting is ethically required in the public sector.⁴ Since societal resources are finite



Table 1 – Ethical challenges across the HRIHS lifecycle

Elements of the Lifecycle	Level	Illustrative Ethical Issues/Challenges		
		Micro	Meso	Macro
Priority setting	Macro/ Meso	<ul style="list-style-type: none"> - Choice of research projects. - Formulation of research questions. 	<ul style="list-style-type: none"> - Distributional justice. - Effective investment of societal resources. 	<ul style="list-style-type: none"> - Distributional justice. - Effective investment of societal resources.
Education	Micro/ Meso/ Macro	<ul style="list-style-type: none"> - A lack of interest in ethics education (including scientific integrity). 	<ul style="list-style-type: none"> - A lack of investment in ethics education (including scientific integrity) for researchers. 	<ul style="list-style-type: none"> - A lack of direction and support for institutional efforts for ethics education (including scientific integrity).
Protocol design	Micro	<ul style="list-style-type: none"> - Scientific validity (“good ethics demands good science”). - Respect for justice and inclusiveness, vulnerable persons, and justification of selection criteria. - A favourable ratio of risk to social benefit (including opportunity costs and non-exploitation). - A detailed plan for recruitment, informed consent, privacy, and confidentiality. 	<ul style="list-style-type: none"> - Articulating and enforcing standards of ethically sound research design. 	<ul style="list-style-type: none"> - Articulating and enforcing standards of ethically sound research design.
Funding review	Micro/ Meso	<ul style="list-style-type: none"> - Integrity of reviewers. - Conflict of interest. 	<ul style="list-style-type: none"> - Integrity of reviewers. - Conflict of interest. 	<ul style="list-style-type: none"> - Policy review. - Appointment of reviewers. - Transparency of decision making.
REB review	Meso	<ul style="list-style-type: none"> - To “help ensure that ethical principles are applied to research involving human subjects” (see section on The Role of the REB below). 	<ul style="list-style-type: none"> - Assurance of REB independence. 	<ul style="list-style-type: none"> - Policies and MOUs supporting independent review.
Recruitment	Micro	<ul style="list-style-type: none"> - Respect for vulnerable persons. - Therapeutic misconception. - Undue inducement. - Honest, respectful, and just subject selection. 	<ul style="list-style-type: none"> - Protection of research participants. - Support for training on appropriate recruitment. - Monitoring where needed. 	<ul style="list-style-type: none"> - Clear policies on ethical recruitment.
Informed consent	Micro	<ul style="list-style-type: none"> - Respect for free and informed consent as an on-going process. - Therapeutic misconception. - Undue inducement. - Capacity assessment. 	<ul style="list-style-type: none"> - Protection of research participants. - Support for training on seeking consent. - Monitoring where needed. 	<ul style="list-style-type: none"> - Support for training on seeking consent. - Monitoring where needed.
Ongoing review/ D&SM	Micro/ Meso/ Macro	<ul style="list-style-type: none"> - Informed consent as an on-going process. - Data monitoring. - Adverse events. 	<ul style="list-style-type: none"> - Informed consent as an on-going process. - Data monitoring. - Adverse events. 	<ul style="list-style-type: none"> - Policies and measures requiring on-going review.
Study termination	Micro/ Meso	<ul style="list-style-type: none"> - Validity concerns. - Participant safety. 	<ul style="list-style-type: none"> - Validity concerns. - Participant safety. 	<ul style="list-style-type: none"> - N/A
Data analysis	Micro/ Meso	<ul style="list-style-type: none"> - Interpretation. - Validity and value. - Publication bias. - Trust. 	<ul style="list-style-type: none"> - Validity and value. - Publication bias. - Trust. 	<ul style="list-style-type: none"> - Validity and value. - Publication bias. - Trust.
KT	Micro/ Meso/ Macro	<ul style="list-style-type: none"> - Return on investment (i.e., social value). - Communication of results to participants. - Publication bias. 	<ul style="list-style-type: none"> - Return on investment (i.e., social value). - Publication bias. 	<ul style="list-style-type: none"> - Return on investment (i.e., social value). - Publication bias.
QA / QI	Micro/ Meso/ Macro	<ul style="list-style-type: none"> - Data accessibility. - Accountability. - Improvement. 	<ul style="list-style-type: none"> - Data accessibility. - Accountability. - Improvement. 	<ul style="list-style-type: none"> - Data accessibility. - Accountability. - Improvement.



and public investment involves opportunity costs, priority setting raises significant questions concerning distributional justice and the effective investment of societal resources at the meso and macro levels. Priority setting also has a direct or indirect impact at the micro level, shaping researchers' choice of projects and the formulation of their research questions.⁵ We also note a complex set of ethical issues arising at the interface of public and private sector priority setting in such areas as tax policy, intellectual property regulations, and public-private partnerships. In sum, priority setting raises a host of issues of relevance to the promotion of socially beneficial research and the maintenance of public trust.

Education

Level: Education should occur at the micro, meso, and macro levels.

Ethical issues: Ideally, perhaps, education would not be subject to the changeable priorities of governments and markets. In actuality, these priorities have a profound influence on both the form and content of education. In recognition of this fact, we have located education after priority setting in the HRIHS lifecycle. Governments, institutions, and individuals (including researchers themselves) invest substantial resources in science education and the promotion and maintenance of scholarly standards (e.g., by establishing criteria for degrees, hiring, and promotion). By contrast, governments, institutions, and most researchers invest relatively few resources in ethics education with regard to research integrity in general, and the ethical conduct of research involving humans in particular.⁶ This state of affairs both reflects and reinforces the misconception that whereas, the norms of experimental design are internal to (or constitutive of) science, ethical norms are somehow external to science, pertaining only to its products. The widespread prevalence of this assumption no doubt contributes to the ongoing identification of research ethics with ethics review. Fundamentally, research ethics is seen as an external impediment to research as opposed to a set of obligations that are internal to it. A regrettable example of this is found in a recent report to CIHR on research priorities (the *Strategy on Patient-Oriented Research*), in which the only mention of participant protection characterizes it as an obstacle to be overcome.⁷ This lack of understanding about both the form and content of research education poses a major threat to all three of the ethical objectives of research

governance (i.e., the promotion of socially beneficial research, the protection of research participants, and the maintenance of trust).

Protocol design

Level: Protocol design generally occurs at the micro level, but research institutions (meso level) and research sponsors (meso and macro levels) have roles to play in conveying and encouraging ethically sound research design.

Ethical issues: Researchers represent a substantial societal investment in and of themselves. Thus, within the limits set by the funding available, protocol design also raises questions concerning the effective investment of societal resources at the micro level. Arguably, health researchers have an ethical responsibility to investigate socially valuable hypotheses. Consequently, both the choice of project and the framing of the research question have major ethical dimensions. More specifically, researchers are responsible for meeting the ethical requirements detailed in the second edition of the *Tri-Council Policy Statement (TCPS2)* and other applicable ethical, legal, clinical, and institutional standards including: (1) the scientific validity of the research plan; (2) justification of the inclusion/exclusion criteria to be used for subject selection; (3) a detailed plan for acquiring the informed consent of participants (including a copy of the consent form); (4) assurance that participation presents participants with a favourable ratio of risk to social benefit (non-exploitation at the micro level); and, (5) provision for compensation for potential harms to participants.⁸ These responsibilities are relevant to all three ethical objectives.

Funding review

Level: Funding review typically occurs at the meso level with appropriate macro level support.

Ethical issues: In the private sector, the decision to fund a particular research project is a corporate one made in the light of corporate objectives and priorities, including corporate social responsibilities. In the public sector, funding decisions are bureaucratic/academic decisions made with reference to the mandate (or priorities) of the sponsor in question. In both sectors peer review committees are charged with assessing the validity and originality of the proposed study, along with fit with the sponsor's priorities and mandate. Ethical concerns



are sometimes raised at this level, but typically ethics review is left to the REB. In Canada, where the pool of researchers in any given specialty is often quite small and/or geographically localized, it is often difficult to ensure that the review process is adequately blinded. This can raise significant concerns about conflict of interest at the micro and meso levels.⁹ On the other hand, ethical issues can arise due to the lack of appropriate expertise or care on the part of reviewers. Failure to mitigate concerns about the research funding review process may undermine public trust in the research enterprise.

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Recruitment

Level: Recruitment occurs at the micro level (i.e., it is the responsibility of the researcher(s)).

Ethical issues: Recruitment, which begins after a protocol has been approved by an REB, raises a number of specific challenges including concerns associated with therapeutic misconception, competitive enrolment and undue inducement, engaging in honest and respectful communications, and addressing justice concerns related to subject selection. If unmet, challenges related to recruitment of study participants pose a threat to the research participants and public trust.

Informed consent

Level: Informed consent occurs primarily at the micro level (i.e., it is the responsibility of the researcher(s) and/or their delegates). However, an adequate process for informed consent requires meso level attention through the REB, which has a responsibility to monitor informed consent processes in potentially difficult cases. Furthermore, macro level institutions (e.g., governments and sponsors) are responsible for setting clear policies around informed consent, including requirements pertaining to accountability mechanisms at the meso level.

Ethical issues: Therapeutic misconception and excessive inducements are a problem for recruitment because they threaten informed consent, a necessary condition for ethical study enrolment. Frequently, informed consent is reduced to the perfunctory and rushed signing of a consent form. Furthermore, lengthy and complex consent forms can vitiate rather than facilitate true informed consent on the part of prospective participants.¹⁰ Finally, though a signature may provide evidence of an informed decision to participate at the time of signing, it does not provide evidence of ongoing informed consent (as required by the TCPS2¹¹). If informed consent is viewed as a living process that continues throughout the duration of a study, it follows that informed consent requires evidence of knowing and willing participation over time. Currently, such evidence is not gathered so it is unavailable to relevant third parties (such as the REB or regulators). Informed consent is vital to research participant protection and to earning and sustaining public trust.

Monitoring

Level: Monitoring occurs at the micro (research team), meso (REB), and macro (Health Canada) levels.

Ethical issues: The previous section underlines the importance of monitoring throughout the duration of a study. Ongoing review of study conduct – including ongoing informed consent, accumulating data, and adverse events – is essential if we hope to protect both current and future participants and maintain public trust. Data monitoring may also play a significant role in establishing the validity and value of a study. Monitoring, thus, is vital to all three factors – research validity, participant protection, and public trust.

Study termination

Level: Study termination occurs at the micro level, but meso level bodies (i.e., DSMBs) and macro level bodies (i.e., sponsors and regulatory agencies) are frequently involved. Furthermore, appropriate requirements for study termination and DSMBs should be set at the macro level.

Ethical issues: Study termination raises scientific as well as ethical issues, many of which arise during protocol design. Choice of study end points, for instance, involves scientific as well as ethical considerations.



Similarly, the delineation of stopping rules requires balancing scientific and ethical considerations. On the one hand, if the stopping rules are too liberal (resulting in early termination) the validity of the results may be called into question, undermining the social value of the research. On the other hand, if the stopping rules are too conservative (resulting in later termination) participants may be put at risk without reason, undermining the ethical justification of the study. Finally, stopping rules may be triggered by safety concerns, or by unexpected results (clear benefit or clear harm). In either case, difficult trade offs must be made between the scientific goals of the study, and the well-being of the participants. All three ethical objectives are implicated.

Data analysis

Level: Data analysis typically occurs at the micro level (i.e., it is the responsibility of the researcher, though interim analysis is sometimes carried out by DSMBs).

Ethical issues: Data do not speak for themselves; they must be interpreted if conclusions are to be drawn. The interpretative process raises difficult ethical questions. For example, should outliers always be included in the analysis? If not, when is their exclusion justified? Depending on how these questions are answered, all three ethical objectives may be implicated.

Knowledge transfer (KT)

Level: Ideally, KT occurs at all levels.

Ethical issues: A study that lacks validity and social value is unethical because it puts research participants at risk for nothing. However, even a successfully concluded study examining a socially valuable question may nonetheless prove valueless if the results are not communicated to the community. Furthermore, effective KT is crucial to the integrity of the scientific enterprise as a whole. Systemic non-publication of negative results illustrates this point vividly. First, non-publication of negative results means that the risks undertaken by participants in these studies are not redeemed by the social value of the knowledge produced. Second, systemic non-publication biases the literature, thereby distorting the meta-analyses and systematic reviews central to evidence-based practice. Finally, failure to communicate results leaves subjects feeling that their participation in research was wasted. In sum, KT is crucial for the promotion of socially beneficial research and the maintenance of public trust.

Quality assurance and quality improvement (QA/QI)

Level: Ideally, QA and QI occurs at all levels.

Ethical issues: Absent salient measures of effectiveness and accurate assessment of those measures, it is impossible to determine whether the research system is achieving what it is supposed to achieve, to assure accountability, or to know where to focus our efforts in order to improve the system. Do we know, for example, whether HRIHS contributes to the advancement of knowledge or social good, as required by regulatory

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policies like the TCPS2? It is far from clear that we do. Indeed, in spite of the regulations, we continue to lack concrete measures of knowledge value (and many other ethically relevant variables). Similar points can be made about the governance system itself. Do we know if the governance system actually encourages socially valuable research, protects research subjects, and maintains trust? Again, it is far from clear that we do. What we do know is that REBs continue to operate in the absence of adequate QA and QI. As a consequence, REB decision-making is often arbitrary, contradictory, and non-transparent. To some extent, these problems stem from the structural limitations of the REB system: REBs are designed to function independently and *in camera*.¹² But these problems also underline the importance of improving QA and QI throughout the HRIHS lifecycle via, for example, the introduction of “virtuous learning loops”.¹³ As long as the status quo persists, we risk significant institutional failure and loss of trust. Ultimately, all three ethical objectives may be undermined by a failure to engage in QA and QI.



In sum, HRIHS is comprised of at least twelve distinct elements, eleven of which have been described above, and research ethics (or the governance of HRIHS) involves addressing the unique ethical challenges raised by each of them. If this analysis is even roughly correct, the upshot is a very broad conception of HRIHS and of research ethics.

The role of the REB

At this point we are faced with an important question: what is the role of the REB in the HRIHS lifecycle? It is worth noting that such a broad conception of research ethics – once it is rendered explicit – in and of itself casts doubt on the identification of research ethics with REB review; *prima facie*, REB review only addresses a narrow subset of the ethical issues arising across the HRIHS lifecycle. As we noted at the outset, however, governments, sponsors, institutions, and researchers tend to view research ethics almost entirely through the lens of REB review. According to these stakeholders, research ethics *is* REB review. If we take this view seriously (in light of the broad conceptions of HRIHS and research ethics detailed above), it would seem to imply a very expansive role for the REB: to wit, the REB is responsible for ensuring that ethical principles are applied across the whole HRIHS lifecycle. In order to accomplish this (Herculean) task, presumably, REBs must leverage their authority as reviewers to enforce appropriate standards both retrospectively (for the steps undertaken prior to ethics review) and prospectively (for the steps undertaken following ethics review).

In reality, however, REBs are neither situated nor resourced to perform this expansive role effectively, even if they do enjoy gatekeeper status in the HRIHS lifecycle. For one, the mandate of REBs is local. According to the *TCPS2*, REBs are mandated by *institutions* to:

review the ethical acceptability of research on behalf of the institution, including approving, rejecting, proposing modifications to, or terminating any proposed or ongoing research involving humans... conducted under the auspices or within the jurisdiction of the institution....¹⁴

Given their local (meso) mandate, REBs are not well positioned to address macro level issues. But some of the elements in the HRIHS lifecycle clearly raise macro level

challenges, most obviously priority setting, regulation, and education. Furthermore, even an REB with a multi-site mandate can only deal effectively with the review process and not with all the other multi-faceted ethical issues associated with the elements in Figure 1.

Second, due to their midstream location in the HRIHS lifecycle, REBs are not well situated to play a substantive role at the beginning or the end of the cycle. Consider priority setting. Study protocols reviewed by REBs often represent the culmination of years or even decades of preclinical and clinical research that was prioritized years or decades prior. REBs may well be in a position to verify the scientific validity of these protocols – indeed they are mandated to do so – but they are not appropriately situated to take a substantive role in the promotion of socially valuable research. Thus, charging REBs with setting and enforcing social priorities makes little sense.

Similar points apply to education and funding review. Since all HRIHS must receive ethics review, REBs are in a position to educate researchers about ethical protocol design (including the ethics of hypothesis selection, recruitment, consent, monitoring, study termination, data analysis, and KT).¹⁵ However, since most researchers consult REBs only after their studies have been designed, funded, and scientifically reviewed, REBs are poorly situated to perform this role. Even if researchers tried to consult with their REBs prior to the launch of research, most REBs would lack the time and resources to respond effectively. Finally, because data analysis and KT typically occurs after a study has been terminated, REBs are not in a strong position to enforce ethical standards applicable to these activities (by contrast with sponsors and journal editors).

REBs are also hampered by a chronic lack of resources, including significant informational shortfalls. REBs are typically restricted to “single-shot, front-end review” of research *plans* (as stated in protocols) because effective monitoring of the ongoing conduct and termination of research post-approval is virtually non-existent. Functionally speaking, the REB’s role in ongoing review and study termination typically amounts to little more than the collection of highly schematic adverse event reports, annual status reports, and study termination notices.¹⁶ For these reasons, REBs are often ill-positioned to effectively carry out tasks squarely within their mandate, let alone take on an expanded set of



responsibilities. Though REBs are well-positioned to review consent forms, for example, they are typically unable to offer any assurance of the ongoing informed consent of participants because they don't have the requisite information or the on-the-ground presence to do so. Similar points apply to recruitment. Indeed, REBs rarely know whether the protocol they approved bears any resemblance to the research actually conducted.

Finally, consider QA and QI. Having REBs do their own QA and QI pulls the REB outside its range of expertise and puts it in a conflict of interest, thereby reducing the accountability of the whole system.

In sum, if we assume a broad conception of research ethics, REBs are not in a position to shoulder the governance burden on their own. Furthermore, due to the structural issues noted above (e.g., their location in the HRIHS lifecycle and incipient conflicts of interest) it is clear that REBs should not play such an expansive role even if they could. Imagine how doing so would multiply cries of REB "mission creep"!!¹⁷

The role of REB: the *de jure* and *de facto* governance systems

A much more realistic picture of the role of the REB was set out in the first edition of the *Tri-Council Policy Statement (TCPS1)*. According to the *TCPS1*, it is the role of the REB to:

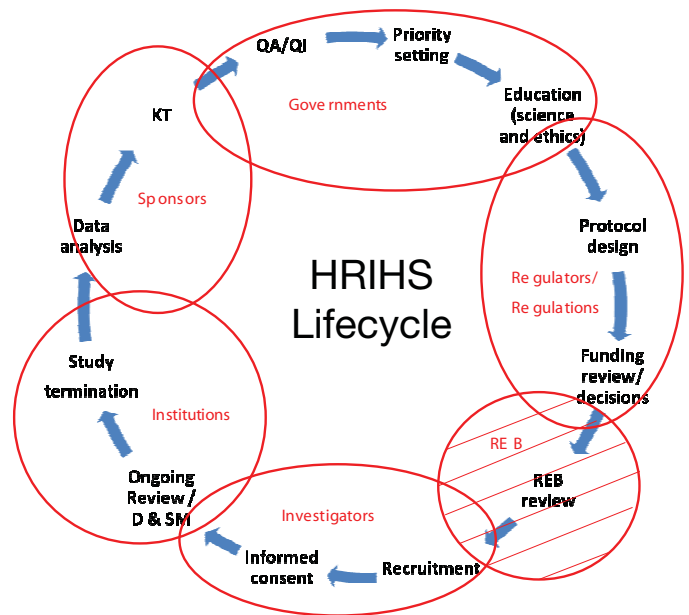
...help ensure that ethical principles are applied to research involving human subjects. The REB, therefore, has both educational and review roles. The REB serves the research community as a consultative body and thus contributes to education in research ethics; it also has responsibility for independent, multidisciplinary review of the ethics of research to determine whether the research should be permitted to start or to continue.¹⁸

Here, then, we have a statement of the formal or *de jure* role of the REB (i.e., the role of the REB as spelled out in standards of governance); to help ensure that ethical principles are applied to HRIHS via education and review.¹⁹ The key word here is 'help'. According to this picture, the role of the REB is to *help* ensure that ethical principles are applied to HRIHS via education and review. Ideally, then, the REB is one of a number

of actors (e.g., governments, regulators (and the regulations they promulgate), sponsors, institutions, and investigators) working together to achieve this goal. This picture of the governance system is represented in Figure 2. As Figure 2 suggests, the role of the REB within the *de jure* governance system (represented by the cross-hatched circle) is quite narrow, and is focused primarily on ensuring that ethical principles are applied to (or reflected in) study protocols. Responsibility for ensuring that ethical principles are applied to the other eleven elements is left largely to other actors (whose roles are represented very loosely by the non-cross-hatched ovals in Figure 2).²⁰

Unfortunately, this view of the REB (i.e., that it is one of a number of actors charged with governing the conduct of HRIHS) has never been fully realized in Canada. It is telling, furthermore, that the word 'help' has been dropped from the role description of REBs in *TCPS2*; no reference is made, either explicitly or implicitly, to a broader research ethics system.²¹ Again, given the reductive view of research ethics espoused by governments, sponsors, institutions, and researchers, this is not entirely surprising. To be fair, however, steps have been taken – albeit in an uncoordinated and incomplete way – to address some of the broader ethical

Figure 2:
The *de jure* governance system.



issues involved in the conduct of HRIHS. Here are some examples:²²

1. The Canadian Institutes of Health Research (CIHR) created the Institute for Aboriginal People's Health (IAPH) in 2000. The IAPH fosters the advancement of a national health research agenda to improve and promote the health of First Nations, Inuit, and Métis peoples in Canada, through research, knowledge translation, and capacity building. Through the combined efforts of the IAPH and the CIHR Ethics Office, the *CIHR Guidelines for Health Research Involving Aboriginal People* was produced in 2007.²³ That document has been well received both in Canada and internationally.²⁴ This is one example of macro/meso level input that is having a significant and enduring impact.
2. National agencies have been created to address various aspects of governance:
 - a. In 1995, the National Council on Ethics in Human Research (NCEHR) was incorporated as a non-profit organization (with support from CIHR, Health Canada, and the Royal College of Physicians and Surgeons of Canada). The mission of the NCEHR is (was) to provide leadership in advancing the knowledge and practice of the ethical conduct of research involving humans through advice, guidance, and education to stakeholders.
 - b. In 2001, CIHR, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada created the Interagency Advisory Panel on Research Ethics (PRE), which is devoted to promoting the ethical conduct of research involving human participants. A key part of PRE's mandate is to update the *TCPS*.
 - c. In 2002, the Canadian Association of Research Ethics Boards was created by REB members in order to represent the interests of all Canadian REBs and to reflect REB perspectives and concerns.
3. Public funders (e.g., CIHR, Genome Canada, the Stem Cell Network) have dedicated small percentages of their funding to the examination of ethical, legal, and social issues. The aim of this designated funding is to facilitate policy making

and education in the areas of research they sponsor. It should be noted that at its inception in 2000, CIHR established an Ethics Office, as well as a Standing Committee on Ethics, and mandated that the advisory boards of each of its thirteen virtual institutes identify one of the board members as an "ethics designate."²⁵ CIHR is unique amongst the Tri-Council agencies in taking such a macro level initiative. It also the one agency that has an explicit ethics mandate in its founding legislation.²⁶

4. Non-governmental-organizations, for example, the Canadian Breast Cancer Foundation and the Multiple Sclerosis Society of Canada, raise and disburse funds for research. These organizations prioritize research in certain areas by providing resources that would otherwise be unavailable.
5. Locally some institutions, for example, Université de Montréal, McGill University, Queen's University, Memorial University, and the provinces (e.g., the Alberta Provincial Health Ethics Network) have established educational programs for researchers and research coordinators working with human participants.

These initiatives attest to the fact that there is already some (albeit intermittent) recognition of the broader ethical issues arising across the HRIHS lifecycle. Unfortunately, it is often the case that, for every step forward, we take two steps backward. Here are some examples²⁷:

1. Funding for health research is increasingly driven by economic priorities. Though economic and health priorities are not necessarily at odds with one another, they are sometimes in tension.
2. A major push for the accreditation of institutions conducting research involving human subjects – led by NCEHR – was rejected by the "Sponsors' Table for Human Research Participant Protection in Canada."²⁸ This happened at the same time as the United States was moving to systems of accreditation through the Association for the Accreditation of Human Research Protection Programs and the Veteran's Administration.²⁹
3. The funding for NCEHR, which was always inadequate, was revoked entirely in 2010.

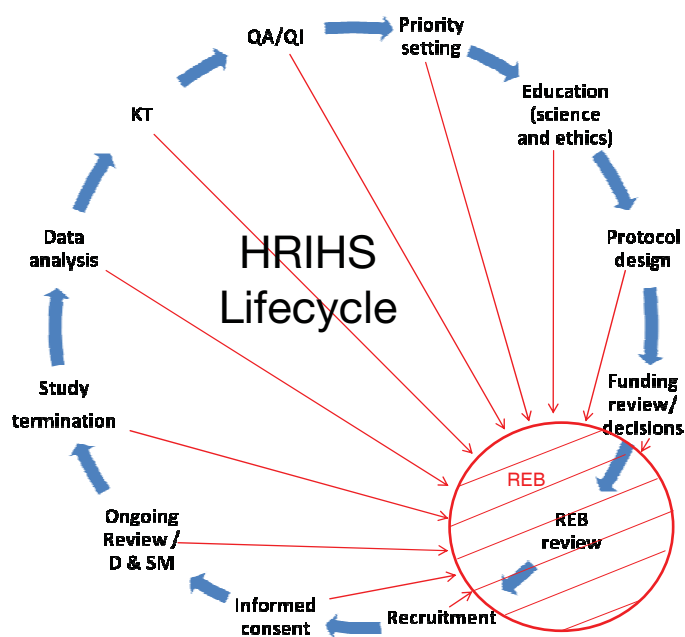


The story of NCEHR is emblematic of Canada's governance deficit. NCEHR was never able to fully meet its mandate due to its tenuous funding. However, it was undoubtedly the national body best situated to address many of the broader (extra-REB) ethical issues arising across the HRIHS lifecycle. If NCEHR's proposed accreditation process had received the support of the Sponsors' Table, furthermore, NCEHR could have played a major role in systematizing and upgrading Canada's governance system.³⁰

Now that NCEHR has ceased its activities, there is a gaping hole in Canada's research ethics governance system. This means that many of the broader (extra-REB) ethical issues remain unaddressed by our current governance system, creating conditions ripe for institutional failure. Until such time that a new national body is designated to take on this crucial education and quality-control role, we are left with a governance system that, *de facto*, off-loads ethics onto REBs, forcing them to bear more weight than they can handle. Consequently, fundamental ethical issues – issues that should be shouldered by other actors – remain unaddressed. The *de facto* governance system is pictured in Figure 3.

Given the substantial risks at stake, it is imperative that key stakeholders recognize that there is much more to research ethics than REB review. As this analysis has shown, health research is a complex endeavour raising a broad array of ethical issues. In our current (*de facto*) governance system, many of these issues are left partly or wholly unaddressed. Why is this the case? At the outset we identified two possible explanations. First, it is possible that key stakeholders presume that REBs can handle all (or most) of the issues arising across the HRIHS lifecycle. We have shown that this presumption is misguided. REBs are not (and should not be) in a position to shoulder the entire governance burden on their own. Second, it is also possible that these same stakeholders simply fail to appreciate the broader ethical issues raised by HRIHS. This explanation is also misguided. Most of these issues have been recognized (albeit intermittently) at one time or another, and steps have been taken (albeit in an uncoordinated, incomplete, and often haphazard way) to deal with them. Finally, another explanation presents itself: inattention and lack of foresight on the part of key stakeholders concerning the considerable risks associated with inadequate governance of HRIHS and/or a lack of political will to make the changes necessary.

Figure 3:
The *de facto* role of the REB



Conclusion

There is widespread consensus concerning the broad ethical objectives of a governance system for research involving humans: promotion of socially beneficial research; protection of research participants; and, maintenance of trust in the research enterprise. If we as Canadians are serious about meeting these objectives, we must move away from the narrow conception of research ethics according to which research ethics is reduced to ethics review, and research ethics itself is seen as an external impediment to research as opposed to a set of obligations that are internal to it. The HRIHS lifecycle raises a host of ethical challenges that lie outside of the mandate of the REB. Broader recognition of the wide scope of research ethics is required, along with a more systematic approach to dealing with the whole spectrum of ethical issues involved. Of paramount importance is the creation of a national body charged with establishing and overseeing a shared vision of research ethics governance via the accreditation and monitoring of institutions conducting research involving human subjects. Sincere, intelligent, and persistent efforts to foster the understanding and



internalization of the evolving norms of research ethics by researchers themselves are also crucial. As long as researchers and the institutions they work in continue to see research ethics as an external impediment to research, as opposed to a set of obligations integral to each step in the research process, it will be difficult to change the *status quo*. The *de facto* limitations of the REB system, along with the persistent tendency to reduce research ethics to ethics review, create conditions ripe for institutional failure. Failure, in turn, threatens to undermine the trust between research community and society that is required for the on-going support and conduct of socially beneficial research. Recognizing the shortcomings in our governance system is a first step toward managing the substantial risks involved.

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Endnotes

- 1 Kathleen Cranley Glass, "In Memoriam: Benjamin Freedman" (1997) 25 J.L. Med. & Ethics 77 at 77.
- 2 Michael McDonald, *The Governance of Health Research Involving Human Subjects (HRIHS)* (Ottawa: Law Commission of Canada, 2000) 296, original emphasis.
- 3 *Ibid.*
- 4 To be concise we have included the not-for-profit sector in the public sector though we recognize that the important non-for-profit sector has different objectives than the purely governmental sector.
- 5 This is particularly true in the current funding environment. Since the success rate in Canada for open competitions for operating grants is so

low, researchers increasingly apply for targeted funding competitions. So, micro level choices are increasingly opportunistic.

- 6 Catherine A. Schuppli & Michael McDonald, "Contrasting Modes of Governance for the Protection of Humans and Animals in Canada: Lessons for Reform" (2005) 13(2-3) Health L. Rev. 97.
- 7 Canadian Institutes of Health Research (CIHR), *Strategy for Patient-Oriented Research: A Discussion Paper for a 10-year Plan to Change Health Care Using the Levers of Research* (Ottawa: CIHR, 2010), online: Strategy for Patient-Oriented Research <<http://www.cihr-irsc.gc.ca/e/41232.html>>.
- 8 CIHR, Natural Sciences and Engineering Research Council of Canada (NSERC) & Social Sciences and Humanities Research Council of Canada (SSHRC), *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, (Ottawa: CIHR, NSERC & SSHRC, 2010), online: <http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS2_FINAL_Web.pdf>.
- 9 Chris Macdonald, Michael McDonald & Wayne Norman, "Charitable Conflicts of Interest" (2002) 39 Journal of Business Ethics 67.
- 10 Ilene Albala, Margaret Doyle & Paul S. Appelbaum, "The Evolution of Consent Forms for Research: A Quarter Century of Changes" (2010) 32:3 IRB: A Review of Human Subjects Research 7; and, Daryl Pullman, "Subject Comprehension, Standards of Information Disclosure and Potential Liability in Research" (2001) 9 Health L.J. 113.
- 11 TCPS2, *supra* note 8 at Article 3.3.
- 12 The structural limitations of REBs (e.g., the fact that they are designed to function independently and *in camera*, and their mid-stream location in the HRIHS lifecycle) underlines the importance of other actors (e.g., governments, regulators, institutions, and investigators) in the governance system. We will return to this point repeatedly.
- 13 Glass, *supra* note 1 at 301.
- 14 *Supra* note 8 at Article 6.1.
- 15 Strictly speaking, the TCPS2 requires that all research conducted in TCPS2 funded institutions (whether or not any particular study is TCPS2 funded) must be TCPS2 compliant. But even if not conducted in a TCPS2 facility, virtually all HRIHS conducted in Canada will require ethics review under one or another overlapping governance system (e.g., GCP, Health Canada, FDA, etc.). Finally, it is virtually impossible to publish without ethics review.



- 16 National Council on Ethics in Human Research used to conduct site visits but the organization has recently lost most of its funding. We will come back to this later in the paper.
- 17 C.K. Gunsalus *et al.*, "Mission Creep in the IRB World" (2006) 312 Science 1441.
- 18 CIHR, NSERC & SSHRC, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: CIHR, NSERC & SSHRC, 1998), with 2000, 2002, and 2005 amendments.
- 19 It is worth noting that many REBs (e.g., all of the REBs at the University of British Columbia) have given up on direct provision of ethics education because it is simply beyond their resources.
- 20 Figure 2 is designed primarily to illustrate the overlapping and interconnected responsibilities of the various actors involved in the *de jure* governance system. The actual roles of these actors in the *de jure* system should not be inferred from this Figure.
- 21 According to the *TCPS2*, the role of the REB is "to review the ethical acceptability of all research involving humans conducted within their jurisdiction or under their auspices", *supra* note 8 at Article 6.1. Again, no reference is made, either explicitly or implicitly, to other actors involved in research ethics.
- 22 See also "Research Ethics in 2020: Strengths, Weaknesses, Opportunities, and Threats" included in this issue of the *Health Law Review*
- 23 CIHR, *CIHR Guidelines for Health Research Involving Aboriginal People* (Ottawa: CIHR, 2007), online: CIHR Guidelines for Health Research Involving Aboriginal People <<http://www.cihr-irsc.gc.ca/e/29134.html>>.
- 24 S. Christopher *et al.*, "Building and Maintaining Trust in a Community-Based Participatory Research Partnership" (2008) 98 *American Journal of Public Health* 1398.
- 25 At this time, the role of the ethics designates is uncertain. The ethics designates committee existed *de facto*, but has never received official approval by senior management at CIHR.
- 26 Canada, Bill C-13, *An Act to establish the Canadian Institutes of Health Research, to repeal the Medical Research Council Act and to make consequential amendments to other Acts*, 2nd Sess., 36th Parl., 2000, (assented to 13 April 2000).
- 27 AUTHOR, *supra* note 23.
- 28 The Experts Committee for Human Research Participant Protection in Canada, *Moving Ahead: Final Report of the Experts Committee for Human Research Participant Protection in Canada* (Ottawa, Sponsors' Table for Human Research Participant Protection in Canada, 2008), online: Sponsors' Table for Human Research Participant Protection in Canada <<http://www.hrppc-pphrc.ca/english/movingaheadfinalreport2008.pdf>>.
- 29 AUTHOR, *supra* note 23.
- 30 Miriam Shuchman, "Research Ethics Council Faces Dissolution" (2010) 182 *Canadian Medical Association Journal* 890.

