The Governance of Health Research Involving Human Subjects (HRIHS)

Ce document est également disponible en français sous le titre “Gouvernance de la recherche en santé avec des sujets humains”.

SECTION B-1

ETHICS AND GOVERNANCE

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In this paper, our main concern is with the governance and ethics of health research involving human subjects (HRIHS). We begin with a discussion of governance.

I. GOVERNANCE

In answer to the question, "What is governance?" the University of Ottawa's Centre for Governance provides a useful starting point (see Figure 1 below).

FIGURE 1

WHAT IS GOVERNANCE?[27]

Guiding

Governance is about guiding. It is about the processes by which human organizations, whether private, public or civic, steer themselves.

The study of governance involves:

- examining the distribution of rights, obligations and power that underpin organizations;
- understanding the patterns of coordination that support an organization's diverse activities and that sustain its coherence;

[27] University of Ottawa Centre on Governance <http://www.governance.uottawa.ca/english/overview/o_defi.htm>

- exploring the sources of an organization's dysfunction or lack of fit with its environment that may result in lacklustre performance; and establishing benchmarks, building tools, and
- sharing knowledge to help organizations renew themselves when their governance system demonstrates a need for repair.

Interacting

Governance pertains not only to organizations, but also to:

- the complex ways in which private, public and social organizations interact and learn from one another;
- the manner in which citizens contribute to the governance system, directly and indirectly, through their collective participation in civil, public and corporate institutions; and
- the instruments, regulations and processes that define the "rules of the game."

Applications

The knowledge of governance has application not only in determining the appropriate guiding mechanisms for organizations or the evolution of society, but also as:

- a *manière de voir*, or coordination perspective, on the workings of organizations;
- a reference point to clinically probe and repair faltering organizations and to support the development of socio-economic policy;
- an analytical framework providing a language of problem reformulation; and
- a tool to generate alternative *manière de voir* to provide insights into new ways to tackle problems of organizational design and social architecture.

Thus, our study is concerned with the governance of health research involving human subjects (HRIHS) at two levels: (a) the level of particular institutions, organizations and agencies involved in various ways in HRIHS; and (b) the interactions of institutions, organizations and agencies identified at level (a).

As indicated in the Ottawa statement on governance, governance is about "guiding" and "processes by which human organizations … steer themselves."[28] So governance involves processes by which organizations oversee, govern, regulate or direct their own activities.

[28] *Ibid.*

Governance structures and processes are ways of affecting changes in human affairs that are themselves subject to change; that is, governance is best understood in dynamic rather than static terms.[29]

> In their important work on governance in the public sector, Day and Klein state:
>
> > Our starting point is that accountability is all about the construction of an agreed language or currency of discourse about conduct and performance and, the criteria that should be used in assessing them. It is a social and political process. It is about perceptions and power. It can therefore be expected to vary in different contexts, depending on the nature of the policy arena and the power of the different organizational actors.[30]

Accordingly, our concern in this study is with the social structures and processes specific to the governance of health research involving humans, including its "currency of discourse," "organizational actors," perceptions and power."

A. Criteria for Good Governance

Various criteria for good governance have been proposed. *The Canadian Institutes for Health Research (CIHR) Public Report on Governance* provides a good example of these:

> Governance generally refers to the processes and structures that an organization uses to direct and manage its general operations and program activities. An organization without a clear and effective governance structure is unlikely to operate at high levels of efficiency and runs a serious risk that decisions will be made that run counter to the organization's objectives. It is also unlikely that the organization would have the capacity to adapt readily to change.
>
> A reading of virtually any text or guide on governance would reveal the most fundamental of elements. These include: a clear mission; responsibility; accountability; transparency; stewardship; flexibility; succession; representation; and simplicity. These concepts are the foundation that organizational structures must respect.[31]

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[29] In political science, there is discussion of various forms of governance: democracy, autocracy, monarchy, etc. In organizational theory, governance is described in terms of various types of oversight by boards of directors or parallel senior bodies.

The Oxford English Dictionary defines governance as "(1) the action or manner of governing…the fact that a [a person, etc.] governs; (b) control; (c) the state of being governed. (2) The office, function, or power of governing; the governing person or body. (3) Method of management, system of regulations. (4) Mode of living, behaviour, demeanour; (b) wise self-command.

Our main interest is in manners of governing and control (1) and methods of management (3). But we have also identified governing bodies and persons (2). Our concern with good governance has some connection with (4).

[30] See P. Day & R. Klein, *Accountabilities: Five Public Services* (London UK: Tavistock Publication, 1987) at 2.

[31] See D. Zussman, *Proposed Governance Structure for the Canadian Institutes of Health Research* (Ottawa: Public Policy Forum, 1999) at 7 <*http://www.cihr.org/?current=library&page=report#appendix1*>.

This description is in line with our description of governance as a second order function.

McNamee takes a different tack in characterizing corporate governance as an "organization's strategic response to risk."[32] This is useful because it locates governance in an organization's larger operating environment. However, McNamee's detailed list of corporate governance features overlaps the CIHR list:

- Strategic Planning: Developing plans and objectives to fulfill the organization's purpose.
- Leadership: Communicating the organization's purpose through vision.
- Organization Design: Establishing the structure that defines communication paths.
- Stewardship: Establishing the accountability for preserving the organization's purpose.
- Risk Management: Putting assets at risk to achieve the organization's objectives.
- Assurance: Providing feedback on the efficiency and effectiveness of the governance processes.[33]

Good governance then involves good risk management, oversight and the many other factors listed above.

B. Conceptualising Governance as Second-Order Oversight

Conceptually we see governance as the way in which organizations –public, private, or not-for-profit– oversee and direct their own activities.[34] Organizations engage in a variety of **first order activities** including the production and sales of goods and services (private sector organizations), education and research (universities), the provision of health services (hospitals) or regulation (government and the professions). With respect to HRIHS, there are private sector organizations like pharmaceutical companies researching, producing and marketing drugs. There are public sector organizations like universities and medical research centres – the

[32] See D. McNamee, *Corporate Governance, Accountability and Management Control* (25 February 2000), Mc2 Management Consulting, <*http://www.mc2consulting.com/govpage.htm*> (10 April 2000).

[33] *Ibid.*

[34] While the clearest examples of governance are from formally constituted groups, e.g., those established by legislation or associations with a charter, it can also be found in informally constituted groups based on an implicit shared understanding about the nature of the group and its purposes.

former providing research and education and the latter providing health services, health research and health education. In addition, there are public sector research agencies like CIHR, NSERC and SSHRC whose business it is to promote and sponsor Canadian research in various areas. From the not-for-profit sector, health charities like the Heart and Stroke Fund of Canada and the Canadian Kidney Foundation provide health services including education and also sponsor research in their areas.

All these first-order (or first-level) activities need to be managed, directed or guided. Such guidance can be described as a "second-order (or level) activity." Hence, **governance can be described as an organization's second-order (or level) activities for controlling, guiding, organizing and in general overseeing its own first-order (or level) activities – whether these are directed internally to the organization's own members or externally to outside institutions and individuals. Thus, governance represents in organizations a kind of reflexive capacity – a capacity to rationally determine the direction of lower order activities.**[35]

In accord with the preceding discussion of good governance, normal second-order governance activities would include the following:

- Setting, interpreting or changing the mandate, direction and priorities of an organization
- Assigning or reassigning responsibilities with the organization;
- Monitoring and evaluating performance of the organization as a whole, its principal parts, and senior management with special attention to significant opportunities and risks, liabilities and assets
- Ensuring the organization meets its responsibilities to its principal stakeholders (be they stockholders, clients, consumers, the general public, third parties, etc.)[36]

Good governance consists of doing these sorts of things well (e.g., ensuring that there are thorough and timely audits of major risk areas and that these are acted upon). Good

[35] Typically, senior bodies in an organization – such as a board of directors, the cabinet, or a university senate – undertake governance activities. However, it is quite possible for a given person or group of persons in a social context to occupy both first and second order roles in their organizations (e.g., a physician in a hospital may sit on its board). Our concern in this description of governance is with the function that the Ottawa Centre for Governance describes as "guiding" in Figure 1, "the processes by which human organizations … steer themselves." Later in this study, we discuss the "interacting" function, i.e., the interactions of organizations.

[36] See Allen Buchanan's illuminating discussion of ethical responsibilities of bureaucratic organizations A. Buchanan, "Toward a Theory of the Ethics of Bureaucratic Organizations" (1996) 6/4 *Business Ethics Quarterly* 419. See Appendix A for other examples of criteria for governance.

governance involves steering a middle course between under and over governance (i.e., failing to provide sufficient oversight or providing too much oversight). A good example of too much oversight is that of micro-management. On our view of governance, micro-management involves the needless and even harmful replication of first-level functions.

Our account of governance as a second-level process provides a useful insight into ways in which things can go well or badly at one level without necessarily doing the same at the other level. Thus, a poorly governed corporation might for a period of time be quite profitable despite the ineptness of its CEO and Board. Its doing well despite poor governance could be due to a variety of fortuitous factors such as the high quality and dedication of its employees, the weakness of competitors, protectionist tariffs or, simply by living off its past reputation. Similarly, an organization might be well governed but run into major problems on the ground due to unforeseeable circumstances.[37] Generally speaking though, an organization that performs well on the ground level is likely to be well governed, conversely a well-governed social entity is likely to perform well on the ground over the long run.

Our description of governance as a second-order activity directed to the guidance of first-order activities may create the impression that good governance would involve having second and first order activities carefully aligned with each other. However, such an alignment is at best a necessary, not a sufficient, condition for good governance. There is the possibility of a kind of myopia or even tunnel vision in which the governors of an organization create a situation in which there is good management of a narrow range of first-order activities but other important first-order activities are not overseen or in some cases not even performed. That is, the organization neglects to do many of the things that it ought to do (e.g., according to its mandate or mission statement). But the things that it does do, it does well at both levels. Like individuals, organizations can become practically and even morally blind to their responsibilities at both first and second levels. They can develop a kind of self-deceptive positive feedback loop that ignores major risks and fosters a mistaken sense of complacency and self-satisfaction.

We shall argue that this is the case with respect to the governance of HRIHS by research institutions and sponsors.[38] While they manage research aspects of HRIHS well, there is a general neglect of the ethical aspects of HRIHS. This, we believe, occurs through the

[37] Of course, there is a part of good governance that has to do with managing in the face of change and so of unexpected circumstances. But such foresight has to be balanced and prudent in that one can over-insure against unexpected calamities.

"bureaucratisation of ethics" (in the REB-approval process). By treating research ethics as equivalent to the REB process, research institutions and sponsors have narrowed the scope of ethical concerns to front-end approvals of research proposals, thus ignoring what happens outside that process. But given that this reduction of research ethics to REB approval, feedback mechanisms in the organization will provide the misleading reassurance that all is well.

C. "To Govern or Not to Govern"

To paraphrase Hamlet, a primary question is whether (and how much) to govern or not govern. Sometimes it is best to leave matters alone and do without the oversight involved in governance. For example, most of us believe this to be the case for adult etiquette – even though there are a few boors who are readily prepared to behave censoriously in this area. If the governance mechanisms of childhood (parents and teachers) have not done their job, we leave it to peer pressure and Miss Manners to exert their informal and unsystematic pressures on impoliteness and other forms of rudeness. Our reasons for not choosing formalised governance structures in this area are instructive. We worry about

Moral intrusiveness – e.g., trampling on rights to privacy
Effectiveness – e.g., would a politeness 'police' make much of a difference?
Costs – e.g., would the costs of second-order oversight be worth the gains?

Some brief comments on each are in order. With respect to moral intrusiveness, we are worried about crossing significant moral boundary lines. We assess effectiveness in systemic terms rather than on an incident-by-incident basis. With respect to costs, we must remember the special weighting that ought to be given to rights. Rights should be seen as "protected interests." Thus, protecting rights requires active governance in the form of protections for the rights and remedies for their violation.[39] With human rights, the commitment is extensive (all humans) and especially weighty (rights to life, non-discrimination, against torture, etc.).

It is worth noticing that cost and effectiveness are especially germane to the question of "how much governance is appropriate?" But this raises a central issue of whether there are

[38] See Section F, "Conclusions and Recommendations".

[39] For a useful philosophical analysis of rights, see C. Wellman, *A theory of rights: persons under laws, institutions, and morals* (Totowa, N.J. : Rowman & Allanheld, 1985) and L.W. Sumner, *The moral foundation of rights* (New York: Oxford University Press, 1987).

situations where good order results without active governance. This is supposed to be the case with Adam Smith's free market, for the market functions essentially as a self-regulating system that brings demand and supply into balance without second-order oversight. Indeed, in the economist's ideal or perfect market, oversight would be redundant and a waste of resources.

The same sort of laissez-faire argument for benign non-governance in well-functioning self-systems has been advanced for freedom of speech generally and academic freedom particularly.[40] Both the poet John Milton and the philosopher John Stuart Mill defend a free market of ideas. Mill does so particularly on the basis of the idea that in such a free market of ideas truth will drive out error and knowledge will vanquish ignorance.[41] As we note in Section B-3, some Canadian academics have recently opposed active governance for research involving human subjects on the grounds that it violates academic freedom and that it is unnecessary because good ethics will drive out bad in an open society.

It is worth noting that while the classical idea of an economic or intellectual free market is only fully exemplified in ideal or perfect markets, most often in real life we deal with imperfect markets that need some degree of regulation and oversight. These imperfect 'mixed' markets are worth considering in regard to the governance of HRIHS. For example, it is worth asking whether reputation effects can serve as a major driver for good behaviour in the partially regulated area of HRIHS. That is, there are important questions about the extent to which various types of governance (e.g., standard setting and monitoring) can be used to reinforce the good tendencies or economic, intellectual or other forms of free markets (concern for long-term reputation), negate bad tendencies (e.g., abuse of research subjects) without being overly costly

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[40] As represented in Lord Broughton's famous dictum from *Queen Caroline's Case*, "An advocate, in the discharge of his duty, knows but one person in all the world and that person is his client", similar arguments have been advanced for legal advocacy in form of total loyalty to a client's interests. M.H. Freeman, "From Lawyers' Ethics in an Adversary Society" in J. Arthur & W. Shaw, eds., *Readings in Philosophy of Law* (Englewood-Cliff: Prentice-Hall, 1984) 488 at 492. For a general discussion of ideal market arguments as ways of ducking moral responsibility for one's own behaviour, see C. Brunk, "Professionalism and Responsibility in the Technological Society" in D. Poff & W.J. Waluchow, eds., Second ed., *Business Ethics in Canada* (Scarborough: Prentice-Hall Canada, 1991) 122 at 130.

[41] See J.R. Lucas, *The Principles of Politics* (Oxford: Clarendon Press, 1966) at 8. Lucas aptly describes the type of society favoured by Milton and Mill as an "Areopagite society". He says, "Areopagites are fallible, and not perfectly informed, but they are possessed by a deep love of truth, and are anxious only to discover the truth, and to establish the rightness of their own views because they are their own. …. And if each Areopagite is liable to some errors of judgement or information, then the more debate and discussion there is, the more errors will be exposed, and the more truth will be established." (*Ibid.*) See also J.S. Mill, "Liberty" in A.D. Lindsay, ed., *Utilitarianism, Liberty, Representative Government*, Everyman Library (London: J.M. Dent & Sons Ltd., 1962).

or counter-productive. This is especially relevant to the various deregulatory steps being taken in regard to health research in Canada.[42]

D. Governance and Ethics

In a 1996 article entitled "Toward a Theory of the Ethics of Bureaucratic Organizations, Allen Buchanan argues that "bureaucratic organizations" should be seen as "complex webs of principal/agent relationships." [43] So an adequate theory of ethics for bureaucratic organizations would centre on the reduction of agency risks:

> Principals engage agents to perform tasks which they are unable to perform themselves, or which they find too costly or inconvenient to perform themselves. Agency-risks are the risks that are imposed on principals due to the fact that agents have interests that may conflict with those of the principals whom they are supposed to serve. Principal/agent theory describes and in some ways formalizes different types of agency-risks and various techniques for reducing agency-risks. For example, if B serves as A's sales agent for a line of merchandise, Survey B may have incentives to shirk or be less aggressive in seeking sales, unless a special arrangement (typically, reimbursement on a commission basis) is used to reduce this agency-risk.
>
> This bare sketch of the essentials of principal/agent theory should suffice as a basis for formulating the main thesis of the analysis presented here, namely, that much of what is central to, and distinctive of, the ethics of bureaucratic organizations can be understood as responses to agency-risks that are characteristic of such organizations.[44]

Buchanan lists the following as typical risks faced by bureaucratic organizations: "inefficient use of resources," "outright misappropriation of resources," "goal substitution" (cases where bureaucrats covertly pursue their own goals … under the guise of implementing authorized policies)," "passive opposition to policies," "shirking (substituting leisure or the pursuit of other unauthorized activities for compensated work times)" and, "expertise imperialism" (e.g., treating ethical problems as if they were simply economic issues).[45]

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[42] See Section B-3, "The Current Context of HRIHS."

[43] Buchanan says that bureaucratic organizations have six main features: (i) a hierarchical structure of authority; (ii) a complex division of labour; (iii) professional administrators; (iv) outputs that are the result joint activities; (v) rule or policy based decision-making; and (vi) practices and decision-making based on principal/agent relations. *Supra* note 15 at 419-420.

[44] *Ibid.* at 420.

[45] *Ibid.* at 425-427.

Buchanan describes the above as "first-order agency-risks", but he says that there are also "second-order agency-risks … in which bureaucrats often engage that serve to thwart the efforts to control first-order risks."[46] These include:

A. appeal to authority ("I was just following orders");

B. failure to document activities and decisions in such a way as to make accurate evaluation of outcomes and assignment of responsibility possible;

C. failure to specify duties concretely and assign them unambiguously to particular agents and groups of agents.[47]

To deal with such second-order agency-risk, Buchanan proposes second-order ethical obligations that tie clearly to the criteria for good governance discussed above:

A. The obligation to see that there are clear lines of authority and responsibility – to see to it that individuals' roles in the organization and their attendant duties are specified concretely and consistently (so far as possible without impairing needed flexibility and creativity)

B. The obligation to ensure that performance is monitored and evaluated adequately and that good performance is rewarded and poor performance corrected and/or penalized.

These two second-order obligations stated above have a corollary:

C. The obligation to provide adequate documentation.[48]

It is relevant to our study of the governance of HRIHS to note that Buchanan's work on the ethics of bureaucratic organizations arose out of the work he did as a policy advisor on the President's Advisory Committee on the Human Radiation Experiments, which produced a major study of the abuses of human subjects in medical and other types of research.[49]

It should be emphasized that assessing the governance responsibilities of bureaucrats in ethical terms need not commit one to the view that the only (or the primary) means of addressing agency-risk is through ethical suasion. Often what is needed is attention to institutional design – the use of incentives and disincentives, reporting relationships, auditing

[46] *Ibid.* at 428.

[47] *Ibid.* at 429.

[48] *Ibid.* at 430-432.

[49] President's Advisory Committee on Human Radiation Experiments, *The Human Radiation Experiments: Final Report of the President's Advisory Committee* (New York: Oxford University Press, . at 433.

and other types of control. Hence, in this study, we are very much concerned with the design of various institutions involved in the HRIHS enterprise – in particular with identifying the institutional incentives and governance processes in place for dealing with the ethical challenges posed by HRIHS.

We recognise that while in some areas governance issues are relatively non-contentious in others they are quite contentious. In this regard, Day and Klein usefully contrast "political" with "managerial accountability." The former they see in terms of "delegated authority being answerable for their actions to the people". In complex modern societies, they argue political accountability raises difficult questions about "linkages between action and explanation are in place and, if in place, adequate to the task at hand" as well as about openness of processes and the availability of information.[50] By contrast, managerial accountability tends to be around "agreed tasks according to agreed criteria of performance."[51] Day and Klein argue persuasively that it is a mistake to combine the two models into a "simple hierarchical model." They argue that

> … it is apparent that political processes do not necessarily generate the kind of clear-cut objectives and criteria required if audit is to be a neutral, value-free exercise; the dividing line between political and managerial accountability is, inevitably, blurred as objectives and criteria are generated in all levels of the hierarchy. The results are the demands for opening up the system as a whole to public scrutiny, and creating a more complex (but not necessarily hierarchical) system …(C)ompounding the arguments both for better links and for a more complex system of accountability, the organizational structure of many public programmes … is characterized by the fact that some service-deliverers do not fit into a vertical or hierarchical model of accountability; they are an instance of horizontal accountability to peers.[52]

The complications of horizontal accountabilities cutting across vertical accountabilities are especially significant in the strongly peer and professional oriented cultures of HRIHS.[53] But even more important for this study is the point that accountability, particularly political accountability, can be complex and controversial. We recognize then that our assessment of the governance of HRIHS takes us into difficult and sometimes disputed areas. Yet as we shall now argue, there is a surprising amount of consensus around central ethical values for HRIHS.

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[50] P. Day & R. Klein, *Accountabilities: Five Public Services* (London UK: Tavistock Publication, 1987). at 26-27.

[51] *Ibid.*

[52] *Ibid.* at 28.

[53] See especially Kinsella, Section D-3, "Research Involving Humans: Current Regulatory Status of the Canadian Medical Profession".

II. THE ETHICS OF HRIHS

To understand the specific objectives of governance for HRIHS, it is necessary to discuss the ethics of research involving human subjects. Our approach in the following is to indicate the values and principles that command a substantial consensus and those that do not. We also highlight specific shortcomings and difficulties in applying consensus standards to human subjects research.

The ethical conduct of research involving humans has contentious areas but, it also has areas in which over time a substantial consensus has developed. That consensus has been greatly shaped by the history of human research particularly since World War II. Whether one dates that history from the infamous Nuremberg Doctors' Trial or the well-documented abuses of vulnerable research subjects in the U.S., Canada and elsewhere – Tuskegee, Willowbrook, the Milgram obedience experiments, the U.S. human radiation experiments, Cameron's CIA and Canadian Government financed psychiatric experiments at McGill, etc. – the history has been extremely important in shaping the dominant national and international norms in this area.[54] That history has led to a significant, albeit evolving, consensus around central norms and processes. In a recent book on international perspectives in bioethics, the well-known bioethicist, Baruch Brody describes that consensus insofar as it is represented in official policies:

> A clear-cut consensus has emerged in all of these official policies about the basic conditions of the licitness of research on human subjects. Procedurally, such research needs to be approved in advance by a committee that is independent of the researchers. Substantively, informed voluntary consent of the subject must be obtained, the research must minimise risks and involve a favourable risk-benefit ratio, there should be an equitable non-exploitative selection of subjects, and the privacy of the subjects and, the confidentiality of the data must be protected. These substantive standards are rooted in fundamental moral commitments to respect for persons, to beneficence, and to justice.[55]

With respect to the ethics of HRIHS, the consensus is around three central objectives:

A. The **promotion** of socially beneficial research

   a. Meets relevant scholarly standards
   b. General social benefits outweigh harms

[54] For useful accounts of this history, see G.E. Pence, *Classic Cases in Medical Ethics* (New York: McGraw Hill Publishing Company, 1990) 397. and D.J. Rothman, *Strangers at the Bedside: A History of How Law and Ethics Transformed Medical Decision Making* (Basic Books, 1991) 303..

[55] B.A. Brody, *The Ethics of Biomedical Research: An International Perspective* (New York: Oxford University Press, 1998) at 36.

B. **Respect** for the dignity and rights of research subjects

C. As an overarching aim, the maintenance of **trust** between the research community and society as a whole.[56]

We see (C) as a product of (A) and (B). For (A) to be achieved, there is general agreement, especially in regard to health research, that (A-1) research must meet relevant scholarly standards (e.g., be scientifically valid) and that (A-2) the likely net benefits of the research outweighs harms. With regard to (B), the research must be conducted in a way that respects the dignity and rights of the research subject. These can be summarised in the form of three questions; these are questions that should be asked before, during and after research involving human subjects is initiated.

Figure 2

1. Does the research meet relevant scholarly standards, e.g., scientific validity for biomedical research?
2. Is it likely that the net benefits of the research will outweigh its overall harms?
3. Does the research respect the rights of the research subject, including protection from undue harm and informed consent?

A. Question 1: Scholarly Standards

In regard to question (1), the underlying idea is that research is morally unjustified if it fails to meet relevant standards for research. Two moral arguments are advanced in favour of meeting scholarly standards. The first reason is that badly designed or executed research unnecessarily exposes research subjects to risks since the research is unlikely to produce any useful results. Such risks may be substantial, e.g., death or major trauma due to the bad design of clinical trials of a new drug or exposure to violence by the breach of confidence of a victim of sexual abuse. Or the risk may be low, in which case there is a misuse and abuse of the research subject's time, effort and good will. The second reason focuses on veracity and promise keeping. Through the informed consent process, a researcher implicitly assures

[56] In Section A-I, we suggested that the maintenance and / or the restoration of "warranted trust" is a crucial criterion for good governance in this area. By "warranted trust", we mean the opposite of "unwarranted trust".

potential subjects that the research is likely to contribute to the advancement of knowledge. Moreover, this is an assurance backed (implicitly, if not explicitly) by the researcher's institution and the sponsors of the research.

1. Diverse areas of HRIHS with different scholarly standards for research

Since health research uses a variety of methodologies and approaches, it is essential with respect to question (1) to be sensitive to legitimate differences in scholarly paradigms and standards. In many international documents, scholarly standards are often described narrowly in terms of "scientific validity." While this may have been appropriate when the systematic study of health was conceived in primarily biomedical terms, it is insufficient given the contemporary wider conception of health research.[57] The complexity and variety of scholarly paradigms sometimes gives rise to disputes about what counts as "sound" or "valid" research. However, the problem here is not as intractable in practice as it might initially appear. First, a significant amount of research fits easily within particular paradigms. Thus, a research sponsor or an REB reviewing a proposal for a randomized clinical trial (RCT) would not find the identification of relevant scholarly standards problematic, e.g., statistical validity, stopping rules and clinical equipoise.[58] Second, in new interdisciplinary fields like bioethics and medical sociology, there has been substantial progress in establishing shared scholarly standards. In many cases then it is possible to "operationalise" standards and provide workable ways of addressing the first question. Nevertheless, as we shall now see, addressing the question of overall value has proven much more difficult.

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[57] It is worth noting that in the design of the new Canadian Institutes for Health Research a wide view has been taken of health research including, for example, the study of health determinants, population health issues, and many non-medical factors related to health (economic, social, cultural, legal, etc.). It should also be noted that there were many criticisms of the 1996 draft *Code of Ethical Conduct for Research Involving Humans* for use of the scientific validity standard and for an overly biomedical tone. This was corrected in the 1997 Code.

[58] Freedman describes 'Clinical equipoise': "Clinical equipoise is a situation in which there exists (or is pending) an honest disagreement in the expert clinical community regarding the merits of two or more forms of treatment for a given condition. To be ethical, a controlled trial must begin, and be conducted in a state of clinical equipoise – as between arms of the study – and must, moreover, offer some reasonable hope that the successful conclusion of the trial will disturb the equipoise (that is resolve the controversy in the expert clinical community." B. Freedman, "A Response to a Purported Ethical Difficulty with Randomized Clinical Trials Involving Cancer Patients" in J.D. Arras & B. Steinbock, eds., Fifth ed., *Ethical Issues in Modern Medicine* (Mountainview, CA: Mayfield Publishing Company, 1999) 577 at 578. Also see B. Freedman, "Equipoise and the Ethics of Clinical Research" (1987) 317 *New England Journal of Medicine* 141.

B. Question 2: Overall Value

1. Benefits and beneficiaries

With regard to question (2), the basic idea is that for research involving human subjects to begin and continue, there must be reasonable promise of greater benefits overall than harms in the conduct and results of the research. That is, relevant parties (researchers, research institutions and research sponsors) must have good reasons for believing that the overall net balance of general value is positive rather than negative.[59] But this requires taking a broad perspective with regard to potential benefits and beneficiaries. For example, potential benefits and harms may well be missed if research impacts are assessed solely in terms of biomedical factors like morbidity and mortality. Moreover, even taken in a broad sense, health is only one kind of good humans value.[60] Research involving human subjects (including health research) produces a wide range of other types of goods (and evils): economic (e.g., increased wealth or poverty), social (e.g., positive or negative changes in social status), personal (e.g., self-knowledge or deception), educational (e.g., greater or lesser skills) and myriad other ways in which human welfare is affected for good or ill. As well, the knowledge produced by credible research can be regarded as a good in its own right.

With regard to who benefits, it is again important to take a broad perspective. With respect to health, for example, there is the general health of populations and the health of research subjects themselves. It is important to note that a significant amount of health research has to be described as non-therapeutic, i.e., as highly unlikely to improve the research subject's health.[61] However, there is a body of research that indicates that hopes of health improvement are a significant motivation for individuals to want to participate in research trials even though they have been explicitly told in the informed consent process that the research is non-

[59] The term 'general value' is used here in a broad sense as including a wide range of 'goods' or things that are generally valued in society. It includes goods valued for their own sake or for the sake of other ends. It includes both non-moral (e.g., happiness and preference satisfaction) as well as moral ends (e.g., greater equity). In other words, we are not committed here to a particular theory of value like those presented in classical or contemporary utilitarian theories or theories of welfare economics.

[60] There has been a debate in the philosophy of medicine and bioethics about the notion of health, and the problems raised by turning 'health' into a surrogate for human welfare. For a discussion of that debate, see M. McDonald, "Health, Health Care and Culture: Diverse Meanings, Shared Agendas" in C. Harold & P. Ratanakul, eds., *A Cross-Cultural Dialogue on Health Care Ethics* (Waterloo, ON: Wilfrid Laurier University Press, 1999) 92.

[61] An important REB concern in reviewing informed consent forms is to make sure that there is due attention to potential harms and that any claims to potential benefits are well-grounded. This moral concern with accuracy and non-manipulation is reinforced by legal liability concerns about ignoring or downplaying potential risks.

therapeutic.[62] As we shall indicate below, this is one of several problems with treating informed consent as a necessary and sufficient condition for research involving humans.

2. Criteria and evidence for overall benefits

We have already commented that the second question (overall benefits) is harder to answer than the first question (scholarly standards). One reason is that general answers to (2) sometimes appear to rest on ideologically based claims that are not evidence-based. Some will find it tempting, for example, to address the question of overall benefits on the basis of assuming or denying that the world of research can be modelled as a type of ideal free market in which unfettered competition advances the common good. If one accepts such a free market model then there would be no need to make an explicit determination of a research project's likely overall value; the market will decide whether it is beneficial and, researchers, their sponsors and institutions should be free to enter the market without restriction.[63] Analogously, some defenders of academic freedom in research could, following John Stuart Mill, argue that over the long run unfettered enquiry is maximally productive of truth. As with its economic counterpart, intellectual consumers in the market of ideas will sort out the good from the bad over time. Ideological critics of free markets will claim the opposite, namely that bad research will drive out good. Thus, many university-based health researchers are deeply suspicious of the introduction of the profit motive into the health sector generally and the health research sector particularly. Such underlying ideological orientations certainly colour debates here. In effect then, we wind up with two polarized models of governance with respect to question two – a free market model of passive governance and a command economy model of activist governance.

But ideological models without supporting evidence are unconvincing. They are also unhelpful in that they do not provide sufficient differential information about the overall benefits or harms of particular research projects. After all, what is being proposed, particularly in higher risk research projects are deliberate interventions into the lives of research subjects that may have major ramifications for them and often for others.[64] It seems to be reasonable to ask

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[62] See N.E. Kass *et al*., "Trust: The Fragile Foundation of Contemporary Biomedical Research" (1996) 26/5 *Hastings Center Report* 25. and Presidential Advisory Commission on Human Radiation Experiments, *The Human Radiation Experiments: Final Report of the President's Advisory Committee* (New York: Oxford University Press, 1996).

[63] Of course a consistent defender of free markets will insist that researchers, sponsors, and institutions respect the right of potential research subjects to freely decide whether they wish to be involved in research.

[64] Consider, for example, the extensive debates around new reproductive technologies (NRTs). Critics of many NRTs argue that they harm the health of women who use them and have socially deleterious effects on the status of

whether such potentially costly interventions into the lives of human subjects are likely to be beneficial or harmful overall.[65] So all the stakeholders in research – from research sponsors to research subjects – need evidence, not just ideology, to address question (2). But it is sometimes difficult to gather sufficient evidence to allow reasonably well-informed predictions of the likely benefit to harm ratio for many research proposals. Especially in new and venturesome areas of research, one cannot amass the powerful evidence that epidemiologists produce through thorough extensive retrospective studies and meta-analyses. The areas in which such evidence is lacking are wider than may generally be believed. Thus, many standard practices in health care are not evidence based. Moreover, in such "soft" but morally crucial areas like quality of life and social effects, research about which effects predominate and matter is really in the early stages.[66]

The net effect of such factors is that question (2) may be difficult to answer and that there may well be a lack of expert consensus on what counts as a good answer. Of course, there will also be clear cases in which on a common sense basis a consensus can be reached on overall value. Still it seems to us that actors in the research system – researchers, research institutions and sponsors and standard-setters – should make a reasonable attempt to address type (2) questions, especially where there appear to be significant consequences for research subjects or society as a whole, e.g., xenotransplantation.[67] Of course, how and from what perspective actors should address question (2) varies from agent to agent. Research institutions and sponsors have different types of obligations concerning the social good, depending crucially, for example, on whether they are in the public (promoting the public interest while respecting private rights) or private sector (advancing the good of stockholders while not harming the public interest).

In any case, we would observe that based on our research and observations, question (2) is much less often addressed than it ought to be. Thus, while research grants are generally

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women overall. It is worth noting that most NRTs have been developed as 'clinical innovations' and not as research projects. Hence, they have not been subject to REB approval.

[65] An analogous question can be asked when public money is invested in research – is this from the perspective of the general social good a wise investment of public resources? When they dispense resources for research, health charities have a similar question to answer; namely, in terms of their particular area of concern (e.g., cancer) is investing in this research project or area of research a better use of resources than investing in other areas of research or in, say, direct provision of health care or education?

[66] See the Burgess and Brunger Section D-1, "Negotiating Collective Acceptability of Health Research".

[67] For potentially high-risk procedures like xenotransplantation, a major social issue is about the placement of the burden of proof. Should it, for example, be set at the level for blood product safety proposed by Krever or does the onus lie on critics of xenotransplantation?

awarded on scholarly grounds (cf. question 1), scant consideration is usually given to the likely overall advantages or disadvantages of particular research projects. It is easy for those awarding research grants to assume that the fact that a particular area is funded means that the sponsors have done a calculation of the expected overall utility for the area of research thus letting the peer review committee off the hook. Similarly research institutions (in the public sector) and REBs may take the fact of external funding as evidence of overall utility. But we wonder whether and to what extent sponsors actually engage in systematic (research-based) assessments of the question of the overall net social value of the research they are funding. All too often relevant parties – sponsors, research competition adjudicators or REBs – fail to address the overall value question in ways that are credible and transparent to the many stakeholders in research. This represents a failure in governance – a lack of accountability to stakeholders. From the research community's point of view, it is unduly risky. If a line of research turns out to have disastrous results the trustworthiness of researchers will be called into question.

C. Question 3: Respect for Rights

Question (3) is about respecting the dignity and rights as well as taking into meaningful account the interests of research subjects. These are responsibilities incurred in sponsoring, housing, conducting and approving research. Historically well-founded concerns about the abuse of humans involved in research put this question on the social, political and legal agenda. Here, we can see a historical shift in terms of a general cultural movement from a war-time context in which conscription was taken to be a justifiable social measure to one in which individual and minority human rights come to the fore.[68] In the context of the total war that marked both the First and Second World Wars, each element of society is seen as a part of the national fighting machine – whether as a part of the military, industry or the farm or, naturally as a research subject. In this context, it was easy to rationalize conscripting individuals, particularly populations "under discipline" like army recruits, conscientious objectors or prisoners, to be subjects for research projects that promote the overall war effort, e.g., by reducing infectious diseases in the army or testing new forms of warfare, like exposure to radiation.[69]

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[68] See Radiation Experiments, *supra* note 62, and Rothman, *supra* note 54.

[69] In the Presidential Report on the Human Radiation Experiments, this case is well argued and well documented, though the authors note that in particular areas of moral sensitivity, e.g., experiments around sexually transmitted diseases, even the U.S. Army was very concerned to secure informed consent. *Ibid.* In the 1960's Canadian prison

In the post war period particularly from the 1960's onwards, there developed a different social ethic that was attuned more to human rights than to collective interests. In many ways, this might be seen as a natural reaction to the horrors of the Second World War – a part of the general move towards the recognition of inherent human rights in various documents, e.g., the UN covenants on human rights, the *Canadian Charter of Rights and Freedoms* and various other human rights acts. What at first sight may be puzzling is that it took so long for this to affect health research, particularly given that the Nazi Doctors' Trials occurred in the immediate post-war period. The historian David Rothman argues that most medical researchers in the Allied countries saw themselves as utterly different than the Nazi doctors, and so little attention at the time was paid to the *Nuremberg Code*.[70] In any case, a much more rights-oriented perspective on the situation of human subjects involved in research came to the fore. This had much in common with the breaking down of racial and gender barriers and increased concerns about other forms of inequality and consumer rights.

Two different kinds of rationale can be urged on behalf of the moral perspective that sees humans generally and research subjects particularly as possessors of rights that ought not to be traded off for the general benefits of research to society as a whole. The first is based on the idea of minimizing agency-risks. Society needs to have in place mechanisms that counter the under-representation or even misrepresentation of research subjects' interests that is likely to occur if researchers, research institutions and sponsors are the only ones in the driver's seat with respect to the governance of HRIHS. The second is based more on an appeal to the intrinsic human rights of research subjects. However, it too argues in favour of accountability and other governance mechanisms over research involving human subjects. For example, steps need to be taken to ensure that the participation of individuals in research is both informed and voluntary. In other words, the arguments reach the same conclusions (rights and remedies to protect the interests of research subjects) but on two different bases: utility and rights.

The first takes the history of research abuse as evidence that researchers, research institutions, research sponsors and governments are not the disinterested judges of overall

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officials offered prisoners as ideal research subjects J. Bronskill and M. Blanchfield, "Experiments in pain: How medical researchers subjected volunteer prisoners to pain, isolation and shocks in 20 years of secretive tests" *The Ottawa Citizen* (Saturday, September 26, 1998) 11 <*www.ottawacitizen.com/national/980926/1637463.html*>.

[70] Rothman, *supra* note 54.

human welfare that they may purport or even sincerely believe themselves to be.[71] It also takes into account the agency-risks that organizations typically face when employees or managers substitute their own interests for that of the organization.[72] This it might be argued is not based on a jaundiced view of the behaviour of humans generally or researchers particularly but on a realistic assessment of the incentive structures in research organizations. Given the pressures (e.g., to publish, to secure patents, or to be the first in one's field of research), it is easy to see how natural it would be to underestimate the interests of vulnerable populations (e.g., prisoners, institutionalized children or seniors) and over-estimate the expected value of the research. That is, all the major actors here – researchers, research sponsors and research institutions – can be seen as having vested interests in the reputation and resources that flow from potentially successful research. So from a governance perspective, what is needed are barriers that protect research subjects. Informed consent is one such barrier. Another is the independent REB, which because it is independent does not have a vested interest in the research being done. Moreover, it can be argued that REBs are needed to add distinct areas of expertise to the research assessment process – expertise from ethics, law, the community and relevant areas of research.[73] Thus, the REB is justified as a guardian of the rights of research subjects on the pragmatic and utilitarian grounds that an arm's length, knowledgeable third party must be in place to protect the rights of research subjects.

The second rationale for a system of governance that is oriented to the interests of research subjects is based on an appeal to intrinsic human rights. Often such appeals are based on Kant's claim that one should "act in such a way that you always treat humanity, whether in your own person or in the person of any other, never simply as a means but always at the same time as an end." This means that one ought always to treat persons as having an inherent worth in their capacity for autonomous action that gives them a dignity beyond all price.[74] Or, to put it in contemporary terms, the idea is that rights are designed to "trump" social

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[71] The argumentative approach that I am exploring in this paragraph is characteristic of the sort of utilitarian reading of rights that Mill advances on behalf of the presumption in favour of individual liberty in his famous essay, Mill *supra* note 41.

[72] *Supra* note 36.

[73] P. McNeil, *The Ethics and Politics of Human Experimentation* (Cambridge: Cambridge University Press, 1993) at 184. He cites Veatch's argument that there is a tension between an "interdisciplinary professional review model" of the REB and a "jury model", R. Veatch, "Human experimentation committees: professional or representative?" (1975) October *Hastings Center Report* 31. The former emphasizes expertise; whereas, the latter stresses impartiality and community representation. Veatch proposed that the tension should be recognized squarely with two separate ethics review boards – one expert and one lay. McNeill argues for a hybrid model with equal representation from both experts (researchers) and lay people.

[74] I. Kant, *Groundwork of the Metaphysics of Morals*, trans. H.J. Paton (Toronto: HarperCollins Canada, Ltd., 1963).

interests.[75] Such a concern for the basic human rights of research subjects can be extended to support demands for justice or fairness in research – both in terms of non-exploitation of vulnerable research subjects and in terms of equitable distribution of the benefits of research. The latter has been especially important in recent years in regard to traditionally under-researched groups, especially women but also children.[76]

In operational terms, it may be argued that the two rationales give rise to two important standards. The first suggests a concern for **minimising research risks for subjects** (compared to potential gains for them).[77] The second line of argument (based on a Kantian concern for the inherent dignity of persons) especially is reflected in the requirement that research may not proceed with competent persons without their **free and informed consent**. For this study of governance, it is very important to understand that the expert consensus in bioethics is that both standards must be met. So it would not be morally acceptable to impose slight research risks on a competent person without that person's free and informed consent to participate in research. But it is also the case that there are levels of risk that may not be imposed on persons even with their permission.[78]

So question (3) about the protection of research subject rights really requires a two part answer: (a) this research is not likely to impose an impermissible level of harm and (b) research will not proceed unless potential subjects (or in the case of an incompetent subjects, their surrogate decision-makers) have given their free and informed consent. Because both (a) the level of potential risk to the subject and (b) the subject's or the subject's proxy's consent are required, we can see the responsibilities here as fiduciary (due care) rather than as strictly contractual or by agreement (*volenti non fit injuria*). That is the relevant parties in research have

[75] R. Dworkin, *Taking Rights Seriously* (London: Duckworth, 1977).

[76] One issue is that significant areas of health research have taken the diseases and symptoms of men as species-typical with unfortunate effects on women's and children's health as well as the neglect of research into their health issues.

[77] This justifies riskier research on sicker patients if there is a commensurate increase in benefits. This is part of the ethical rationale for Phase I/II CTs.

[78] The level of harm that is permissible varies depending on the competence of the potential research subject. One can justify imposing higher levels of risk on competent than on incompetent individuals on the grounds that competent individuals can freely and knowingly decide to accept risks to themselves whereas incompetent individuals cannot. We take it that those who have care of incompetent persons have a duty to protect the interests of their wards and so may not beyond the level of minimal or relatively insignificant risk expose their wards to harm. It should be noted that following the Eve decision, see *Re Eve*, 31 D.L.R. (4th) S.C.C [1987] 2 S.C.R. 388 (S.C.C) determining the level of minimal risk for research involving incompetent persons has been a matter of some dispute. This has generated a fair amount of concern around research involving (incompetent) children and adults.

an obligation to make sure, even with competent subjects, that the "research deal" they offer is reasonable and fair.[79]

However, it should be noted that minimal harm standards can be hard to formulate – when does research cross the line between permissible and impermissible risk?[80] Different researchers and different REBs may have conflicting answers to this question. This is, we suspect, one of the reasons why there are concerns on the part of many REB members about accepting the judgements of other REBs.[81] Moreover, there may be disagreement about the nature or extent of a researcher's fiduciary responsibilities. On the surface, it looks a lot easier to administer and monitor the informed consent process than that of minimal harm. In fact, informed consent is very easy to monitor if the ethics of HRIHS is reduced to subjects' signatures on consent forms. However, informed consent is much more than a signed consent form. At best the signed form offers some, though by no means conclusive, evidence of consent at the time. Consent rather is a process of willing and knowing participation over time. Moreover, consent should be seen as only a part, albeit an important part, of the research ethics process. However, as we claim in our conclusions, what has happened is that by and large we have a research ethics system that is operationalised around consent forms and pays little attention either to informed consent as a process or to levels of research risk.

[79] Similarly in commercial law, there are areas of business where the caveat emptor model does not obtain; rather the vendor must take care to be sure the product is safe and effective. This recognises the imbalance in power that can exist in many types of sales, e.g., telephone sales.

[80] An interesting comparison can be drawn between the way in which minimal risk was formulated in the 1997 draft Code and the 1998 TCPS. The TCPS is much more permissive of harms to subjects than the Code. Tri-Council, *Tri-Council Policy Statement on the Ethical Conduct of Research Involving Humans* (Ottawa: Tri-Council, 1998).

[81] See Beagan, Section E-1.

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SECTION B-2

HRIHS: PROCESS AND CONTEXT

Michael McDonald[82]

In this section, we describe the normal processes through which HRIHS is conducted and administered. As indicated in the previous section, we are interested in governance at two levels: (a) the level of particular institutions, organisations and agencies involved in various ways in HRIHS; and (b) the interactions of institutions, organisations and agencies identified at level (a). So we are especially interested in the institutional actors and processes that are central to the governance of HRIHS.

We also intend this section as a useful primer or road map for the reader who is interested in but unfamiliar with this area. For those who are familiar with and who perhaps work or serve within this area (e.g., as researchers, members of Research Ethics Boards (REBs), research sponsors, regulators, or as research subjects), we hope that this introductory part of the study will both 'ring true' with a significant part of their experiences and, also serve to articulate the ways in which the study team's observations and assumptions differ from the readers'.

I. THE RESEARCH PROCESS

To describe both (a) and (b), we start with a simplified model of the research process (Display 3). We identify four stages:

[A] Research initiation

[B] Research approval

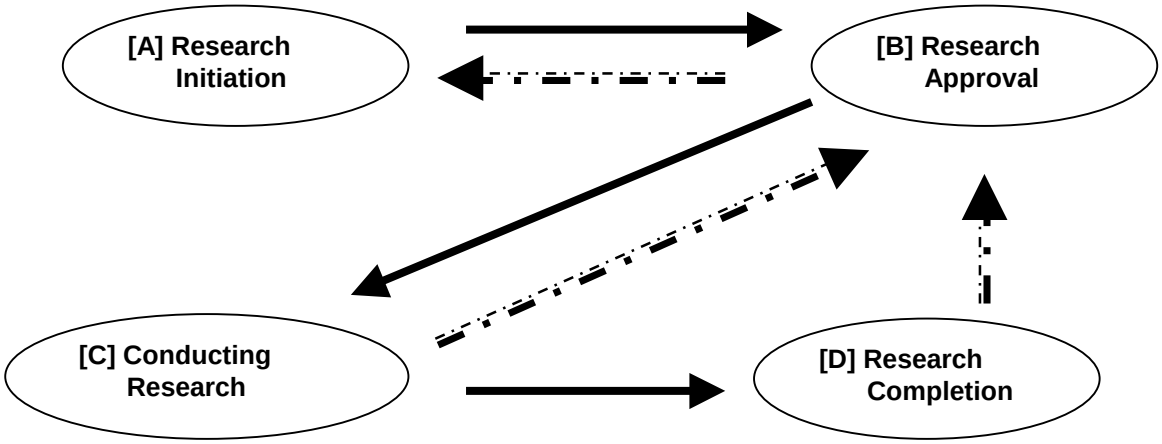
[C] Research

[82] I wish to acknowledge the important role that my colleague Dr. Barbara McGillivray has played in the formation of this section of the study.

[D] Research completion

These are presented as four circles – [A] through [D] – connected by arrows indicating sequences of activities.

Display 3



The solid arrows represent the normal or usual flow of activities in the research process. The arrows with broken lines represent processes where in some cases research approval of some sort is sought before or after the normal stage of research approval. Thus, when researchers want to do a pilot study involving human subjects they are supposed to seek REB approval. During research, modifications in the protocol or adverse incidents may lead the researcher to return to the REB or even the research sponsor to seek approval or to notify them of such changes. As noted in Joly's paper (Section D-2) on public health research, a public health intervention may result in publishable research; but since many journals now require that the REB have approved the research being reported in the publication, the researcher may seek retrospective REB approval.[83]

[83] For the difference between "retrospective" and "retroactive" rules see M. McDonald, "An Inquiry Into the Ethics of Retroactive Environmental Legislation: the Case of British Columbia's Bill 26" (1995) 29 University of B.C. Law Review 63.

A. Social Contexts of Research

However, research does not just happen. It occurs in a social context. We identify two types of social context that are directly relevant to the conduct of HRIHS. The first is the social context that sets conditions or boundaries on ethical research involving humans. We see these as determining what counts as (a) acceptable scholarship and (b) respectful treatment of humans involved in research. The second concerns the direction of research – a process that might be broadly referred to as "setting the research agenda".

1. Parameters of research

In Display 4, the outer circle (X) represents the parameters or boundaries of what is regarded as research that is acceptable from a scholarly perspective (Ethics Question 1) and research that is sufficiently respectful of the rights and dignity of humans recruited as research subjects (Ethics Question 3).[84] In the interest of simplicity, both (a) and (b) are represented as a single circle X rather than two only partially congruent circles X_a and X_b. The parameters represented by X express what we would describe as an **informed consensus position** on acceptability. The consensus embodies shared social values, yet it also is a morally credible consensus because it commands (or would command, if the question were asked) the agreement of the parties to it. This consensus position could also be described as "minimal" in the sense that the standard and processes represented in it are common across a wide spectrum – a lowest common denominator expression of scholarly acceptability (question 1) and respect for the rights of research subjects (question 3). We note that a consensus does not have to include everyone – there may be outliers. However, the main bodies and their leaders have to generally share values for there to be a consensus.

From a social consensus perspective, research outside these boundaries would be viewed as morally unacceptable by most observers including typical members of the research community, the pool of potential research subjects and the general public. As we have already noted, there are disagreements and uncertainties about where the boundaries are. Values are subject to change here. In terms of Display 4, X might be envisioned as in some places hazy (a fuzzy grey line) and in other places a sharp or precise boundary. Moreover, X would also expand or contract as boundaries of acceptability shift. Without getting into an extended

[84] See Figure 2, p. 33.

discussion of objectivism and relativism in ethics, we will simply say that the consensus can move in better or worse directions as seen from some historically situated point of view. We certainly do look back in time and criticize the standards applied in previous generations. How much continuity there is in a social consensus over time and whether it is possible to hold previous generations responsible for what are now seen to be serious moral errors is an important question that can be answered meaningfully.[85]

2. Setting research directions

In a broad way, we talk about research in various areas having a direction or moving in certain directions. On the classical view of science, the direction of scientific research comes from a process of making empirical hypotheses and testing the hypotheses by observation or experimentation. From a sociological or historical perspective, scientists interacting with each other and the broader population set the direction of science. The groups that significantly influence the directions of future research are listed in box [Y] in the upper left-hand corner of We identify five groups as individually or in combination affecting, influencing and sometimes deliberately setting research directions.

- The scholarly community (which is really an assemblage of many disciplines, sub-disciplines and cross-cutting research groups) through various processes (peer reviewed publications being one of the most salient) establish directions for research.
- Sponsors of research set directions through research funding, especially targeted funding.
- Research institutions, be they public or private, hire and promote researchers, decide on institutional research objectives, build research facilities, etc.
- Government sometimes appears as a research sponsor but the role that we are identifying here is the less direct but nonetheless very important ones that governments have through taxation (e.g., policy on tax deductions for research), regulation (e.g., setting the rules for the approval of new pharmaceuticals[86] and medical devices or the patenting of new inventions) and control (e.g., rules about competency or freedom of information) and,
- Interest groups and the public have an effect upon the above but also are in turn influenced by them.

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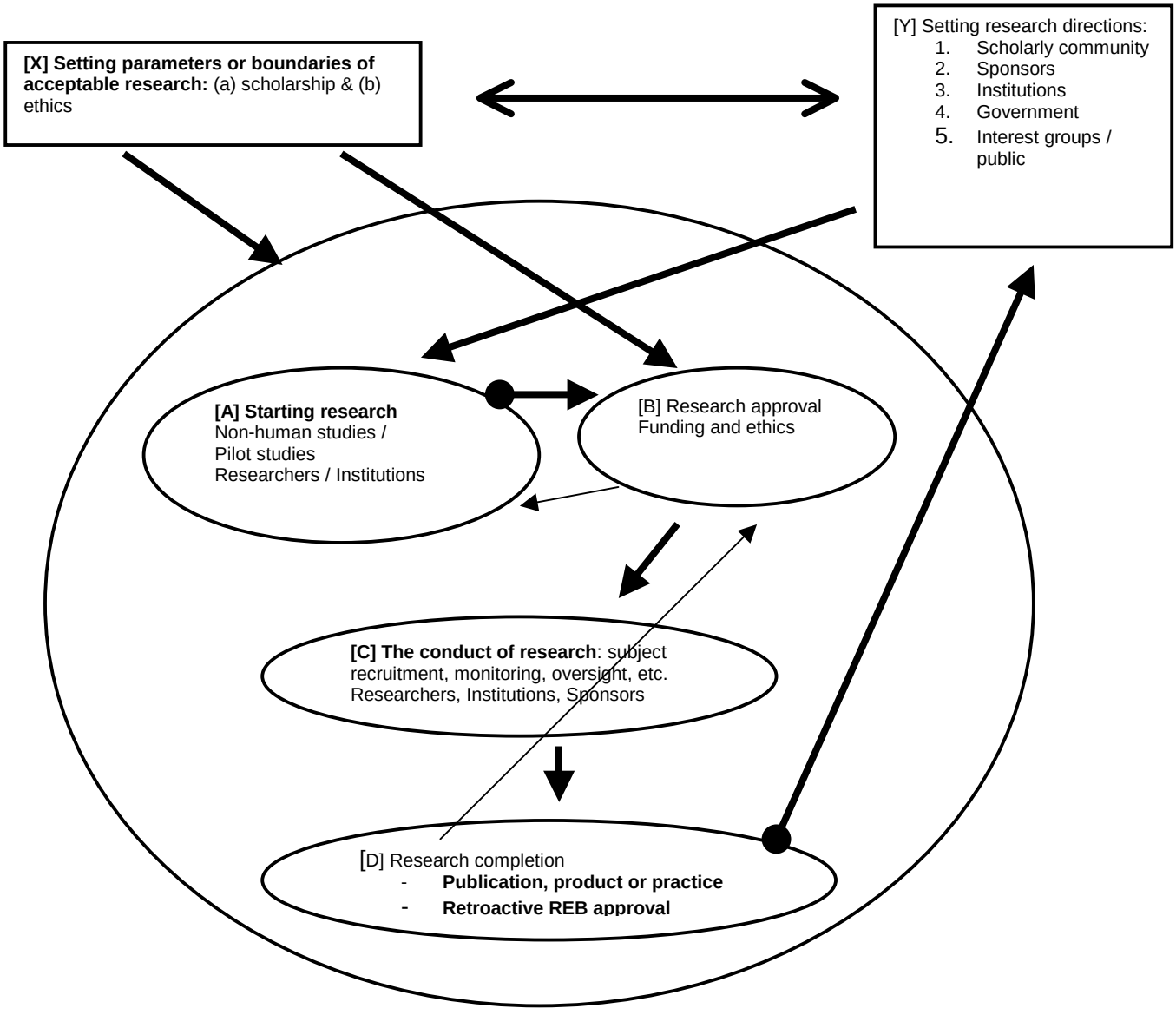
[85] There is a very good discussion about the conditions in which it is fair to hold previous generations accountable to contemporary moral standards by Alan Buchanan, in the President's Advisory Committee on Human Radiation Experiments, *The Human Radiation Experiments: Final Report of the President's Advisory Committee* (New York: Oxford University Press, 1996) at 113.

[86] See for example the new regulations proposed by the federal government for clinical trials: Department of Health, "Regulations Amending the Food and Drug Regulations (1024 -- Clinical Trials)" Canada Gazette Part 1 (22 January 2000) 227.

In Display 4, we represent the overall picture as follows. Arrows indicate the direction of influences. Broader arrows represent larger influences; narrower arrows represent smaller influences.

Display 4



B. Agents and Activities

We now develop a more fine-grained analysis of each of the elements in Display 4. We are especially interested in identifying the relevant actors in each stage and their current governance relationship. This allows us to identify a number of areas that are the subject of this study, namely, matters of concern for the ethical governance of HRIHS.

1. Scholarly parameters (X_a)

Meeting acceptable standards for scholarship has been identified as a key issue for ethically appropriate research. We see three groups as pivotal in setting standards:

The first is the broad scholarly community or **community of researchers**. Since there are different forms of scholarly research, it is probably best to think of the scholarly community as a community of overlapping communities that, at the most general level, has shared values regarding acceptable and unacceptable scholarship (e.g., originality and plagiarism). The values are more concrete and unifying in constituent disciplinary communities – e.g., medicine, sociology and law and even more concrete in sub-communities, e.g. paediatrics or medical anthropology. Scholarly standards are conveyed through a variety of mechanisms, such as, education, mentoring, peer review, accreditation and publication. One might take this as best expressed by the American pragmatist philosopher Charles Peirce's notion of science as what scientists accept as science. The standards are both substantive – an accepted body of knowledge, research paradigms and methodologies – and procedural – for example, independent peer review. We see these standards being expressed in a variety of forums: meetings of academic associations, comments on papers submitted for publication, hiring and promotion decisions, and so on. In short, there are very powerful mechanisms at the level of the research community for maintaining scholarly standards.

Second, research institutions – including universities, research and teaching hospitals, pharmaceutical companies, freestanding think tanks and in-house government research departments or agencies, reinforce these mechanisms. However, research institutions should not be regarded simply as extensions of the scholarly community. They usually have other roles, e.g., in education, disease prevention, clinical care, health promotion and regulation. This complicates the scholarly validation processes. Suffice it to say, such institutions have a major role to play in the promotion and maintenance of scholarly standards; they house, hire and

reward researchers through tenure, promotions, honours and the like. They also play an important role in the governance of research through a whole series of processes: certifying researchers (e.g., through granting academic degrees), establishing educational criteria for courses and programmes, quality assurance processes and on-going review of individuals and departments and most importantly, hiring and promotion processes. Research institutions also have other instruments of governance in research, e.g., data and safety monitoring committees, research integrity processes, financial control and oversight of research funds, the establishment or endorsement of ethics approval mechanisms either within the organisation (e.g., an REB in a university or hospital) or outside (e.g., a company using a private REB). Research institutions also make decisions about research priorities based on strategic, fiscal, or safety reasons and sometimes mandate (e.g., a cancer agency or a Roman Catholic health care institution).

Research institutions have significant incentives for ensuring that research involving humans meets appropriate scholarly standards. First, research institutions have a direct stake in the quality of research being conducted by their researchers. The institution's reputation and often its fiscal viability depend on the production of credible research. As well, there may be legal disincentives for not making reasonable efforts to ensure the quality of research in their institutions, e.g., for contract research. Second, many Canadian research institutions have explicit or implied agreements with research sponsors concerning the ways in which research subjects will be treated in their institutions and by their researchers. A leading example of this is the insistence by the Tri-Council group – MRC, NSERC and SSHRC – that makes compliance with the TCPS for all research involving humans conducted at the institution a condition of receiving research funding. Similarly, U.S. agencies like the NIH require compliance with applicable U.S. federal regulations including on-site monitoring for compliance. Other research sponsors have similar requirements. Since the acceptability of scholarship is a consensus condition for the ethical acceptability of research, research institutions have at least on paper 'bought into' these requirements. These requirements, it should be noted, are both substantive and procedural. In particular, relevant ethical guidelines (e.g., TCPS) call for a prior assessment of the scholarship of each proposal for research involving humans before research is begun.

The third group that sets parameters for research scholarship are those that commission and sponsor research – **research sponsors**. Many different types of sponsors sponsor health research in Canada: federal research agencies (MRC), federal regulators (HPB), provincial research agencies (FCAR in Quebec), provincial regulators (public health agencies), private

sector companies (Merck Frost), health charities (Heart and Stroke Fund), etc. In many cases, research institutions also provide internal funding for small-scale research projects, especially pilot studies. Since "he who pays the piper, calls the tune," research sponsors are in a position to insist that an assessment of scholarship be done before research involving humans is initiated. Like the research community and research institutions, research sponsors have major incentives for ensuring that research meets scholarly standards – the loss of "reputational capital" for not being duly diligent in this regard would be staggering.[87] More importantly, research sponsors justify their existence by the success of their endeavours. They need research credibility to get support from public, private or not-for-profit sector "investors" -- be they shareholders, taxpayers or donors.

These observations about scholarly parameters are summed up in the following display:

Scholarly parameters

1. Scholarly / scientific community: peer review, journals, scholarly associations, consensus conferences, etc.
    a. Substantive standards: research paradigms, (e.g., scientific validity) and methodologies
    b. Procedural: independent peer review
2. Research sponsors:
    a. Research award processes
    b. Scholarly integrity standards
    c. Research audit processes
3. Research institutions
    a. Training and certification of researchers, e.g., degree programs
    b. Hiring, promotion and tenure decisions
    c. Areas of permitted research (e.g., safety, corporate focus, religious orientation)

Display PP-1

2. Ethical parameters (X_b)

We have already discussed some of the consensus standards on ethical research with human subjects in terms of positive answers to three questions.[88] In additions, there is common agreement about processes. We represent this consensus on ethical parameters (PP-2):

[87] For a discussion of reputational capital in the corporate sector, see L.J. Brooks, "Reputational Capital and Business Ethics" *The Corporate Ethics Monitor* (September-October 1999) 65.

Consensus ethical standards

1. Content: 3 issues are basic for review, approval, and conduct of RIHS
    a. Scientific / scholarly validity
    b. Overall benefits of research must outweigh potential harms.
    c. Protection of research subjects' rights and interests
2. Process
    a. Independent arm's length review by an REB
    b. Effective monitoring of ethics, safety, academic integrity, etc.

Display PP-2

As noted in Section B-1, the minimal consensus is stronger and sharper on some elements than on others. Thus, it is quite strong around the requirement for informed consent and the need for something like prior REB review of research involving humans. But it is weaker and foggier around notions of overall benefit and standards of harm. With respect to standards of harm, there is general agreement in most sectors of health researchers that a minimal harm standard is appropriate; yet, there is considerable uncertainty and disagreement about what counts in practice as "minimal harm" or "a threshold of morally acceptable risk".[89]

Next we turn to the official sources where ethical and legal standards are expressed. We see three levels: international, Canadian and foreign. In some cases, governments and quasi-governmental bodies set the standards; while in others, associations, e.g., health care professionals, create the standards. Still in other cases, there is a combination of public, private and professional sources (e.g., GCP). In any case, there is with most of the "direct" standards set at the international and national levels a fair amount of consultation amongst various interested parties – professionals, researchers, research institutions and governments; however, these consultations have not extended to research subjects or their representatives. In Canada, we have divided legislative and judicial sources of norms and standards into two kinds: those that are created by a legislature or court expressly for RIHS or, even more particularly, for health research and those that are created for some other purpose (e.g., for protection of the privacy of personal records in government hands) but that have an indirect effect on RIHS.

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[88] See Figure 2 above.

[89] As noted above, this is not an easy concept to state clearly. Further evidence for this is found in the considerable debate around the legal and moral acceptability of minimally harmful research involving infants and (non-competent) children.

Official sources for ethical/legal standards

Standard Setters

1. International
    a. Intergovernmental, e.g., ICH, UN, WHO
    b. Associations, e.g., CIOMS, Helsinki
2. Canada
    a. Legislatively or judicially determined
        i. Direct intended (e.g., Quebec, HPB regulatory)
        ii. Indirect unintended (e.g., Bill C-6)
    b. Research sponsor determined (e.g., TCPS)
    c. Professional (e.g., CMA Code of Ethics)
    d. Discipline determined (e.g., epidemiology)
3. Foreign
    a. Research sponsor (NIH, FDA)
    b. Site of research (local authorities)

Display PP-3

3. Governance concerns: Parameter-setting

A major concern of this study is whether the modes of governance prevailing in the area of HRIHS provide "a form of governance that is effective, responsive, transparent and just".[90] These four characteristics – **effectiveness**, **responsiveness**, **transparency** and **fairness** – form the core of what could in general be described as "ethical governance." As suggested by the University of Ottawa's Centre for Governance, governance questions have to be directed at two levels: (a) the level of individual organisations and (b) at the level of the interaction of organisations with each other and with members of the affected population. As illustrated in Display 4, there are many organisations and other types of formal or informal social entities that play roles in HRIHS. The interaction of these social entities is very complex. We are interested in effectiveness, responsiveness, transparency and fairness at both levels. Again in table form, we set out some major areas of concern:

[90] LCC, *Request for Proposals: Contract # 98-09-01; Governance Relationships* (Ottawa: Law Commission of Canada, 1998).

Ethical governance

A. Areas of concern

1. What is in place for **quality assurance**: maintaining standards, monitoring for harm, consent, safety and other ethically relevant issues?
2. What is in place for **quality improvement**: learning from our successes and mistakes, e.g., for improving researcher and REB performance?
3. How are **factors underlying ethical or unethical performance** (e.g., knowledge, judgement, attitudes, organisational / professional cultures) addressed?
4. How do those who set standards **assure stakeholders**, especially in the community, that the standards are appropriate and effective?
5. **Who sets the standards?** Who gets a say and who doesn't?

B. Structural Concerns

1. How is **effectiveness** to be gauged?
2. What are the **processes**?
    a. Who does what? What role (if any) do **subjects** have?
    b. **Transparency**? Transparent to whom? How?
    c. Where is **independence** important?
    d. Is there **effective feedback** from the field to standard setters, sponsors, etc.?
3. **Who** is accountable for **what** to **whom**? **How** are they held accountable?

Display PP-4

(A-1) and (A-2) raise concerns about effectiveness. Do research institutions and sponsors have in place the mechanisms for reasonable quality assurance and quality improvement? Of course, this also raises questions about transparency and accountability. Do the research institutions' or sponsors' stakeholders receive a proper accounting of the organisation's performance in these areas?

The same questions arise more acutely at the inter-organisational level, e.g., interactions between research sponsors and institutions. Between institutions things can fall between the cracks. Accountability may become unclear and diffuse; there may well be confusion over who is responsible for what. This is especially the case in the Canadian setting, e.g., with a major federal role in research along with our constitutional separation of powers in health and education. As we shall argue below, this is complicated by the realities of a globalised market place.

(A-3) is meant to raise questions about the cultures of the multiple organisation and social groupings involved in HRIHS. At all the stages and levels of the research process from setting the parameters to research completion, there are many cultures. It is essential to ask if

they are cultures that work effectively, for example, to ensure respect for the dignity and interests of research subjects. From a governance perspective, this concern can be rephrased in terms of whether governors are effectively encouraging and nurturing ethical cultures. This of course leads to many other questions – some at very fundamental levels, like “do ethical cultures just occur naturally or can they be socially engineered?” and others at a very practical level like “Does the institution have a budget and plan for ethics education for REB members and researchers?” Concerning an organisation’s level of commitment it is worth determining if the same degree of concern and commitment is expressed with regard to maintaining an ethical culture in research organisations as is given to maintaining a research culture. Thus while to some extent it is inevitable that good organisational cultures are partially a result of happenstance, we believe that deliberate planning and nurturance have an important role to play.

Concern (A-4) focuses on accountability to stakeholders. This raises a question about who gets counted as a stakeholder. One of our major conclusions is that research subjects are rarely thought of as active stakeholders. By and large the practice at all levels – from standard setting to research governance – has been to treat research subjects as passive stakeholders. In the interviews, very few thought that asking people about their experiences as research subjects had anything to do with judging the effectiveness of REB and researcher performance.

Concern (A-5) is with those who set standards. A penetrating question to ask is who has not been present at the standard-setting table that should be there? Again we observe that it is researchers, research institutions, research sponsors and governments that dominate the area of standard setting. Do these parties ever investigate what research subjects might want and what happens to people involved in research? Are research subjects involved in standard-setting?

Under (B), we raise questions about (1) effectiveness, (2) processes and (3) accountabilities. Two preliminary observations are in order. The first is that at a systemic level these are very difficult issues in the decentralised Canadian context. The second is that given this decentralisation there would seem to be a strong case for individual research institutions and research sponsors to make a concerted effort to ensure they measure up in these areas – not just on their own but working collaboratively with other institutions and groups.

C. Setting Directions for Research (Y)

In the following five displays (SD 1-5), we map out the main players and issues for box Y in Display 4. In SD 1, our concern is with identifying those who set research directions:

Who sets / influences directions in research?

1. **Scholarly community** – current and emerging research interests, methods, tools, etc.
2. **Research sponsors** (companies, research councils, health charities, etc.) in strategic planning, grants programmes, etc.
3. **Research institutions** (universities, hospitals, companies, etc.) in hiring, promotions, areas of emphasis, etc.
4. **Researchers** as a talent pool with skill sets, plans etc.
5. **Governments** through regulation, taxation and incentives
6. **Interest groups** and the **public** as investors, consumers, patients, voters, etc.

SD-1

For organisations, there are a number of relevant considerations (SD-2):

What directions to set?

Considerations
- Mission
- People
- Financial resources
- Research opportunities
- State of science / scholarship

How to get there?
Activities
- Research sponsor targets research or has open competition
- Company makes research investment decisions
- Research teams set directions for future research

SD-2

For these, all the groups identified in SD-1, there are a number of relevant ethical concerns specific to HRIHS (SD-3):

ETHICAL CONCERNS

1. Ensuring that the research directions set meet the sponsor's responsibilities to stakeholders
2. Setting research directions that are compatible with the rights of research subjects
3. Fairness issues addressing public concerns about a non-exploitative and inclusive research agenda

SD-3

As with setting the parameters of research, there are a number of ethical governance questions. Those listed in PP-4 are all relevant. But there are some that seem especially apt for setting directions (SD-4):

Ethical Governance Issues

1. **Internal**
   a. Responsible use of resources (public or private)
   b. Transparency and accountability to public / private stakeholders
   c. Skill sets and organisational cultures: scholarly, ethical, administrative, etc.

2. **External - co-ordination issues:**
   a. Who does what?
   b. Who identifies gaps in research, e.g., research on women's health? Who takes responsibility for filling these gaps?

SD-4

II. STAGES OF RESEARCH

We now lay out the four stages of the research process: research initiation, research approval, during research and, research completion.

A. Research Initiation

Research typically begins with research questions. For many types of medical research, the next step is non-human studies. This may be followed with a pilot study on a small group of patients or subjects. Then researchers are in a position to decide if it is worth proceeding to a larger scale study.

Research Questions
- Observations
- Hypotheses
- Methodology

Non-human studies
- Literature searches
- Cells / computer models
- Animal studies (Animal Care approval)

Local pilot study (human subjects)
- Site agreement
- REB approval

Design a larger study

RI-1

An example of such a sequence can be taken from an area like cancer research (RI-2):

Examples from Cancer Research

1. Non-human studies
2. Pilot study on human subjects
   a. Local study
   b. Agreement of local site (e.g., hospital)
3. REB Approval
4. Results presented to a(n) (inter)national consortium
5. Establish expert group if ripe for national / international study,
   a. Set research questions & methods
   b. Coordination plan for local studies
6. Apply for funding of a multi-site trial

RI-2

Pilot studies raise a number of ethical questions, some of which we have already discussed but others that need to be introduced now, e.g., safety-monitoring and protection of confidential health records.

Ethical issues for pilot studies

General ethical questions

1. Is this valid / sound research?
2. Do the overall potential benefits of the research outweigh potential harms?
3. Does this research respect the rights and interests of research subjects?
    a. Harm / benefit issues
    b. Informed consent issues

Special issues around pilot studies

1. Blurring clinical treatment / research boundaries
2. Concerns re limited numbers
3. Adequacy of research proposal

Oversight issues

1. Drug / other intervention monitoring
2. Adherence to professional standards
3. Adherence to scholarly standards
4. Adherence to ethics guidelines, legal rules and regulations

RI-3

The research initiation stage raises a number of concerns for ethical governance of HRIHS. These include the following (RI-4):

Ethical governance for research initiation

Areas of concern

1. Do researchers/REB attempt to assess the effects of projected research on subjects?
2. Selection of topics / areas for research, e.g., avoidance of neglected areas of research / neglected populations and issues
3. Adequacy of non-human models / studies and pilot studies
4. Thoroughness of ethics and site reviews, e.g., is there a lower level of concern for pilot studies than for regular studies?

Types of Concern

1. Are there any retrospective analyses of good / bad pilot studies?
2. Is the ethics of HRIHS a real concern of all at this stage for researchers and REB members or, is this deferred to the next stage?
3. What slips through the cracks for ethics, safety, confidentiality, clinical responsibility, etc.?

RI-4

B. Research Approval

In our current governance structures, it is at the research approval stage that the most attention is paid to the ethical treatment of human subjects in research. When researchers and research administrators talk about the ethics of research involving humans, this is usually the stage that is the object of discussion – that of REB review of research protocols. Indeed, for most researchers, REB members and in research administrators, this is the sum and substance of the ethics process. At this stage, REBs apply ethical standards (principally the TCPS and GCP and sometimes foreign standards as apply for example to NIH-funded research) to determine if research projects should be approved or modified before acceptance or, rejected.

Nonetheless, there are other parts of the research approval process that are important. In particular, most studies cannot proceed without funding. In the private sector, this is a corporate decision; while for governmental research agencies, it is a bureaucratic/academic decision following the mandate of the agency (e.g., a DND study of risks of exposure to chemical agents). However, in public sector institutions like universities and health research centres, the pattern is generally that a researcher applies to an external funder or research sponsor – public, private or not-for-profit. The research sponsor has then to make a decision about whether to fund in whole or part the research project (RA 1):

Review for funding

Selection of peer reviewers by the sponsor (e.g., NSERC)

Reports of peer reviewers on:

- Contribution to knowledge (validity, originality, methodology, etc.)
- Fit with sponsor specific guidelines (e.g., does it fit under a strategic theme)

Peer review committee

- Reviews reports from peer reviewers
- Arrives at its own assessment of the contribution to knowledge (validity, originality, etc.) and fit with sponsor specific guidelines
- Sends a ranking of research projects divided into recommended for full or partial funding, recommended only if more funding is available, or not recommended with supporting reasons
- Occasionally will raise concerns about ethical issues

Agency / committee level

- Reviews recommendation of peer review committee
- Decides whether or not to fund
- Communicates decision to the applicants

RA-1

If funding is granted, then the process shifts to the research institution. There may be site-specific approval mechanisms in areas like the following:

Site-specific approvals

- Safety concerns: biohazards, dangerous materials, contagious diseases, equipment hazards, safety training and qualification of personnel, etc.
- Concerns re: laboratory space, fiscal concerns (e.g., to collect overhead charges), ensuring that the research is not prohibited for other site-specific reasons (e.g., abortion research in a Catholic or Salvation Army hospital)
- Adherence to other site related policies (e.g., financial reporting, conflict of interest, etc.), use of clinical records, etc.

RA-2

Some of the above may be dealt with by the REB, another body or administrator.

Next we move to REB approval. The first thing to consider is where the approval takes place and the information base available to the REB (RA-3):

Ethics approval

Where?

- If single site, local REB
- If multi-site, approval at the lead site and all other sites

Information base

- Research protocol
- Funding decision (if peer reviewed taken as evidence of scholarly / scientific merit)
- Research budget (sometimes)
- Ethics review application including informed consent process and forms, and proposals for monitoring (new for TCPS) or adverse incident reporting (mandatory for GCP), stopping rules, etc.

RA-3

We have already indicated the main issues to be considered by REBs. However, we list them again in RA-4:

REB needs positive answers to 3 questions

1. Is this valid / sound research? This is usually based on prior science review by the sponsor; otherwise, see pilot study process.

2. Do the overall potential benefits of the research outweigh potential harms?

3. Does this research respect the rights and interests of research subjects?
    a. Harm / benefit issues
    b. Informed consent issues

Plus conformity to other applicable ethical, legal, clinical and institutional standards

RA-4

In the following sections, we have much to say about ethical governance issues at the research approval stage. In the interviews (Section E), we found that REB members say that how the REB is perceived focuses on the REBs' role in the approval process. A significant number of participants report that researchers see REBs as either a necessary evil or as another step in a wasteful bureaucratic process. The research community is then very concerned with the REBs' speed and efficiency in approving research. This suggests a high risk of "ethics" being reduced to bureaucratic administration with its attendant demands for paper work.

Further it should be noticed that in terms of the total process from initiation to completion of research, "ethics" is a very small portion. That is, REBs, researchers and research institutions tend to see "ethics in research" as limited to the ethics approval phase – what happens before and after is functionally outside "the research ethics zone." Institutionally who can fault this impression? The only place research institutions invest resources (and scant resources at that) is in the REB process. Canadian standard setters and regulators also are almost exclusively focussed on the REB approval phase. Whether things will change with the TCPS and HPB requirements for monitoring is yet to be seen; however, as can be seen from the interviews, monitoring is for most REBs a large question mark.[91]

[91] For the HPB proposal, see Department of Health *supra* note 86.

More importantly, when we reflect on the underlying culture of research, we should be asking how much of a concern is there for ethics compared to, particularly, concerns for scholarship and success in research? Recall what was said above about the mechanisms for promoting sound and insightful research in terms of education and training, hiring, promotions, peer adjudication of research proposals and the rest. Then consider by comparison the scant attention paid to education and training of researchers and REB members around the ethical treatment of humans involved in research.

In RA-5, we list multiple governance concerns:

Ethical governance issues for the research approval phase

1. Is there a good fit with other parts of the site-specific approval process? Does the REB have all the information it needs to make its decisions, e.g., does it see full research protocols and budgets?

2. Is the REB an arm's length review body that in substance and appearance is independent and objective in terms of membership, processes, and reporting relationships? Who does the REB report to? Who appoints its membership?

3. Are the interests of prospective research participants adequately represented on the REB? How? Are lay or community representatives effective members of the REB? Do the represent the interests of research subjects?

4. Are there transparent and effective accountability relationships to those who set standards?

5. Who, if anyone, addresses gaps and inconsistencies in standards and processes? How?

6. Does the REB spend the bulk of its time on bureaucratic matters or on substantive ethical concerns? Does it address the full range of ethical issues (cf. the three questions) or is its time mainly spent on consent forms? How does it deal with issues around the likely overall value of a research proposal? How does it deal with issues of minimal harm?

7. Are REBs consistent and fair in their application of standards? How is this shown to relevant stakeholders?

8. Does REB approval improve ethical performance? In particular, does the approval process actually protect research subjects in the way that it is supposed to? Does the REB, research institution, or research sponsor have good means of answering such questions?

9. Where are the mechanisms and measures for quality assurance and quality improvement for the REB approval process? For the researcher application process?

10. Is there ethics training for REB members and researchers? How is adequate expertise on the REB ensured?

11. Is there accreditation and certification for REBs?

RA-5

C. During Research

With REB approval, the research institution will release funds to the researcher to proceed with the human experimentation phase. During research, there are various types of monitoring in place. Many of these vary depending on the nature of the research. For example, as noted in Appendix Two for this paper, clinical trials (CTs) are monitored in ways that other types of research are typically not monitored. Who the research sponsor is also makes a difference. For example, US federal research sponsors require access to all research records, including records of REB meetings, for all the research they fund. US agencies will undertake planned and surprise visits and even random audits, e.g., of REB records. They will issue and enforce (through withdrawal of funding) orders of compliance. Similarly, commercial sponsors of pharmaceutical research regularly monitor research through paper reporting mechanisms (e.g., adverse event reports and regular reports of experimental results), on site visits and, similarly US federal authorities will on occasion audit research they fund. It is worth noting that the federal Tri-Council and other Canadian research sponsors do not use such measures.

Here is a brief overview of some of the monitoring arrangements in place for Canadian HRIHS (DR-1). Others are discussed in the appendix to this article.

On-going monitoring and oversight

1. **Financial**
    a. Research institution manages research funds
    b. Research sponsor / funder requires financial reports,

2. **Medical**
    a. National / local trial co-ordinators report re clinical trials
    b. Independent health care providers (if any) may report
    c. Sponsors (e.g., pharmaceutical companies, NCIC, FDA) require medical reporting to meet regulatory requirements

3. **Other subject relevant concerns** (non-medical harms, consent issues, third party effects)
    a. Dealt with on a reactive basis; no monitoring
    b. REB or its delegate – new TCPS

4. **Research quality**
    a. For clinical trials: national trial co-ordinators, sponsors (e.g., pharmaceutical company or NIH)
    b. For other research protocols
        i. If not NIH or similar body, no monitoring
        ii. Dealt with on a reactive basis
        iii. Fraud / plagiarism dealt with on a reactive basis

DR-1

The regulatory provisions for monitoring clinical trials are more extensive than for other types of health research. Hence, we provide a display for this area (DR-2):

Multi-site clinical trials

1. **Local trial coordinators**
    a. Meet every 6 months
    b. Feedback local adverse events to national level
    c. Monitor for adverse effects on health of subjects

2. **National trial group**
    a. Deals with randomization and other trial conduct issues
    b. Compiles adverse incidents and research results
    c. Decides on continuing, modifying or stopping study

3. **Ombudsman, office of research, or REB chair receives concerns or complaints from**
    a. Subjects (telephone number on consent form)
    b. Nurses, trial co-ordinators or researchers
    c. And refers these to
        i. Academic affairs (plagiarism)
        ii. Equity (harassment)
        iii. Department heads (academic issues)
        iv. Financial affairs

DR-2

As we have already noted, the ethical treatment of subjects has by and large not been explicitly and systematically addressed outside the research approval phase. This gives rise to a number of ethical governance concerns for the research phase of the process (DR-3):

Ethical governance issues

1. What processes are in place to make sure that subjects are heard during the research phase? Is the system proactive or simply reactive, i.e., requiring subjects to take the initiative to formulate and lodge complaints?

2. How, if at all, are researchers and those charged with the administration of RHIS educated about the likely concerns of research subjects in the types of research being conducted? Are the educational processes grounded in evidence or are they unsystematic and anecdotal?

3. Do monitoring processes, if any, provide effective and reliable quality assurance and quality improvement? In particular, is information gathered during the research process about ethical issues that may arise (e.g., unexpected third party effects, changes in competency, threats to privacy, shifts in the threshold of minimal risk)? Is that information analysed and used to improve future research performance?

DR-3

D. Research Completion

When research is completed, a number of things happen, e.g., reports are filed with sponsors, findings are presented at conferences and in publications and, patents are sought. We summarise these in the following table (RC-1).

Research Completion

1. Presentations: local, national and international
2. Abstract publication
3. Comments by colleagues
4. Submission for publication
    a. Blind review for scholarly / scientific merit
    b. Usually need evidence of REB approval of protocol
5. Publication
6. Implementation, e.g., clinical or professional practice, changes in Q.A. or Q.I.
7. Submission of product / device for approval
    a. Clinical trial evidence
    b. REB approval of protocol
    c. Approval of product/device for marketing

RC-1

As will be seen from Joly's discussion in Section D-2 of public health based research, there are cases in which initiatives that started out around ordinary health protection or the ordinary provision of health care can wind up with significant publishable research results. We group these in the following table (RC-2). In addition to public health interventions, this can happen when what at first appeared to be a routine clinical intervention turns up significant research results. Moreover, a distinction is customarily drawn between clinical research and clinical innovations. The former requires REB approval; the latter does not. So the provenance or labelling of a particular procedure as either "research" or "innovation" may mean that at one institution a procedure is treated as one while in a neighbouring institution it is treated as another. For example, many advances in reproductive technologies have never been subject any formalised ethical scrutiny since they were introduced as clinical innovations rather than clinical research.

Non-standard research

1. Arising from clinical practice especially from clinical innovations
   a. Recognition of research publication or research product potential
   b. If publication is sought, may seek retrospective REB approval based on paper record (e.g. chart reviews)
2. Public health (e.g., infectious disease)
   a. Government housed
   b. Public health act
3. Population health enquiry
   a. Government initiated call for proposal, e.g., cost-effectiveness of maternal serum triple screen)
   b. Researcher initiated, e.g., request for access to publicly held records
   c. Freedom of information and privacy legislation
   d. Sometimes also REB approval (especially in provinces where REB approval is legally required under freedom of information acts)

RC-2

A number of questions arise concerning ethical governance for this final stage of the research process (RC-3).

Ethical governance issues

In terms of the three questions – scholarly merit, overall benefit and human subjects protection:

1. How do sponsors, institutions, REBs, researchers and human subjects know if the completed research met reasonable expectations re: the ethical treatment of human subjects?
2. Does the research as predicted contribute to the advancement of knowledge? To the greater social good?
3. How do standard setters (cf. setting parameters) know if prescribed standards and processes are appropriate? Are there retrospective ethical analyses done of completed research projects, e.g., on a random basis? Are subjects ever debriefed?
4. Is / would this knowledge be used to improve performance?
5. Is there sufficient transparency and accountability to inspire and deserve the trust of all relevant stakeholders, especially human subjects and the general public?

RC-3

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APPENDIX ONE

CURRENT FORMS OF MONITORING

This is a brief overview of current monitoring practices for HRIHS in Canada. Issues regarding monitoring for clinical trials are discussed in the following appendix (Appendix Two) and Section B-2. We start with reports to REBs (Mon-1).

Reporting (to REBs)

1. Annual reports (some, but not all, REBs)
2. Notification of completion or end of study (some, but not all, REBs)
3. Adverse incident reports to sponsors and REBs
4. Protocol revisions
5. Mandated interim reports for higher risk research

Mon-1

Next there are fiscal monitoring and reporting regarding the use of research funds.

Institutional monitoring of research funds

1. Institution holds funds until REB approval
2. Institutional financial controls
    a. To avoid deficit situation
    b. To assure sponsor funds used for designated purposes
3. Institution reports to research sponsor on a regular basis and on completion of the project regarding the use of sponsor's funds for research.

Mon-2

As noted earlier, research sponsors play a role in monitoring (Mon-3):

Monitoring by sponsors

1. Who? Pharmaceutical companies and some foreign sponsors (e.g., FDA, NIH, NCIC)
2. How? Scheduled and sometimes unscheduled on-site visits, sometimes surprise visits, paper audits of researcher and REB records, required compliance plans
3. What? Accuracy of data, reporting issues, allegations of fraud, etc.
4. At stake, continued funding and potential legal liability

Mon-3

It is important to understand monitoring and other oversight taken by MRC, NSERC, and SSHRC. With the move towards a unified policy on research involving humans, the three Councils moved to have the National Council on Bioethics of Human Research (NCBHR) widen its mandate beyond health research to include other types of research involving humans. NCBHR had been created by MRC, Health Canada and the Royal College of Physicians and Surgeons to provide education in the area of biomedical research involving human subjects and to advise REBs who operated under the MRC Guidelines on Research Involving Human Subjects.[92] Two additional sponsors – NSERC and SSHRC – joined the original sponsors to create the National Council on the Ethics of Human Research (NCEHR). NCEHR's role is described in the following table (Mon-4).

NCEHR

1. Sponsored by MRC, NSERC, SSHRC, Royal College of Physician & Surgeons and Health Canada
2. Educational role re TCPS
3. Site visits voluntary and provides advice to institution
4. Advisory role in policy-making and accreditation; lacks the power to withhold research funds

Mon-4

NCEHR has a counterpart on the animal research side – the Canadian Council on Animal Care (CCAC). CCAC has a long history and is known internationally for its various guidelines on research involving animals. CCAC has oversight powers with respect to institutional committees for reviewing and approving research involving animals – Animal Care Committees (ACCs). These powers are much more extensive and, in our view, are much more

[92] MRC, *Guidelines on Research Involving Human Subjects* (Ottawa: Medical Research Council of Canada, 1987).

able to demonstrate important positive effects on the welfare of research animals than either NCEHR or its predecessor NCBHR in regard to the rights and interests of human subjects. CCAC is described in the following (Mon-5).

Governance for research involving animals

1. CCAC is funded by MRC and NSERC and some private sponsors (from industry).
2. Mandatory site visits
3. Institutions must show they are compliant with CCAC Guidelines for all research involving animals within the institution (or develop a plan acceptable to CCAC) to receive research funds from MRC and NSERC
4. CCAC sets, implements and enforces rules for research involving animals
5. Non-university agencies conducting research involving animals may for a modest fee be inspected by CCAC and if in compliance with CCAC rules be recognised as such. (In the near future, CCAC will institute a programme of granting Good Animal Practice (GAP) certificates.

Mon-5

Nevertheless, we would also note that in addition to NCEHR the Tri-Council group has other relevant initiatives with respect to research involving humans (Mon-6).

Other Tri-Council Efforts

1. Statement that research funding may be withheld if institution deemed by Councils to be in non-compliance
2. Required letters from research institutions assuring compliance with TCPS or providing a plan for compliance
3. Considering compliance monitoring

Mon-6

APPENDIX TWO

CLINICAL TRIALS

Many of the previous tables centred on HRIHS in the context of university and health research institutions. To close this portion of our overview, it is necessary to look at industry research, particularly at research that is in house. While some of this has been touched on earlier, we draw the material together here in the following tables that centre mainly on pharmaceutically based clinical trials (CT).[93]

Steps toward human research

Cell culture studies

1. Animals (sometimes subcontracted)
2. Safety studies for human exposures
3. Proceed to Phase I

Ind-1

Phase I

1. Required for drug approval
2. Pure Phase I non-therapeutic clinical trials on healthy subjects
    a. Paid to volunteer
    b. Sometimes on site or subcontracted
    c. Acute dosages toxicity / safety
3. Phase I/II Clinical Trials on sick patients,
    a. To test for toxicities and efficacy
    b. Also to improve survival or quality of life of subjects
    c. In hospital, e.g., for cancer – no treatment or failure of 2 attempts at treatment
    d. Independent access, e.g., AIDS patients
4. Ethics approval by in-house or private (for profit REB)

Ind-2

[93] Issues regarding new federal regulations for CTs are discussed in Section B-3.

Phase III

1. Required for drug approval
2. Test for efficacy / short-term toxicities
3. Clinical trials in hospitals
4. On-going monitoring by corporate sponsor or clinical trials subcontractor
5. Limited room for institutional REB to modify proposals

Ind-4

Phase IV

1. Post-marketing surveillance studies of long-term efficacy and toxicity of marketed drugs
2. Often in private offices of physicians

Ind-5

These give rise to a number of governance concerns.

Governance concerns

1. General concerns: sample sizes, data accuracy, stopping rules, inclusiveness, oversight for the broad range of ethical concerns
2. Phase I – independent oversight and monitoring for health, voluntariness, and appropriate compensation
3. Phase I/II – patient vulnerability and consent; harm issues
4. Phase III – monitoring for consent and harm
5. Phase IV – worries re marketing masked as research: researcher qualifications, lack of oversight by professional bodies, potential conflicts of interest on part of participating researchers

Ind-6

SECTION B-3

THE CURRENT CONTEXT OF HRIHS

Michael McDonald

We now turn to the context of HRIHS. We have divided contextual features into two broad categories. The first includes pervasive general factors shaping contemporary health research around the world. The second includes factors specific to the Canadian context of governance with respect to RIHS.

I. GLOBAL FEATURES SHAPING HRIHS

We see four major factors shaping contemporary health research:

- **Rapid scientific and technological innovation and advances**
- **Multiple disciplinary and interdisciplinary research modalities**
- **Commercialisation and privatization**
- **Globalisation and harmonisation**

While these are closely related factors that on the whole reinforce each other, the first two can be seen as factors internal to health research and the second two as larger external or, in the broad sense of the word, environmental factors. Genetic research provides a good example of the interplay of these factors.

While genetics had its origins in the late eighteenth century, it is only in the last few decades with Crick and Watson's discoveries that genetics has assumed its modern form. In the early 1970's with the discovery of restriction endonuleases, genetics took off as a major area of research with enormous intellectual, social and economic impacts. There are now major international and national programmes in genetic research, including the Human Genome

Project. There is extensive private sector research and development in genetics including, in directly, health-related areas (pharmaceutical research) and in areas that are potentially health affecting (plant and animal biotechnology). Research in genetics has been typically quite expensive, and its commercial impacts are substantial. As well, research in genetics has global dimensions with major research centres in many countries and (just as important) research on populations around the world, including particularly indigenous peoples. There have been substantial pressures for regulating genetic research both domestically and internationally. In turn, this has prompted multi-disciplinary research into various aspects of genetics – psychological and social impacts, ethical and legal aspects and, economic effects. Moreover the results of research for health, the economy, social well-being and even our very conceptions of ourselves as genetically determined beings are potentially extremely high.

While rapid scientific and technological innovation is particularly apparent in genetics, it is also significant in other areas. For example, computerisation has made possible the accumulation of large databases; these have revolutionized research methods in many areas, such as cancer research and public health. At the same time, these also raise questions about striking the right balance between the potential benefits of such research and concerns for privacy. As noted in the case of genetics, methodologies used in health research have broadened from those used primarily in the natural sciences to include those used in the social sciences and the humanities. In part, this has been prompted by a concern with health behaviours and outcomes (such as healthier life-styles). But it has also been encouraged by a concern with quality of life and ethical issues.

Rapid scientific advancement and new research methodologies have encouraged and been encouraged by commercialisation and globalisation. Thus, the rapid advances in genetic sequencing have created major opportunities for pharmaceutical industries that in turn have created new research opportunities; genetic advances have also reinforced the tendency toward the formation of large multi-national corporations in this sector. Commercialisation, we believe, has created an impetus toward the privatization of legal relationships, i.e., towards making human subject research a matter of private rather than of public law. Similarly, globalisation has created pressures for the harmonisation of various normative régimes, e.g., toward the international harmonisation for pharmaceutical testing.[94]

[94] This is reflected in the proposed changes in federal regulations for clinical trials Department of Health, "Regulations Amending the Food and Drug Regulations (1024 -- Clinical Trials*)" Canada Gazette Part 1* (22 January 2000) 227.

At the same time, globalisation and commercialisation are part of a larger social and political context that directly affects Canadian health research. For example, the rapid increase in private sector support for health research along with a relative decline in public sector support has changed institutional cultures in Canadian universities and medical research centres. In order to maintain positions supported on 'soft' dollars (as opposed to base budgets), Canadian research institutions have felt compelled to scramble for scarce research dollars. This in turn has created pressures on Research Ethics Boards and others involved in the research ethics governance process. In short, these four factors shape the contemporary context of Canadian health research in ways that profoundly affect governance relationships and their effectiveness.

Many of the significant changes that are occurring internationally are usefully summarised in the following chart from the US Office of the Inspector General's report, *Institutional Review Boards: A Time for Reform* (p. 5). Our main change for the Canadian context would be with the description of the first change mentioned – "Expansion of Managed Care" – which we would replace with "Pressures on Health Care Costs".

A CHANGING ENVIRONMENT FOR IRBS		
CHANGE	EXPLANATION	KEY IMPLICATIONS FOR IRBS
Expansion of Managed Care	Emphasis on cost control and competition. Squeeze on research support for academic health centers.	• Pressures to accommodate research sponsors who can provide research-related revenues for the parent institution. • Increased difficulty in obtaining staff and other resources. • More pressure on staff physicians to generate income with less time available for voluntary commitments to IRBs.
Increased Commercialization of Research	Heightened industry role in sponsoring research. Sponsor emphasis on rapid product development.	• Institutional and sponsor pressures for quick reviews. • Sponsor shopping for customer-focused IRBs. • Added complexity on issues involving liability, academic freedom and, patient disclosure.
Proliferation of Multi-Center Trials	Proliferation of trials spread across hundreds of sites, even across the world.	• Diminished influence of "local" review. • Flood of adverse-event reports to review. • Lack of access to significant information concerning the status of ongoing research.
New Types of Research	Advances in biomedical research in the areas of gene testing and gene consent and appropriate research. Therapy increased research on mental health issues	• Need for new, highly specialized areas of expertise. • Emergence of thorny ethical issues involving informed • Increased importance of having non-institutional board members

Increased Number of Proposals	Intensified efforts to obtain government funding and to develop new products.	• Significant increase in workloads. • Without sufficient increases in staff and/or efficiency, less time is available to review initial protocols and to conduct continuing reviews of approved research.
Rise of Patient Consumerism	Increased consumer demand for access to research.	• Presents major challenges in: Ensuring equitable recruitment of subjects. Ascertaining local attitudes and values. Maintaining distinctions between therapy and research.

II. CANADA-SPECIFIC FEATURES SHAPING RIHS

In addition to these four general factors, there are a number of more Canada-specific factors affecting the governance of RIHS. One of the most important of these is the recent introduction of the *Tri-Council Policy Statement* (TCPS) by the MRC, NSERC and SSHRC. A second is the formation of the Canadian Institutes for Health Research (CIHR). The third involves recently proposed changes in federal regulations for clinical trials.[95] Fourth is the impact of private funding on Canadian health research. As well, there are other factors that are discussed in the papers that follow this section – federal and provincial legislative moves in regard to privacy (e.g., Bill C-6) and freedom of information (which Dickens discusses in Section C-1) and some regulation by provincial health professions in regard to RIHS (which Kinsella discusses in Section D-3).

A. *The Tri-Council Policy Statement* (TCPS)

The TCPS was adopted in 1998 by the three Councils and applies to the conduct of all research carried on by research institutions administering funding provided by the Councils for research purposes. The Councils provide funding to researchers in particular research institutions on condition that *all* research involving human subjects is conducted in accord with the Tri-Council Policy Statement (TCPS) – not just the portion funded by the Councils. In turn, research institutions make following the TCPS a condition of employment for their researchers. In this respect, TCPS continues the arrangements represented in earlier Council policy where

[95] *Ibid.*

following SSHRC and/or MRC Guidelines for all RIHS was a condition for receiving Council funding.[96]

Where TCPS represents a major change from the former regime governing RIHS at Canadian universities and hospitals is in its creation of a unified set of prescriptions for all research involving humans to replace the previously separate reviews for behavioural research governed by SSHRC Guidelines and biomedical research governed by MRC Guidelines. To explain how the TCPS has changed the Canadian context for HRIHS specifically and RIHS generally, it is useful to briefly review the reasons for the creation of a unified policy statement and the process by which it was developed.

1. NSERC had no guidelines for human subjects' research even though it funded human subjects' research in experimental psychology and biomechanical engineering.
2. In 1993 the three Councils found common moral ground in developing a unified policy on research integrity.
3. Existing guidelines for RIHS were dated -- SSHRC's *Guidelines* were adopted in 1976 and MRC's dated from 1987. Whole new areas of research, especially in health science areas, had developed since the previous guidelines had been adopted, e.g., genetics and reproductive technologies.[97] As well, new research technologies and advances (e.g., genetic sequencing, new reproductive technologies, and even more pervasively computers and electronic databases) had major impacts in such morally sensitive areas as privacy and confidentiality.
4. Interdisciplinary research had come to the fore. Particularly in health research it came to be realised that health results were not simply a function of health technologies or even health care but were related to a large range of health determinants – economic, social and environmental. Having separate behavioural (SSHRC) and biomedical (MRC) guidelines seemed to run contrary to the idea of integrated interdisciplinary health research.
5. In any case, it was generally recognized that there are common moral values which govern all types of research involving humans, e.g., the values found in informed consent and the avoidance of unjustifiable harm.
6. In various areas of research, it was argued that current *Guidelines* were inadequate, in particular, for multi-site clinical trials, research involving human

[96] Prior to 1998, only two of the Councils had rules for the conduct of RIHS. The MRC had *Guidelines for Research Involving Human Subjects* (1977; revised in 1987), while the SSHRC had *Ethics Guidelines for Research Involving Human Subjects* (1979). NSERC funded researchers carrying out RIHS had their research approved by either a biomedical REB following MRC *Guidelines*, e.g., on biomedical devices, or SSHRC *Guidelines*, e.g., experimental psychology.

[97] See SSHRC, *Ethics Guidelines for Research with Human Subjects* (Ottawa: Social Sciences and Humanities Research Council of Canada, 1979). MRC, *Guidelines on Research Involving Human Subjects* (Ottawa: Medical Research Council of Canada, 1987).

> tissues, research involving women, research involving children and research involving collectivities. Some of the impetus for change in these areas came from researchers as well as ethicists and lawyers. But there had also been changes in international, professional and other norms. For example, the 1993 *CIOMS International Guidelines* gave significant recognition to ethical conduct with respect to research in developing countries and part of that recognition was the identification of researcher responsibilities with respect to research involving vulnerable collectivities.[98]

The net result was that in 1994 Presidents of MRC, NSERC and SSHRC formed the Tri-Council Working Group on Ethics with researchers from a number of areas sponsored by the Councils.[99] In 1996, the Tri-Council Working Group completed a draft *Code of Ethical Conduct for Research Involving Humans* and distributed it throughout the Canadian academic community for comment.[100] The Working Group received over 2,000 pages of comments from over 250 respondents – almost all the respondents were from the research community – individual researchers, disciplinary groups, university and hospital administrators, research ethics boards, university departments and research institutions as such. In light of those comments and further discussions, the Working Group produced a final version of the *Code* and submitted it to the Councils in May 1997.[101] At this point, the Tri-Council Working Group was disbanded and played no further part, collectively or individually in the production of the ensuing TCPS.

In late 1997 and early 1998, the Council consulted with various interest or stakeholder groups. As far as we know these consultations were again centred on the research community – researchers and research sponsors particularly – and did not include research participants or their potential advocates. For example, through the Social Sciences and Humanities Federation of Canada, SSHRC conducted extensive consultations with the social science and humanities associations that compose the Federation. There were consultations by MRC with deans of medical faculties and by NSERC with research administrators. As well the Councils used their own internal processes for consultation, e.g., the MRC Standing Committee on Ethics played a

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[98] Council for International Organisations of Medical Sciences Guidelines CIOMS, "International Ethical Guidelines for Biomedical Research Involving Human Subjects," World Health Organization (Geneva: CIOMS, 1993).

[99] Several members of the research team for this project were members of the Tri-Council Working Group – Jean Joly chaired the Working Group, Michael McDonald was deputy chair. Michael Asch, Bernard Dickens, Douglas Kinsella, and Barbara McGillivray were members of the Working Group.

[100] Tri-Council Working-Group, *Code of Conduct for Research Involving Humans* (Ottawa: Medical Research Council of Canada, 1996).

[101] Tri-Council Working-Group, *Code of Ethical Conduct for Research Involving Humans (Final)* (Ottawa: Tri-Council, 1997).

large role in MRC's deliberations. As well the text of the TCPS was given to the Department of Justice for review.

While many researchers viewed the *Code* favourably, some were quite resistant to particular provisions and its overall tone. In particular, there was a strong campaign organized by the Canadian Association of University Teachers around areas of the *Code* that were described as threats to academic freedom. The section on research involving collectivities came under particular fire. The concern expressed in the section on collectivities for vulnerable groups and the desire, where possible, to respectfully negotiate significant differences in moral understandings was seen by many critics as potentially inhibiting research on powerful institutions and public figures. CAUT urged instead that the only legitimate ethical concern for research in this area applied *sui generis* to Aboriginal groups.[102] This ultimately was the approach taken by the three Councils. However, on the recommendation of the Department of Justice, the section of the TCPS on research involving Aboriginal groups has been held in abeyance pending negotiations with indigenous peoples in Canada and abroad.

But there was also considerable controversy about the wisdom of a common approach to the ethics of RIHS on the part of the three Councils, particularly by social scientists in political science, psychology and history. At the extreme, there were suggestions that there should be no prior review of proposed research involving humans – that peer review alone would be a sufficient safeguard against ethical abuse. As well, some claimed that while medical researchers had good reason to be concerned with potential research harms to research subjects, this ought not to be a concern for social scientists and humanists. Some urged this position on the grounds that social science research could never harm research subjects whereas medical research was inherently risky.[103] Others critics argued that informed consent was a sufficient safeguard for research conducted by social scientists so that issues of harm and benefit could be ignored. The separate sets of guidelines for medical and non-medical

[102] CAUT's defence of a *sui generis* approach to research involving collectivities is out of step with *CIOMS Guidelines* which are designed to apply generally to populations in developing countries and not just indigenous groups. CIOMS, "International Ethical Guidelines for Biomedical Research Involving Human Subjects," World Health Organization (Geneva: CIOMS, 1993). Furthermore, from a moral perspective, there are two major concerns with whether special provisions for indigenous peoples can be justified. The first is that it seems anomalous not to extend concerns to similarly disadvantaged groups. The second is that *sui generis* provisions can be seen as stigmatizing and stereotyping indigenous peoples as uniquely collectivist, that is as being "peoples" unlike non-indigenous who are just plain people (morally significant only as individuals and not as members of groups).

[103] It is worth noting that these critics actually had much in common with the subset of medical researchers who count as significant only physiological and biological harms in that social, psychological and other harms are regarded as insignificant and generally unworthy of any concern.

researchers represented more than two different regulatory processes; they also symbolized two quite different research cultures around research involving humans – a biomedical culture and a non-biomedical/behavioural culture. [104]

Rather less public, but we think no less important, were concerns expressed by research institution administrators about the potential costs of meeting the provisions of the proposed *Code* and also with the difficulties of dealing with reluctant researchers particularly in the social sciences and the humanities. Serious concerns had been articulated about potential competitive disadvantages in attracting research funding if standards were raised especially if other research institutions did not simultaneously raise their standards. One university head ruefully agreed with the description that amongst research institutions there was a potential "race to the bottom."[105] This was joined with concerns about institutional autonomy and liability. As well some university research directors questioned the legitimacy of Councils imposing policy given the Council declining role in research funding.

The end result of these criticisms was that the three Councils dramatically revised the 1997 draft *Code*. The Councils have been criticized for a behind the doors revision process and a lack of public consultations – especially compared to the very open process used by the Working Group in revising the 1996 draft *Code.*[106] Members of the former Tri-Council Working Group have publicly and privately expressed concerns about the quality and coherence of the revisions made to the 1997 draft *Code*.[107] As well, those involved in research on collectivities have complained about a lack of guidance for research in their area.

Since the Councils adopted the TCPS in 1998, the Councils have asked affected research institutions to prepare a plan for complying with its provisions. By the end of 1999, research institutions had to indicate that they were in compliance with the TCPS or provide a plan for coming into compliance. As evidenced in the interviews, many institutions have had to

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[104] The formation of different sensibilities was a result of many more factors than common guidelines and procedures. There are different factors shaping the two communities. In the case of medical research, there is at the core a set of professional expectations – many biomedical researchers are members of self-governing professions. The idea of professional self-governance is not one that finds many adherents on the social sciences and humanities side where a more *laissez-faire* view prevails. Moreover while incidents of misconduct by medical researchers were widely reported, misconduct by non-medical researchers has been much less publicized. As a result, the first target of regulation in most countries has been medical research with other types of RIHS as a kind of after-thought.

[105] December 1997 conference on research ethics sponsored by the Canadians for Health Research.

[106] F. Baylis *et al.*, "Women and Health Research: From Theory, to Practice, to Policy" in A. Donchin & L. Purdy, eds., *Embodying Bioethics: Recent Feminist Advances* (Lanham: Rowman & Littlefield, 1999) 253..

implement important changes in processes and procedures, e.g., with respect to REB membership, number of REBs in institutions, processes for evaluating student conducted RIHS, and requirements for face to face meetings. The requirement for monitoring research has posed major problems.[108]

We have already noted the advisory and educational role played by NCEHR with respect to the TCPS. As well, there is a Tri-Council Committee working on various changes to the TCPS including achieving harmonisation with the GCP. Both MRC (and likely its successor CIHR) and SSHRC have committees concerned with the ethics of RIHS.

B. The Formation of the CIHR

While the creation of the TCPS has considerably changed the scene with respect to a substantial part of Canadian RIHS, the formation of the Canadian Institutes for Health Research (scheduled officially for April 2000) and various changes in Canadian health regulation, are also affecting the area especially in regard to health research involving human subjects.

CIHR is not only intended to replace the MRC but it is also supposed to bring about a new and enhanced role for the federal government in sponsoring health research. Part of the enhancement is in the form of increased funding for health research. But another part of the CIHR mission is to produce integrated health research that results in improved health for Canadians. One move is the development of partnerships with other Canadian health research sponsors, e.g., the Heart and Stroke Foundation of Canada and the Canadian Kidney Foundation. There is an emphasis on interdisciplinary research that bridges traditional biomedical sciences and non-biomedical disciplines, like economics, law, ethics and medical anthropology and sociology. SSHRC has been given a significant role in funding such research in the form of an express partnership with CIHR. In the legislation establishing the CIHR, ‘ethics’ is mentioned four times. There have been several proposals for the integration of ethical processes and just as importantly research in relevant areas of ethics into each of the health institutes being created for CIHR and for the CIHR governing process.[109]

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[107] McDonald and Dickens made this point at the 1998 meeting of the Canadian Bioethics Society.

[108] This requirement originated in the 1996 draft *Code.*

[109] See B. Knoppers, *Report of the Interim Governing Council Subcommittee on Ethics: "Working Paper The Ethics Mandate of the Canadian Institute for Health Research: Implementing a Transformative Vision* 1999, Interim Governing Council, Canadian Institute for Health Research,

C. Federal Regulatory Changes

Over the past several years, there have been relevant changes in federal regulation of health matters. Most relevant to our concerns have been the following. The first is changes to achieve international harmonisation with respect to pharmaceutical and medical device approvals. The second is very much related to the first. It has to do with increasing reliance on drug and device testing by industry and by university based researchers and much lessened reliance on direct testing by government agencies, e.g., with respect to food and drugs. There are a number of reasons for the devolution of responsibility from government to industry and universities. This can be seen as part of general downsizing on the part of governments in Canada and elsewhere particularly in regard to regulatory bodies. Part of the motivation for this move is to eliminate the duplication of efforts for testing the safety and efficacy of new products. This also has very much to do with enhancing Canada's competitiveness internationally. The most dramatic recent example of this is the forthcoming move by Health Canada (HC) to shorten approval times for some clinical trials.[110] For example, under the new rules a pharmaceutical company would apply to HC for a Phase I Clinical Trial (testing for toxicity) or a Phase I/II trial (testing for short-term efficacy with possibly very ill patients). Unless HC replies in the negative within two working days, the Phase I or I/II trial – the most acute types of CT trials – could be launched immediately.[111] One of the reasons for the proposed change in approval times is to make Canada competitive in attracting CTs from international companies. The Minister has suggested that on an annual basis this could bring nearly one hundred million dollars to Canada – a boon for Canadian researchers and research institutions in its own right and a major boost for Canada's position in drug research.[112]

<*http://fusion.klickit.com/lee/cihr/file/files/ethicsenglishfinal.PDF2000*>; *S. Sherwin et al., The Ethics Mandate of the Canadian Institutes for Health Research: Integrating Bioethics and Health Law in the CIHR 1999, Social Sciences and Humanities Research Council of Canada,* <*http://www.sshrc.ca/english/programinfo/sherwin.pdf2000*>; and J. Storch *et al.*, *An Institute for the Integration of Ethics, Law, Culture and Health" SSHRC Web Site* 1999, Social Sciences and Humanities Research Council of Canada, <*http://www.sshrc.ca/english/programinfo/storch.pdf2000*>. Knoppers chaired the IGC Subcommittee that authored one report and was a member of the team that prepared the Sherwin report. McDonald was a member of all three groups.

[110] See Department of Health, "Regulations Amending the Food and Drug Regulations (1024 -- Clinical Trials)" Canada Gazette Part 1 (22 January 2000) 227.

[111] We would predict that if the accelerated approval times for Phase I and I/II trials are well received default approval times for other phases will also be initiated.

[112] S*upra* note 110.

In some ways the accelerated time schedule and greatly increased responsibilities for REBs can be viewed negatively as potentially weakening mechanisms for research ethics review for Phase I and Phase I/II clinical trials. However, it may have a positive impact in terms of improving the quality of REB review. In the *Regulatory Impact Statement* accompanying the proposed changes, it is argued that:

> The proposal would provide federal recognition of the important service provided by REBs. It would improve consistency relating to the roles and responsibilities of these boards by providing a standard for generally accepted principles of GCP. It is hoped that this regulatory requirement will draw attention to the need for to have a formal accreditation system for the REBs. This will promote compliance with generally accepted principles of the GCP. The proposal requires that sponsors obtain their approval prior to conducting trials. This may facilitate new funding mechanisms for these Boards.[113]

Of course, it remains to be seen if consistency of decision-making, accreditation and greater support for REBs result. The new regulations certainly raise the stakes for the credibility of current REB approval processes and place significant strains on scarce resources.

D. Impact of Private Funding[114]

In the last twenty years Canadians as well as Americans and Europeans have witnessed major changes in the funding of research projects involving human persons. From an endeavor that was essentially financed by federal and, in some instances provincial governments, research funding is now an activity that is largely financed by for-profit corporations. This is especially true in biomedical research where the recent fiscal constraints had a major impact and led to an ever more present private sector financing.

Parallel to this expansion of private funding in biomedical research, the increasing cost of developing and licensing drugs by health authorities in various countries forced the pharmaceutical industry into cost-containment practices and hence standardization of research practices in different jurisdictions, so that a set of data obtained in one country could be applied in a different country for regulatory purposes. This has spurred the development of internationally accepted *Good Clinical Practice Guidelines* (GCP).[115] These are accepted

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[113] Department of Health, *supra* note 110.

[114] This section was authored by Jean Joly and modified by Michael McDonald.

[115] ICH, *Good Clinical Practice: Consolidated Guidelines, ICH Harmonised Tripartite Guideline* (Ottawa, Ontario: Minister of Health, 1997).

standards of research involving human subjects that are quite detailed and cover a wide range of requirements, from the collection of data to the composition of the REB and various ethical concerns.

These guidelines were developed by a few national governments (United States, Japan and the European Community countries) and the pharmaceutical industry and co-opted by almost all other countries afterwards (including Canada). [116] As mentioned earlier, for the drug industry, the principal motivating factor behind the development of these standards was economic.

Prior to the adoption of these guidelines, Canadian researchers relied heavily on the *Medical Research Council Guidelines* that were first published in the 1960s and updated each decade afterwards. As noted above the last revision made with MRC as the only stakeholder was in 1987, the 1997-99 revision being a joint enterprise of the three Canadian Councils. The guidelines that existed prior to the implementation of the current Canadian guidelines and the *Good Clinical Practice Guidelines* were vague and led to major problems when multi-centre Canadian trials were undertaken: rules adopted in one institution could be quite different from those adopted in a second institution across the street. This led to confusion and loss of information. Data derived from a given center by the pharmaceutical industry could sometimes not be used in their application for drug approval to Health Canada.

A consequence of the development of *Good Clinical Practice Guidelines* is that a researcher or an institution that would not follow them or have requirements that are different from these guidelines (either sub-standard or for whatever reason far above them) would most probably be cut from any private funding from the pharmaceutical industry, especially if the study is for regulatory purposes.

A serious risk of this harmonization of ethical standards across different countries is the imposition of requirements that may be culturally unacceptable or context insensitive. For example, there might be the loss of practices that are appropriate to local cultural circumstances, e.g., oral consent for subjects recruited from oral as opposed to written cultures but, that are deemed to be inferior to international standards for written consent.[117]

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[116] Canada had observer status during the development of these guidelines.

[117] It should be noted that the 1997 draft *Code* was especially sensitive to such issues.

E. Other Changes

There are then major economic forces driving this devolution, not just on the part of private sector industries but also on the part of Canadian research institutions. As well, there is considerable interest on the part of those seriously affected by major threats to health and their families for beneficial research. Those at risk desire research that significantly improves their health outcomes. Given the absence of attractive therapeutic alternatives, they may well want to participate in clinical trials and/or receive experimental therapies. In some cases, articulate interest groups with strong agendas have formed to lobby for research in areas affecting their health, e.g., people with AIDS or those with or at risk of hereditary forms of breast cancer. This has also complicated the picture we currently have of the ethics of research involving humans, so that it is no longer just a question of protecting research subjects from the potential harms of research (as would have been seen to be a principal task of research ethics processes in the 1970's and 1980's). It introduces then difficult and far-reaching questions about justice or fairness in research -- what types of research get funded, as well as who gets to participate in research trials and under what conditions. More generally, it raises the issue of whose health is deemed significant enough to get on the health research agenda.

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SECTION F

CONCLUSIONS AND RECOMMENDATIONS

Michael McDonald

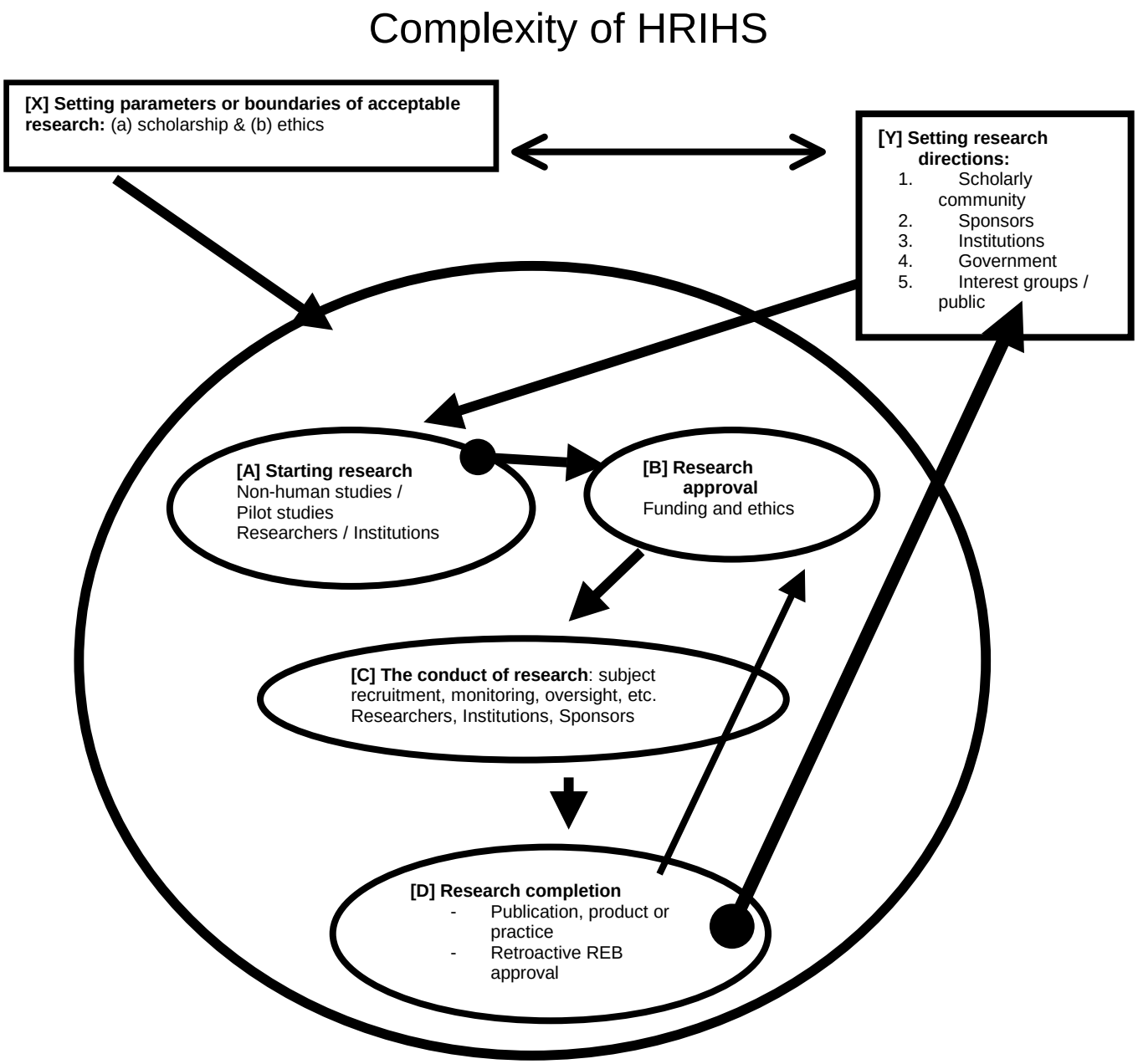
Our focus in this study has been on the ethical governance of health research involving human subjects (HRIHS). Our interest in "ethical governance" has been two-fold. First, we have been concerned with whether or not current governance for HRIHS promotes the ethical treatment of research subjects as individuals and as a class, including non-participants who are affected by research. Second, we wanted to know whether or not current governance meets the ethical responsibilities of those organisations and groups that play key roles in health research involving human subjects, e.g., legal authorities, research sponsors, research institutions, and researchers (collectively as members of research communities and individually as investigators on particular projects).

I. THE COMPLEXITY OF CANADIAN GOVERNANCE ARRANGEMENTS FOR HRIHS POSES MAJOR ETHICAL CHALLENGES

Our first observation is an obvious but important one. Canada's complex, decentralised, multi-sourced arrangements for governing HRIHS poses major ethical challenges in terms of consistency, transparency and accountability. Our study has identified three contributory factors: (1) the research process itself, (2) international factors, and (3) Canada-specific factors.

A. The Complexity of the Health Research Process

We identified four stages in the research process: (A) research initiation, (B) research approval, (C) the conduct of research, and (D) the completion of research. But these stages took place within socially constructed parameters concerning: (X) shared understandings about scholarly and ethical parameters for HRIHS, and (Y) The research agenda or directions determined by multiple parties. We represent this complex picture with the following diagram.



B. International Factors

This complex research process is very much affected by four pervasive international factors:

1. Rapid scientific and technological innovation and advances
2. Multiple disciplinary and interdisciplinary research modalities
3. Commercialization and privatization
4. Globalisation and harmonization

C. Canada-Specific Factors

In addition, the conduct and governance of Canadian HRIHS is very much affected by factors specific to the Canadian context including, particularly (a) the debate and changes arising from the creation of the *Tri-Council Policy Statement* (TCPS), (b) the complex constitutional division of legal powers insofar as it affects the multiple modalities relevant to HRIHS (e.g., health, research, privacy, the registration and regulation of medical products, etc.) and (c) other factors now affecting Canadian research (e.g., federal regulations for clinical trials and both federal and provincial regulations for the management of health records).

We have then (1) a complex system of research with multiple parties whose governance is affected by (2) international and (3) Canadian factors. However it is a very disjointed 'system' in several respects. There is, for example, no uniform set of standards that applies across the board to the protection of Canadian research subjects. Knoppers used the case of Quebec to show how provincial, Tri-Council and GCP standards can be in conflict. But the system is disjointed in many other ways. We do not have the sorts of unifying legal and regulatory authorities that countries like France and the U.S. have for most research involving humans. There are no uniformly accepted standards for accrediting REBs – a matter of considerable urgency given impending federal and (in some cases) provincial recognition of REBs in regulations and laws.[196] Such oversight as there is of REBs is piecemeal and haphazard at both

[196] The need for credible accreditation is recognised in the "Regulatory Impact Analysis Statement" for the proposed (January 2000) changes in federal regulations of clinical trials (p. 239) Department of Health, "Regulations Amending the Food and Drug Regulations (1024 -- Clinical Trials)" Canada Gazette Part 1 (22 January 2000)

local and national levels. With respect to public health research and research conducted by independent physicians, Joly and Kinsella have respectively shown major gaps in oversight and accountability. Burgess and Brunger have pointed out the much debated but seriously under-researched issues with respect to research involving collectivities.

II. THE "NARROWING" OF CONCERNS FOR ETHICS IN HRIHS

A. The Broad Picture

The broad picture of Canadian governance for HRIHS is a multi-staged and progressive narrowing or funnelling of concerns for ethics. In Section A-1, we claimed that with respect to ethical conduct of HRIHS there were 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.[197]

These objectives enjoy broad social endorsement and are represented in the numerous international, national and professional codes and 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. We see the situation as follows:

227, which refers inter alia to Auditor-General, *Report of the Auditor General of Canada* (Ottawa: Auditor General of Canada, 1999).

[197] In Section A-I, we suggested that the maintenance and / or the restoration of "warranted trust" is a crucial criterion for good governance in this area. By "warranted trust", we mean the opposite of "unwarranted trust".

1. REBs are unduly focussed on the review of consent forms as opposed to consent as a living process. The focus is understandable since the forms are tangible and immediate to the REB in the approval process. Moreover, this is what researchers, the research institution, and sponsors expect of REBs.

2. On the whole, REBs overemphasize consent and pay insufficient attention to potential benefits and harms for research subjects. In practice, there is considerable uncertainty and disagreement about what thresholds to set for unacceptable levels of risk to subjects. In part, this is due to time and resource pressures on REBs and also to failures in guidelines (in particular the TCPS) for offering plausible principles and guidance in applying those principles. More importantly, there is a paucity of independent, research-based evidence about the effects of research on subjects.

3. For researchers "ethics" has become in practice a matter of successfully navigating the ethics approval stage of research. In the minds of many researchers and often of REB members, the main business of the REB is to efficiently and rapidly process research protocols that may or may not bear much resemblance to the actual conduct and results of the research. However, the research approval stage is only one part of the research process. The research approved by sponsors and REBs may ultimately bear little resemblance to the actual conduct of research and its results. For this and a variety of other reasons, it is clearly imprudent to rely on a single-shot, front-end review of research protocols by REBs for ensuring the ethics of HRIHS particularly and research involving human subjects (RIHS) generally.

4. In terms of governance structures and the institutional resources devoted to them, research institutions also view "ethics" as a matter of efficiently processing applications for REB approval. REBs are supported to the extent that allows efficient and cost-effective processing of applications. Most REBs are generally pressed for time and have scant opportunities to reflect on larger issues and to both monitor and assess in meaningful ways the results of their work. Few institutions devote any resources to the education of REB members, let alone the ethical education of researchers generally.

5. Standard setters reinforce this funnelling. The operational agenda of domestic standard-setters has been mainly around REB performance particularly in the ethics approval stage. But none of those charged with responsibilities for governance – be they a standard-setter, research administrator or REB member – knows or really tries to find out whether REB ethics approval has anything much to do with whether subjects are treated well or badly in particular research projects.

For the research institutions, research sponsors, standard setters and the various communities of researchers, the scholarly quality of research has been the major preoccupation; by comparison the ethical quality of RIHS is given scant and unsystematic attention. This is reflected in both the formal and informal processes for research education and evaluation. While generally[198] there are in place very elaborate structures of peer review and regulatory mechanisms for assessing the quality of research and of researchers – all the way from the

[198] As Kinsella has noted with respect to professional oversight, there are also gaps in current governance arrangements.

training and accreditation of researchers to grant reviews and the publication of results – there is little or no attention devoted to assessing the ethical preparedness of researchers. Almost nothing is done in the way of ethics education for researchers and REB members. Moreover, in important areas of human subjects research (e.g., research involving collectivities), little serious scholarly discussion has been devoted to the complex ethical issues such research raises. While research skills are carefully nurtured, honed, and monitored over the full life of research projects and of research careers, ethical skills receive far less attention. In short while scholarship, especially leading edge research scholarship, is seen to require a substantial and continuing investment by all parties concerned, ethics is not seen as requiring a similar investment of time, energy, insight, and resources. Operationally then, all the major parties seem to operating on the assumption that researchers are ethical by nature rather than by nurture or training.

Results. The underlying moral equations seem to be:

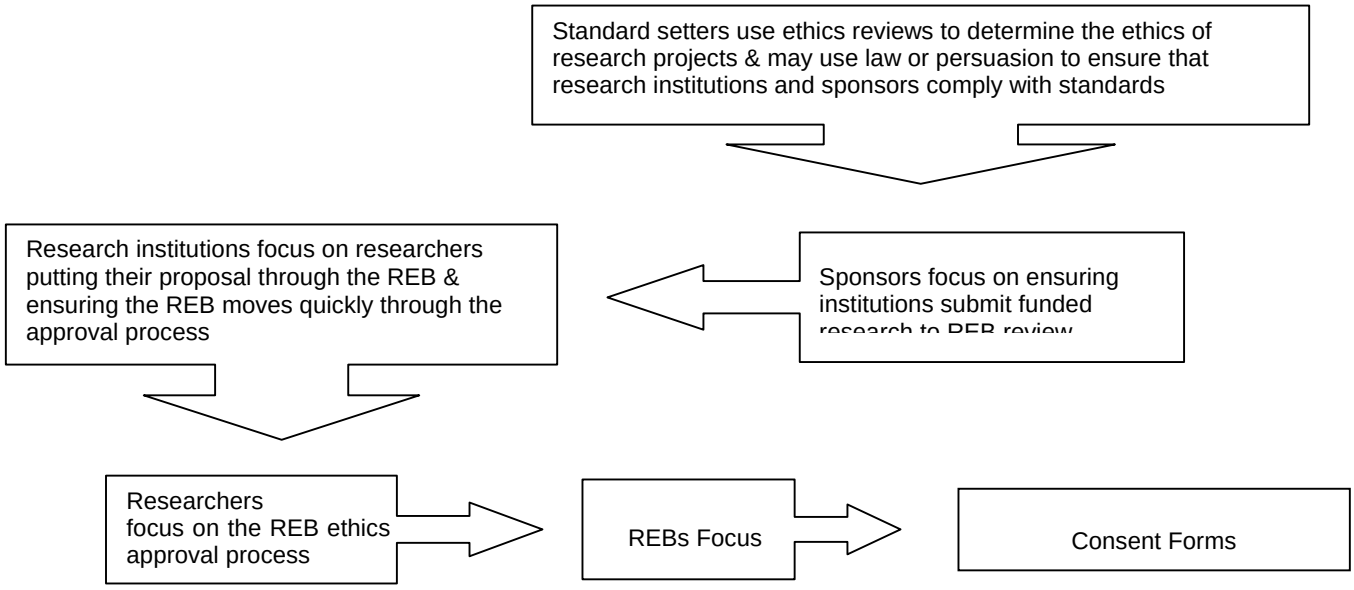
(a) [The ethics of RIHS = REB approval];

(b) [REB approval = Processing research applications]; and

(c) [Processing research applications = Modifying and approving consent forms].

This tunnelling and funnelling can be represented graphically in the following diagram:

Narrowing of concerns – ethical tunnel vision



In short, ethics is funnelled into a bureaucratic process, and the process itself is reduced to a bare minimum. That bare minimum consists of the tangible parts – consent forms and other items, like adverse incident reports. Harms are reduced to simple measures of pain, morbidity and mortality. An important general result of this funnelling and narrowing down of ethical concerns is that important issues are missed at all levels and at all stages. For example, the focus on consent forms tends to distract attention from the realities of consent – that for example, many subjects neither heed nor even read consent forms. It ignores the extent to which subjects make their decisions on the basis of trust.[199] More generally in terms of governance processes and structures designed to promote ethical RIHS, the REB is seen as the focal institutional tool and in turn its role is defined in terms of front-end research protocol approval. This ignores other possible tools or structures for promoting ethical research. It also ties too much of ethics in research to a particular stage – a very preliminary one at that – taken in isolation from the rest of the research process. The big picture is missed – concerning the larger cultural environment of research.

To generalise, what is missing in current governance arrangements are the following:

What is Missing

1. Consent forms and even consent are not enough.
2. There is more to ethical governance than the REB and the ethics approval process.
3. A major result is inattention to quality assurance and quality improvement.
4. An 'ethics culture' requires cultivation.

B. Corrective Tendencies

However, this is a big picture painted with a broad brush. There is some evidence of contrary indications. The concern for monitoring expressed in the TCPS and the proposed new regulations for clinical trials represents an important corrective tendency.[200] The recognition given to REBs in proposed federal regulatory changes for clinical trials is likely to lead to a

[199] See Part III of OIG Office of the Inspector-General, *Institutional Review Boards: A Time for Reform* (Department of Health and Human Services (U.S.), June 1998), and N.E. Kass *et al.*, "Trust: The Fragile Foundation of Contemporary Biomedical Research" (1996) 26/5 Hastings Center Report 25.

[200] See Department of Health, *supra* note 196.

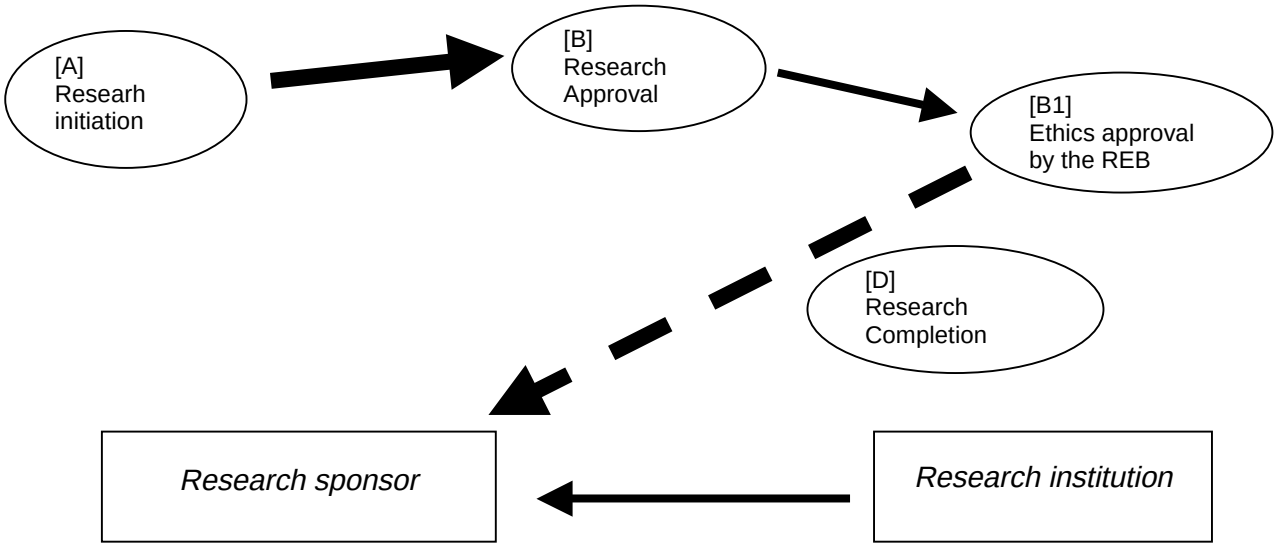
process of REB accreditation, which should cover both regular and private sector REBs. Depending on how monitoring is done, these regulatory changes increase the chances for more transparent processes and more effective REBs.[201] As indicated in Beagan's interviews, two institutions have experimented with monitoring including random audits. At least some institutions have conducted research ethics workshops or, even more impressively, have integrated research ethics into the academic curriculum for new researchers. At the national level, NCEHR is working on gathering resources and conducting workshops for ethics education for REB members. We are also very much impressed with the calibre of scholarly, ethics and legal expertise represented on many REBs. And at a general level, Canadian scholars are prominent internationally in research regarding legal and ethical aspects of human subjects research.

III. MISSING LINKS: EVIDENCE, EFFECTIVENESS AND LEARNING

In B-2, we said that there are four stages in the research process. When we consider governance of HRIHS with respect to the ethical treatment of human subjects, we ask how the stages are connected in terms of information flow and accountability.

[201] With respect to the new clinical trials regulations, there are important questions still to be answered: "Who monitors what for whom?" "How is the monitoring done?" and "How are monitors accredited?"

Ethics information / accountability flow



What is interesting in the diagram is how few and anaemic are the reporting relationships. In other words, what is important in the diagram is what is not there. Missing are linkages that are essential to good governance. The linkages we mean are those that allow organisations to learn from their successes and failures and over time improve their performance.[202] What is needed are "**virtuous learning loops**"– that is learning loops that lead to improved ethical performance. Or in more familiar terms, what is missing are the information gathering, learning and accountability processes necessary for quality assurance (QA) and quality improvement (QI).

Currently, REBs have little knowledge of what actually happens in research after protocols have been approved.[203] Institutions and sponsors have a far better idea of what happens to research funds than what happens to research subjects. Almost without exception, research offices are reactive rather than proactive with regard to the concerns and interests of

[202] Of course, having such linkages is meaningless without also having standards of performance against which one gauges actual performance, which in turn allows organisations to adjust, refine and revise not just performance but the standards of performance. As we point out below, developing appropriate standards of performance requires research.

[203] The US OIG Report *A Time for Reform* recommends several changes in reporting relations to better inform IRBs about "feedback on developments concerning multi-site trials", reports of actions taken by the FDA against investigators, and to "require sponsors and investigators to notify IRBs of prior reviews". See recommendation 2. Office of the Inspector-General, *supra* note 199.

research subjects.[204] Many sponsors require reports about publications, patents and other products of research but do little to find out what happens to subjects beyond demanding assurance that research is REB approved. But it is fair to ask sponsors (and research institutions) how they know if (i) REBs are doing their jobs well and beyond that if (ii) researchers and other agents in the research process are playing their appropriate parts?

For both quality assurance and quality improvement, an important baseline of information is missing because of the lack of high quality research on the multiple ways in which subjects are affected for good or ill by research.[205] Good qualitative studies of how subjects are affected in different types of research could help fill this gap. Such research could lead to the development of reliable indicators of effectiveness and also help to identify many of the multiple variables that determine whether a subject's experience with research is good, bad or indifferent.[206] But such research won't be done unless sponsors are interested enough in the well being of the subjects whose participation is essential for research progress in health and other types of research.[207]

A. Who Needs the Information for QA and QI?

To start with, REBs could use reliable information to improve their own performance over time. For example in evaluating a research protocol, an REB will explicitly or implicitly make an assessment of the project's risks and benefits. It then seems reasonable to ask if the REB's prediction was on target or not. Research institutions should be in a position to determine how good its REBs are at forecasting risks and requiring effective mitigating strategies. In turn, research sponsors should be concerned about how well the research institutions they support deal with issues of risk to research subjects. Here, a basic question would be to ask whether the institution has the virtuous learning loops necessary to improve its performance. A research

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[204] Whether offices of research are the appropriate place to take such proactive steps is a matter we discuss below.

[205] Important exceptions to this are the studies done for the Presidential Commission on Human Radiation Experiments on contemporary research practices, particularly the subject interview study in Part III of President's Advisory Committee on Human Radiation Experiments, *The Human Radiation Experiments: Final Report of the President's Advisory Committee* (New York: Oxford University Press, 1996).

[206] A weakness in the recommendation of the US OIG Report *A Time for Reform's* proposal that IRBs conduct be evaluated on the basis of outcomes including those that reflect the "perspective of and experiences of [subjects of] research as well as researchers" is that subjective measures of participant satisfaction are not sufficient measures of the performance of REBs/IRBs without the development of clear baselines through validated research. Office of the Inspector-General, *supra* note 199 at 12.

[207] See section V below on innovative research.

institution should be concerned with how its researchers deal with human subjects.[208] Beyond this, researchers individually and collectively should be interested in the effects of their research on research subjects and on the population of which the subjects are a "sample". Individually, a given researcher should want reliable comparative information on how her treatment of research subjects compares to other researchers working in similar areas. Collectively, communities of scholars should discuss general issues of risk in their areas of research, share mitigating strategies, and develop common norms around standards for good human subjects research in their areas that can be used for education and quality improvement. Social barriers to recruitment and representativeness of research samples might be addressed by ethical discussions, thereby improving the quality of research and its "public" relevance.

Standard setters, be they in industry or the public sector – or provincial, national, or international – ought to be intensely concerned about the effects of the research they sponsor on research subjects and in particular for ensuring that appropriate and effective standards are in place. In a broad sense, such information is vital to the public legitimacy of the conduct they regulate. To ask for this information and to act upon it would seem a basic and essential part of governance for standard setters. A standard setter ought also to try to discover if the standards and processes they adopt are appropriate, realistic, and effective.

To sum up, we list some of the key missing links:

Missing Links

1. Good governance requires virtuous learning loops so all the actors can learn from their successes and failures.
2. Virtuous learning loops should be based on evidence-based standards.
3. Thus, there is an urgent need for research on what happens to human subjects in research.
4. Such research requires resources from sponsors and research institutions; it also requires a commitment to use the research results in improving governance.
5. Failure to establish evidence-based learning loops represents a serious failure in governance for which research institutions, sponsors and standard setters should be held accountable.

[208] In The US OIG Report *A Time for Reform,* the FDA asks a number of pertinent questions, e.g., "How do we know if protocols that should be submitted for review are not submitted? Or if approved protocols stray in ways that are not identified in paperwork submitted to the IRB?" *Ibid.* at 23.

IV. MISSING SUBJECTS

We have argued that our current governance processes funnel ethics into the REB approval process and that the approval process is all too focussed on consent forms. In the research process, the only active role played by human subjects is as signatories on consent forms and potentially as complainants. Typically research subjects have no role in the governance of HRIHS. Others, usually research sponsors in concert with the research community and research institutions, design the policies that govern RIHS. While there are supposed to be "lay" or "community" representatives on many REBs, there is no requirement that lay representatives be knowledgeable about research subjects, let alone have been involved in research as subjects or as parts of groups that are often studied.[209]

We have already noted many gaps in accountability **for** the use of human subjects in research. What is less obvious are the many gaps in accountability **to** research subjects. We see major differences in principle and practice between a system in which the stress is on accountability **for** the treatment of certain people and one that adds a significant degree of accountability **to** those people. We argue in favour of a system of governance for HRIHS that has much greater accountability **to** research subjects on several grounds:

1. As a matter of moral respect
2. As a potential source of wisdom
3. As a basis for public trust
4. As a means for achieving greater balance in the system of governance.[210]

We see two missing "accountabilities **to**" subjects. First, our current system for dealing with actual and potential concerns of subjects is entirely too passive and reactive. Simply listing on a consent form the name of a contact person in the research office does not demonstrate appropriate zeal for the welfare of research subjects. It assumes that subjects will complain if they feel they have problems. But that may be a mistaken assumption. Politeness, timidity,

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[209] We depart here from U.S. recommendations that contemplate the use of outside academics, e.g., scientists from outside areas being reviewed by the REB, as lay members (cf. *Ibid* at 18).

[210] Cf. *Ibid* at 17. Recommendation 4a. "Individuals not associated with the institution or with the research enterprise can provide a valuable counterbalance to pressures that threaten IRB independence. But to do so, it is important that they be well-trained, but also that there be enough of them on a board so that their voices are more likely to be heard and their sense of belonging more likely to be enhanced." It is noteworthy that this recommendation is described as meeting a 1997 commitment made by the U.S. President regarding the infamous Tuskegee syphilis experiments.

ignorance of the rules, cultural traditions, fear of authority figures, simply misplacing a copy of the consent form, or even fear of retaliation or withdrawal of regular health services are only some of the reasons why subjects may not take the initiative. Given this, would it not, for example, be appropriate to have skilled interviewers occasionally ask sample research subjects about their research experiences and then use that information to deal with specific problems and to improve performance generally? It is essential then that research institutions, REBs, NCEHR, research sponsors and researchers seek the opinions of human subjects and where appropriate act upon them.

The second missing "accountability **to**" subjects is in terms of representative participation in governance. At the moment we have a system of governance that is, so to speak, almost completely producer-driven. A more consumer-driven model has much to recommend it. It would be a smarter and more robust system in terms of maintaining and enhancing public trust. Moreover, encouraging representative research subjects to participate in the administration and design of standards and processes for governing research involving humans would (if properly managed and sincerely conducted) be a win-win situation for both the research community and research subjects.[211]

V. INVOLVEMENT, INDEPENDENCE AND INNOVATION

To address many of the issues of accountability and effectiveness of governance, we see the need for "three I's" -- a mixture of (1) greater **involvement** on the part of major actors; (2) more **independence** in specific areas for ethical oversight, monitoring and standard-setting; and (3) much more **innovation** in terms of careful experimentation with alternative forms of governance and more research on the effects of research on human subjects.

[211] We recognise that the selection of 'representative' community members for participation in any form of governance is likely to raise a number of generic issues that are not specific to HRIHS. For example, there could be capture of a public process by special interest groups or manipulation and co-option by those with the power to appoint.

A. Greater Involvement

The first "I" is involvement. Our governance system for HRIHS needs much more involvement on the part of major actors, e.g., research subjects who are now largely treated as passive participants in the research and its governance. We have also said sponsors, institutions and researchers should take greater ownership of the larger responsibilities for ethical research. The ethics of research involving humans is much more than REB approval and signed consent forms. But whose involvement is needed where? We would suggest attention to the following areas.

1. REBs

REBs must have adequate resources to do their jobs – before, during and after the ethics approval stage. This includes support for:

- Secretarial and other office services
- Time-release or other in-kind compensation for researchers, ethicists, lawyers who serve on public sector REBs
- Reimbursement of the expenses of community members and where necessary reasonable remuneration, e.g., to allow economically disadvantaged individuals to serve as community members
- Regular educational events for REB members, e.g., attendance at research ethics conferences, annual retreats, visiting speakers, orientation for new members
- Resources to allow REBs to conduct workshops for researchers on research ethics
- Support for one or more bioethicists as part of a professional support staff for high-volume REBs, especially those that deal with higher risk research.

Adequate support for REBs involves providing back-up and support services at appropriate levels. In a report on Quebec REBs, Parizeau offers a number of useful suggestions about support staff.[212] Parizeau also suggests remuneration as well as covering the costs of community members. Institutions should provide appropriate time-release from other responsibilities or other types of in-kind compensation for academics and health professionals who serve on REBs as well as appropriate career recognition for such service to the research

[212] See M.-H. Parizeau, *Rapport d'enquête concernant des comités "ethique cliniques et comités de la recherché au Québec* (Québec: Ministère de la Santé et des Services sociaux, September 1998).

community. We think that a strong case can be made that high volume REBs be supported by a professional staff with one or more full-time bioethicists on it. This is especially important given the moral complexities posed by new forms of health research – e.g., genetics and new reproductive technologies – and the significant regulatory changes taking place with respect to clinical trials. For these complex and controversial areas, it may be advisable to consider shared resources in the form of professional support and specialised REBs that could act on a regional or national basis.

How should this be paid for? In some cases, this should be seen as a recoverable cost of research, e.g., for privately sponsored clinical trials. But here efforts must be made to protect REBs from becoming dependent on revenue from reviews. In other cases, research institutions need to reach an understanding with various research sponsors about the costs and support of REBs. In return research sponsors should expect that protocol approvals and monitoring issues will be addressed fairly and efficiently by an appropriately trained, duly accredited REB, supported by a suitably trained and professionally accredited staff where the volume and value of research warrants.

2. Virtuous Learning Loops

We have pointed out that there is a lack of the virtuous learning loops that would ground quality assurance and quality improvement for ethical RIHS. Virtuous learning loops are needed at two levels. The first is **within** particular institutions that are involved in health research and its governance, especially for research institutions and research sponsors. For example, research institutions like universities and health centres should carefully assess their own research activities for areas in which there are significant gaps in knowledge about what happens to research subjects. The education and training of researchers on relevant issues in research ethics should be a high priority. We would stress however the importance of making such an educational effort intellectually credible. This is something that researchers demand in their own work; no less should be expected for providing research ethics education with a sound basis in research ethics scholarship.

The second level is **amongst** the many institutions that interact in the research process. We see the need for better communication between, for example, research institutions and sponsors about appropriate accountabilities in HRIHS. Accountabilities go well beyond the REB ethics approval process and should include monitoring, quality assurance and quality improvement. Thus, boards of not-for-profit health research sponsors should be determining

how they could best reassure their stakeholders (donors, public supporters, professional staff, etc.) that the research they sponsor is being conducted ethically. But this requires dialogue with researchers and research institutions about the kinds of accountability that would be appropriate for this task – illuminating, effective and not overly bureaucratic. To initiate second level, inter-institutional initiatives, a number of bodies need to work together. For example, in the case of health research involving humans, this would include organizations such as CIHR, private sector research sponsors, NCEHR, health charities, Deans of Medicine and other health related faculties, and related academic groups like the Canadian Bioethics Society to name but a few. A series of stakeholder meetings would also be an effective means of creating an inclusive dialogue.

3. Involving Research Subjects

There has been little involvement of research subjects in the processes and policies for the governance of HRIHS. This contrasts markedly with the significant and beneficial role that animal welfare advocates play in the governance of research involving animals.[213] We realise of course that there is not a human equivalent of the animal welfare movement in Canada. But we do think that people who have had experience as research subjects, especially in higher risk areas of health research (e.g., cancer therapy trials) would likely bring important new perspectives to the governance of this area, e.g., as members of REBs, NCEHR, ethics secretariats for research sponsors, ethics advisory groups for directors of research. Representatives should be sought from groups whose members are frequently studied in health research involving humans, e.g., from the communities of those living with AIDS, cancer survivors, ethnocultural groups, and disability groups.

4. Creating a Research Ethics Culture

This is one of the most important of our recommendations but one of the hardest to implement. It is an area that readily invites window-dressing in the form of superficial efforts and

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[213] In a recent study (released in March 2000) of the governance role of NCEHR, the authors argue that CCAC enjoys the "credibility and trust" of "the broad research community". Centre on Governance, University of Ottawa, *Governance of the Ethical Process for Research Involving Humans* (Ottawa: Centre on Governance, University of Ottawa, March 15, 2000) at 36. This is contrasted with the lack of support in the social sciences and humanities research community for the TCPS (*Ibid.*). The authors however do not comment on whether the research subject communities (animal and human subjects) and their advocates find the policies and processes credible and trustworthy. Our suggestion is that the prominent role played by representatives of the humane movement on CCAC contributes not only to CCAC's credibility with animal welfare advocates, but also with the research community generally. This is in part because animal welfare and animal rights advocates have motivated the animal research community to seek effective policies.

ineffective delegation in the form of asking others to take the first steps. Yet we think that it is only through continuous and concerted activities of research communities, research institutions, research sponsors, and regulators that research ethics will become a central part of the culture of research. We think research sponsors – particularly public sector sponsors of research and the pharmaceutical industry – should be encouraging innovative teaching and research on significant current ethical issues in health research involving human subjects. Academic leaders should play a major role in putting ethics on their particular research community's agenda. Centres for bioethics and health law are important resources that could be utilised to much greater advantage by research institutions.

Ethics education and mentorship should be central parts of the process by which new researchers are educated and socialised. Ethics should be as central to the educational curriculum as research methodologies.[214] Indeed, it is by critically reflecting on methodologies and their uses in practice that offers some of the best insights into major ethical challenges in research. However, this is not something that can be imposed on researchers. Rather it is a matter of encouraging and supporting credible researchers who are willing to take the initiative in their own disciplines. Here again we think that what will be needed is support for partnerships between, for example, bioethicists and anaesthesiologists, in designing appropriate educational materials.

B. Independence and Trust

The second "I" is independence. Counter-balancing our recommendation for greater involvement in HRIHS by all parties is our recommendation for greater *independence* in key areas where it is essential to avoid conflict of interest or its appearance. We have pointed out that those with vested interests in its outcomes – researchers, research institutions, and research sponsors – dominate the research process. While there is nothing illegitimate about these interests *per se* (in fact a strong interest in generating valuable knowledge through research is a laudable interest), current governance arrangements are such that the process appears or may actually be biased in favour of research interests. It is not, we think, enough for researchers, research institutions and research sponsors to ask research subjects and the general public to trust blindly that all is well.

[214] CCAC is currently developing a model curriculum that can be used in whole or part by research institutions for the education of those conducting research involving animals.

1. The Case for a "Trust but Verify" Approach

In this respect, we agree with the U.S. OIG recommendation for "insulating IRBs from conflicts that can compromise their mission in protecting human subjects".[215] The U.S. Report states:

> Two long-time analysts of IRBs have described IRB regulations as "a permeable shield with no strong framework to ensure that the subjects' interests take precedence over institutional ones." They added that in balancing risks and benefits, an IRB "that consistently makes the calculus in favour of research will hardly ever be identified." While many Federal and IRB officials are likely to object to this assessment, the minimal information they have on the effectiveness of IRBs makes it difficult for them to rebut it. Even more troubling, in an environment where IRBs are expected to be responsive to the financial pressures facing their parent institutions and/or sponsors, some IRBs are finding it difficult to maintain sufficient focus on their core mission … (p. 17)[216]

The authors of the U.S. report just cited go on to say that:

> We suggest that an IRB with sufficient independence is one that is not under any institutional or ownership pressure whatsoever to approve protocols or related documents; bases its reviews on the merits of a proposal and attendant risk/benefit ratio, without regard for business concerns; does not report directly to the part of the institution responsible for bringing in research funds; is not compensated based on the outcome of a review; and has recourse should it be subject to any pressure.[217]

In short, the American recommendation is for a "'trust but verify' thrust".[218]

To be frank, we see the pressures on Canadian REBs as potentially much greater in Canada than the U.S. In Canada we lack the strong counterbalance provided in the U.S. by independent federal governance of research ethics approval and by the significant level of research support provided by NIH and other U.S. agencies. Moreover, American institutions of higher learning – especially the most highly productive research institutions – enjoy much greater public and private support than do their Canadian counterparts.[219] This makes Canadian institutions much more vulnerable to the need to compete for scarce research funding.

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[215] Office of the Inspector-General, *supra* note 199 at 17.

[216] *Ibid.*

[217] *Op cit*, 287.

[218] *Op cit.* at 290. By contrast, the Commission reviewing Australian ethics committees reached the opposite conclusion: "The Review Committee has no persuasive evidence of unsatisfactory or poor conduct in the current operation of IECs to justify the introduction of more stringent inspection (for example, external independent audits) of IECs." Review of the Role and Functioning of Institutional Ethics Committees IECS, *Report of the Review of the Role and Functioning of Institutional Ethics Committees* (Canberra, Australia: Australian government, March 1996). We comment below that governance including inspection is a positive responsibility and not simply a negative one.

[219] Even so, Americans are concerned about the independence of their universities from corporate interests. Cf. A. Press & J. Washburn, "The Kept University" The Atlantic Monthly (March 2000) 39.

2. Independent REBs

If we are right in thinking the risks for compromising the independence of ethics review and monitoring are substantially higher in Canada than in the U.S., Canadian research institutions, sponsors, federal and provincial governments, and researchers need to take greater steps than their U.S. counterparts to insulate REBs and parallel bodies (e.g., data safety monitoring boards) from pressures that would compromise their independence. It is crucial we think – both for substantive reasons and for the sake of appearances – that REBs not report to or be appointed by offices of research. In commenting about the U.S. model of ethics review by local IRBs, Edgar and Rothman ask, "Does it make sense to give the leadership of an institution, which by its very nature cannot survive without funds and fame brought in by clinical research, the responsibility of appointing the membership of a monitoring committee?"[220]

This is not to say that REBs should work independently of research offices. Clearly REBs in universities and hospitals should work cooperatively with offices of research in regard to the registration of research protocols, the management of records, and the like. Research offices may well be better suited to handle monitoring functions than REBs. But the current widespread reporting relationship of REBs to university and hospital offices of research sends the wrong message to research subjects and the research community and enhances the possibility of significant conflicts of interest, especially when the institution has a major stake in research being approved by the REB (e.g., when the institution has an equity position in a company's whose research is being reviewed or with joint employment responsibilities).

REB independence would be strengthened by clearer rules for membership on REBs. Edgar and Rothman make the following useful suggestion:

> IRBs processing a substantial number of protocols should, however, include experts drawn from scientific groups outside the institution. Moreover, there should be more focus on the appointment and renewal process. We should also seek to quasi-professionalise the role of outside members, linking them to groups that could come together to study common issues, so that there might be greater uniformity given to concepts like minimal risk.[221]

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[220] H. Edgar & D.J. Rothman, "The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation" (1995) 73/4 The Milbank Quarterly 489 at 490.

[221] *Ibid.* at 504.

3. Independent National Oversight

At the national level, we would make a parallel recommendation. NCEHR should enjoy the same status and a proportionately equivalent degree of support as CCAC. The current situation in which national oversight of research involving animals is far more effective and independent than that for research involving humans would we believe be profoundly upsetting to the Canadian people. The Tri-Council does not do itself, other research sponsors, research institutions, or the research community any favours in maintaining the current close and controlling relationship to NCEHR and the TCPS in regard to policy setting, interpretation and enforcement. To maintain and deserve public trust, it is essential that there be an appropriate distance between the arms of government that promote research and those that protect human subjects. Moreover, the arm that protects human subjects must be in a position to verify the effectiveness of its efforts.

If, however, NCEHR, is to be a credible and knowledgeable national oversight body for REBs, then it will need a membership that is representative of its stakeholders' interests: sponsors, research institutions, researchers, and, most crucially, research subjects. The membership must be knowledgeable – including experienced members of REBs; experts in ethics, health law, and research; those with experience in research ethics standard setting; etc. Like CCAC, it should not try to do everything internally, rather it should reach out to commission expert opinion and enlist support from its many stakeholders. There may be a role here for supplementary expert specialist panels on specific research areas, e.g., xenotransplantation, genetic testing, new reproductive technologies, collectivities.[222] NCEHR needs a firm base of funding for an experienced and enhanced professional and support staff. Ideally it should enjoy a broad base of financial support from both public and private research sponsors. There also should be a clear and effective mechanism for periodic review of NCEHR's effectiveness and direction. Like CCAC, NCEHR faces the challenge of working as a standard setter with limited powers of enforcement due in large part to the complex constitutional division of powers in Canada. So it will have to lead by persuasion, public advocacy, and reputation.[223]

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[222] Edgar and Rothman have an interesting suggestion for such committees *Ibid.* at 503.

[223] An interesting recent development at CCAC is for the legal registration of its "Good Animal Practice" certificate. This provides a way for CCAC to gain greater public recognition and to provide a publicly recognisable standard for the humane treatment of animals involved in research.

4. Why Arm's Length?

For both REBs and NCEHR, we would draw a parallel to external auditing. External auditors are valued because they provide independent expert verification of the financial (or in the case of federal and provincial auditors general, the functional) status of private and public sector organisations. While it is reasonable for such organisations to have internal auditors and other means of internal control, these cannot replace expert external verification.[224] But to have credible external verification, those doing the verifying must be trained and accredited. This in turn involves independent oversight by an arm's length body, e.g., by an independent professional association. Such oversight includes education as well as the granting and, if appropriate, withdrawal of accreditation.

There are then two stages of verification with external auditing. First, there is the verification of the books of a company by an external auditor. Second, there is the verification of the verifiers by an independent accrediting body – associations of professional accountants. At both stages, the process is open to public scrutiny. Something similar has to happen with ethics review and monitoring. Steps have to be taken at the first stage to ensure the visible independence of REBs from research institutions. We have already suggested closer attention to membership rules and the addition of outside experts would help here. Below we also suggest strengthening the role of community members. At the second stage, there is a need to have independent assessments of the effectiveness of REBs. NCEHR could play an important role here. However, more may be needed. If, for example, one wants to ensure that there are properly qualified bioethicists on REBs – which should be a minimal requirement for health research REBs – then it would be natural to ask for credentialing for such bioethicists.[225]

Finally in our comparison with external auditing, we would note that the external auditing function has value not only for affected third parties (e.g., financial investors) but also for the companies whose books are audited. That is, those audited recognise the clear value **to them** of having arm's length verification because their reputation and credibility depend on such verification. For what is at stake is "reputational capital". In this regard, Canadian management

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[224] See W.E. Chadwick, "Tough Questions, Tougher Answers" Internal Auditor (December 1995) 63 on typical issues faced by internal auditors.

[225] Professionalising bioethics has been controversial in Canada. See F. Baylis *et al.*, "Women and Health Research: From Theory, to Practice, to Policy" in A. Donchin & L. Purdy, eds., *Embodying Bioethics: Recent Feminist Advances* (Lanham: Rowman & Littlefield, 1999) 253. Our concern here is for professional accreditation for a certain role – membership on REBs as a bioethicist – and not for professionalisation generally although we suppose a similar argument could be made for bioethicists on clinical ethics committees.

professor and business ethicist Leonard Brooks says that we have moved "from the 'trust me' world, to the 'tell me' and finally the 'show me' world of public and multi-stakeholder opinion".[226] We need a parallel move in Canada to the "show me" stage for research involving humans.

5. The Ottawa Governance Study

Our position here on NCEHR and in general on REBs is quite different than the position taken in the University of Ottawa's Centre on Governance recent study of the management of the TCPS, especially in regard to NCEHR's role.[227] The authors raise the concern that "since the objective of funding university research falls on the three Councils (MRC, NSERC, and SSHRC) that they are in a conflict of interest position regarding the protection human research." The response of the authors of the Ottawa report is instructive:

> We reject that argument. The previous chapter outlined 25 years of efforts to ensure ethical research. There is no indication that suggests that the three Councils have no regard for protection of human subjects in research. The development of a common policy and structure suggests otherwise.
>
> Some have suggested that there is an inherent adversarial relationship where one group of stakeholders promotes research of whatever ethical stripe while another exists to protect human subjects from their efforts. We reject that dichotomy. Our view is that <u>all</u> the primary groups involved in this process, the three Councils, the universities, and the researchers desire to promote ethical research and to see a system put in place that is both effective and fair.[228]

We think this response to the conflict of interest problem is quite unconvincing. For one thing, it would have been quite remarkable if Canada had not developed some sort of policy for the protection of research subjects given the world-wide push to this end. So the existence of policy is not on its own convincing evidence of sincere commitment. Even if "**all** the primary groups … desire to promote ethical research," the central question is whether there is actually in place a system that is "both effective and fair."

The primary question as we see it is not that of "good will" or "good intentions". It is rather that of creating an effective system that balances the promotion of research and the protection of research subjects. In other words, we see the governance issues here as less about the stated intentions of institutional actors and much more about the design of those

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[226] L.J. Brooks, "Reputational Capital and Business Ethics" The Corporate Ethics Monitor (September-October 1999) 65.

[227] Centre on Governance, *supra* note 213.

[228] *Ibid.* at 16.

institutions and their performance. We take the problem of agency-risk seriously; professed good will – no matter how sincerely intended – is not enough.[229] The institutions in question have been designed to promote research. REBs and ethics policies were put in place to counter-balance research promotion. Institutional commitment to ethical research is shown in large part by how much the institutional actors are willing to place effective constraints on the pursuit of primary objectives in order to protect innocent third parties.[230]

6. Accrediting and Monitoring Private REBs

We also see the need for the registration and accreditation of private (for-profit) REBs. If private REBs are going to play a credible role in the research process, there has to be a publicly accessible and independent way of verifying their independence, expertise, good judgement, and capacity. Competent private REBs should welcome such a move as a way of ensuring their 'reputational capital'. Given that there are U.S.-based private REBs active in Canada, it is essential for accreditation to ensure that all REBs overseeing Canadian research be knowledgeable about Canadian laws, regulations, and moral sensitivities. There are important differences between the U.S. and Canada that must be acknowledged especially in health research. For example, there are very serious issues about the off-loading of research costs on to the Canadian public health care system in the form of sponsors expecting provincial health care systems to pay the costs of adverse health effects resulting from research.

7. Effectiveness in Protecting Research Subjects

REB certification and accreditation must encompass more than the research ethics approval stage. REBs must also demonstrate the capacity for monitoring or continuing review.[231] We very much like the two-pronged suggestion of the U.S. OIG to recast requirements to "grant IRBs greater flexibility and hold them more accountable for results."[232] This involves (a) eliminating or lessening procedural requirements "to enable IRBs to be more strategic in how they use their limited time and resources and … concentrate their attention on

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[229] See the discussion in Section A-1 of Buchanan's ethical theory for bureaucratic organizations. A. Buchanan, "Toward a Theory of the Ethics of Bureaucratic Organizations" (1996) 6/4 Business Ethics Quarterly 419.

[230] McDonald has described this as "hands-tying manoeuvre". M. McDonald, "Hands: Clean and Tied, Dirty and Bloody" in P. Rynard & D.P. Shugarman, eds., *Cruelty and Deception: The Controversy over Dirty Hands in Politics* (Peterborough: Broadview, 2000) 1987.

[231] Office of the Inspector-General, *Institutional Review Boards: Their Role in Continuing Review* (Boston: Department of Health and Human Services, Office of the Inspector General, June 1998) and Office of the Inspector-General *supra* note 199.

[232] Office of the Inspector-General, s*upra* note 199 at 11.

those research practices posing the greatest risks to human subjects" and emphasising "performance-focussed evaluations."[233] For the latter, they say,

> Among the basic questions … that we believe warrant particular attention are the following: "1) Are IRBs successfully representing the interests of human subjects in research and not merely those of the sponsoring institution?" and "2) Do IRBs generally fulfil their goals?"[234]

We also like the idea of performance-focussed review being conducted by "independent, outside parties". But to have adequate review of performance, we see the need for both innovation and research (see below). We note that the context of clinical research has shifted considerably in recent years. Rather than seeing participation in research as a burden and "a dangerous activity,"[235] many potential subjects now see such participation as a benefit involving, for example, increased attention and access to care, state-of-the-art treatments and trust that their physician, the researcher or the institution would not offer research with substantial risk. In this situation, it is quite possible that subjects will not be sufficiently self-protective or evaluate the potential benefits of research participation and so, for example, ignoring the warning about risks on consent forms. If this is so – and there is reason to think that it is so – then there is an even greater burden on REBs to accurately assess risks and benefits. This again strengthens the case for performance-focussed reviews of REBs.

8. Conflict of Interest Provisions

The current context of funding for significant areas of health research, including among other things the drive to produce marketable products and commercial applications, makes it imperative to ensure adequate conflict of interest provisions. *Mutatis mutandis*, there are analogous pressures on many health researchers in less commercialisable areas of health research, e.g., to maintain research funding for the sake of reputation, tenure and promotion, or simply to ensure continued employment for those on soft (i.e., research grant) money. For research with significant commercial potential, we think that it would be wise preferably to "preclude investigators from recruiting patients and conducting clinical evaluations where the product being tested is one in which they hold a commercial stake"[236] (or more minimally to add a significant level of independent third party oversight). Random inspection and audit

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[233] *Ibid.*

[234] *Ibid.* at 12.

[235] Edgar and Rothman p. 499.

[236] *Ibid.* at 504.

procedures commissioned by REBs or NCEHR would likely be a worthwhile endeavour especially for higher risk areas of research.

C. Innovation and Research

The third of the "three I's" is innovation. Under the heading of innovation, we include two thrusts (p) experimentation and (q) research. We see (p) and (q) as intimately linked. They arise for the same reasons – gaps in knowledge particularly of appropriate standards (e.g., for performance-focussed review) and the need for evidence-based governance processes. We are particularly lacking in empirically grounded work on the effects of research on human subjects as well as on the effectiveness of governance procedures. There is another important linkage between (p) and (q), namely that there is little point in experimentation (e.g., in different forms of monitoring) without careful research-based assessments of processes and results. Vice-versa, research in the governance of HRIHS without experimentation is unlikely to provide a sufficiently wide range of plausible policy options – especially given the general trend towards devolution in regulation.

1. Monitoring

An area ripe for experimentation and research is that of monitoring or continuing review. As Fortin and Leroux point out in their 1997 article on monitoring, there are a number of policy options and models with respect to monitoring.[237] They look at four different models ranging in strictness from informal visits through site visits within a formal agreement or framework to formalised accreditation on the model of CCAC to a legislatively based "investigative" model. In the Canadian constitutional context they see a number of tradeoffs.

[237] L.-N. Fortin & T. Leroux, "Reflections on Monitoring Ethics Review of Research with Human Subjects in Canada" (1997) 8/1 Communiqué 11.

Models	Strengths	Weaknesses
Informal Visits	• Education • training	• no guarantee of universality
Visits within formal framework	• more consistent monitoring • atmosphere conducive to information exchange	• no guarantee of universality
Accreditation or certification	• status is clear	• Repercussions of non-compliance uncertain
Investigation	• compellability • universality	• complex structure • rigorous formalism

We see the first two models as inadequate. We would like to see a hybrid model that combines the merits of the accreditation and investigation models but is reasonably simple and avoids needless formalism. We see the need for a more experimental approach to monitoring (for example) whereby NCEHR would encourage research institutions to try different modes of monitoring and assist these institutions in assessing the merits and demerits of various modes for various contexts – type of research, institutional resources, degree of risk, etc. Thus, we would expect that some types of monitoring would work better for the more controlled and regulated contexts of clinical trials than for other areas of health research. Similarly, some modes of monitoring that work well in large health research institutions will not be readily adaptable to smaller institutions.

A major question for monitoring is who should do the monitoring. Should it be REBs, the professional staff of the research institution or sponsor, NCEHR, or other outside agencies (e.g., TPP inspectors as suggested in the proposed regulations for clinical trials of new pharmaceuticals)? There are governance issues with respect to appropriate accountability and reassurance. There are also efficacy issues with respect to how well human subjects are protected and the achievement of the social benefits of research. One cannot adequately address governance in a vacuum without looking at efficacy, but efficacy requires a context of responsibility – an answer to the question of "Efficacy for what purposes and to whose satisfaction?"

2. Context-sensitivity vs. Uniformity

Another crucial area where judicious experimentation and research would be useful is in terms of the inherent tension between governance processes that address specific contexts and those that serve the ends of uniformity and universality. Is the right model of the ethics approval process for the REB to function as a wise case-sensitive assessor of specific research proposals, to be assessed in terms of the research context and the likely subjects of research, or is the model one of an administrative tribunal striving to achieve universality and consistency in its judgements?[238] Posed this way, the choice looks stark and uninviting since we want to have it both ways; so realistic choices will be between hybrid models. Yet depending on the more favoured model of the two extremes, there will be different emphases in each hybrid. For example, in recruiting REB membership, we called for a substantial component of REB membership being genuinely representative of the non-research community and particularly of those who are part of the research subject population. But this may turn out to be in tension with the desire to run an REB that can meet the requirements of natural justice, e.g., to provide clear and consistent decisions backed by generalisable reasons under previously promulgated rules.[239] Here, we suggest that there is room for both experimentation and research with different combinations of the two models.

3. Concern for Subjects or Researchers?

Similarly, we have to see what are the tensions between having standards of performance, monitoring, accreditation, and processes that are sensitive to the needs, concerns and rights of research subjects and those that stimulate and facilitate research. As a society, it is not a question of "either / or": Canadians want **both** the benefits of research **and** the

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[238] In jurisprudential writing, a familiar image for the first model is that of "palm tree justice". The English political philosopher J.R. Lucas contrasts four types of judges: (1) "Judex I decides individual cases, but does not record decisions or give reasons"; (2) "Judex II decides individual cases, treating like cases alike, and records his decision but does not give reasons"; (3) "Judex III decides individual cases, treating like cases alike, records decisions, and gives reasons; and (4) "Judex IV subsumes individual cases under general, antecedently promulgated laws, but ideally, has not authority to interpret the law or make any innovation in it." J.R. Lucas, *The Principles of Politics* (Oxford: Clarendon Press, 1966) at 368. Judex I represents ideal palm tree justice. Lucas says: "Judex I is the ideal customary law judge. He is a good man who lives in his tent and judges Israel righteously. Every morning he goes to the gates of the city, and there hears all the disputes the children of Israel bring him; and after hearing what either side has to say, gives his decision, for the one party or the other, as the Lord saith unto him. And then goes on to the next case." Judex II is "the original common law judge". Judex III is "the judge of law reports"; while Judex IV is "the ideal legal code or statute law judge" J.R. Lucas, *The Principles of Politics* (Oxford: Clarendon Press, 1966) at 135. Lon Fuller in his classic story of "eight ways to fail to make law" takes a much less sanguine view of palm tree justice, L.L. Fuller, *The Morality of Law*, Revised Edition ed. (New Haven: Yale University Press, 1969) at 33.

[239] See previous footnote (re Judex I through Judex II).

protection of research subjects. Insofar as there are tensions between these objectives, then these need to be identified, studied, and acted upon. There are numerous debates here that cannot be settled *a priori* or simply by resort to anecdotal evidence. For example in the debates around appropriate TriCouncil policy for RIHS, there were allegations that provisions in the proposed 1997 Code for research involving collectivities and for research involving deception or partial disclosure would undermine various types of research. But this was asserted rather than evidenced. It would be far more productive to debate such issues in ways that are informed by the sort of careful research that distinguishes cases and is sensitive to different contexts.

4. Support for Experimentation and Research

If there is to be experimentation and research then two preconditions need to be met. First for experimentation to be useful, key institutional stakeholders – research institutions, sponsors, researchers and research subjects – have to be open to the various kinds of social experimentation, e.g., with different processes of monitoring, performance-focussed standards of assessment, etc. Moreover, they will have to be open to the sorts of open and honest research that can accurately gauge results. Secondly, research and experimentation will have costs – both financial and other – if they are to be done well. Unless research sponsors provide the support and commission the research and unless well-qualified researchers also take up the challenge, we will face increasing knowledge gaps with respect to RIHS generally and HRIHS specifically. The new CIHR with its strong emphasis on ethics in its mandate as well as its integrative and transformative vision of health research (from bench to application to results) is in an ideal position to play a leadership role here. The same is true of SSHRC, which has also staked out an important role in supporting health research. Indeed, one of the primary modalities for such research is qualitative research joined to solid bioethical/health law research.

In larger terms, we see this as an opportunity for Canadian researchers and research sponsors to play an important role in forwarding international research in the area of HRIHS. To take one important example, research in developing countries is a matter of considerable concern both from social justice and cross-cultural ethical perspectives.[240] Canada has important and multiple interests in this area that are linked to trade, international relations, and

[240] WHO and NIH convened an international conference on this topic in Bethesda, Maryland in November 1999 with a view to future conferences on the same area. A significant undercurrent issue at the conference was whether the NIH was trying to impose U.S. federal standards for research ethics review on developing countries.

human rights. Through research, we can also learn from the experience of other nations on governance issues with respect to RIHS.

VI. GENERAL CONCLUSIONS: REFLECTIONS ON NORMATIVITY AND GOVERNANCE

From talking to many people about this project, we know that all too often "research ethics" is read in a negative, prohibitive way. "Why," we have been asked, "are you so negative about researchers, research institutions and sponsors? Is it because you see lots 'going wrong'?" This, we think, is the wrong take on research ethics and related governance issues. Rather we would emphasize the need to have things "go right" and especially to "go visibly right." This should move the discussion a considerable step beyond the negative and reactive view of the ethics of research as essentially "responding to wrongdoing." An adequate system of governance should be more than 'putting out brush fires' and managing paper flows. It should be pro-active, transparent and accountable to its stakeholders. We recognize that institutional inertia makes it difficult to gather support for a pro-active approach; however, maintaining the status quo in the face of significant concerns has, we believe, much greater costs. One would do well to think here of the Krever enquiry into the management of Canada's blood supply.[241]

Although we made recommendations on specific aspects of the governance of health research involving humans, our main concern is with the broader picture. Unlike other studies[242], this report has not been centred on ethics committees and the ethics approval process. Indeed, one of our primary concerns has been with the limitations of an REB-centred perspective (as important as we take REBs to be in the total research process). Ultimately, our concerns have been directed at the culture of research and the larger social, political and economic climate in which research is supported and regulated. It is only with this larger picture – marked with globalisation and commercialisation as well as rapid scientific advances and changing social sensibilities – that one can accurately gauge the challenges that must be met for the ethical governance of research involving humans in Canada.

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[241] H. Krever, Ontario Commission of Inquiry into the Confidentiality of Health Information. *Report of the Commission of Inquiry into the Confidentiality of Health Information* (Toronto: J. C. Thatcher, Queen's Printer for Ontario, [1980 or 1981]).

[242] See for example, for the United States (Office of the Inspector-General, *supra* note 199), Quebec (*supra* note 212), and Australia (Review of the Role and Functioning of Institutional Ethics Committees IECS, *supra* note 218).

From this larger picture, we return in the end to the fundamental concerns that motivate health research involving human subjects – the desire for socially beneficial research and the concern for the protection of human subjects. It is our conviction that this cannot be posed as an "either-or" choice. It is a "both-and" choice. We need both socially beneficial research and the protection of human subjects. Without these two together, there is the serious risk of undermining the fundamental trust relations that underwrite health research – the public's trust in researchers, research institutions and sponsors and more specifically the trust of research subjects whose continuing participation in research is so essential not only to health research but also to health care. Governance is about maintaining, enhancing and, where necessary, restoring trust in transparent, accountable and effective ways. It is around this goal of trust that this study has been oriented.

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