




# Harmonization of the Ethics Review Process

## An Environmental Scan



Michael Smith Foundation for  
Health Research

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## 1. Executive Summary

The increasingly global, multidisciplinary and collaborative nature of research challenges the capacity of British Columbia's institutions to meet current and projected demand for ethics review of research proposals involving human subjects. As in many other international and national jurisdictions, stakeholders in the B.C. research community have identified the need for improvements to the current local ethics review processes to work toward a more effective and coordinated provincial approach to ethics approval.

Options for a reform of ethics review processes in B.C. vary widely, from maintaining the status quo, making modifications to the existing institutional review board system, adoption of harmonized core guidelines, and institutional review reciprocity to a coordinated, shared, provincial ethics review mechanism.

At the request of provincial health research stakeholders, and with the endorsement and support of the Ministry of Health and the Ministry of Advanced Education, in early 2007 the Michael Smith Foundation for Health Research agreed to facilitate a process to explore potential options for system reform in greater depth. Part of this project (represented by this report) sought to identify efforts undertaken in other jurisdictions to improve the effectiveness, efficiency and quality of the ethics review process.

The foundation for this environmental scan of options for ethics review was a combination of literature review and internet research, paired with a series of interviews with key representatives of organizations that have implemented harmonized ethics review models. The interviews gathered information regarding how some of the models function in the real world of human subjects research across Canada and in the United States, the European Union and Australia.

Other portions of the MSFHR project included a survey of B.C. researchers regarding their experiences with the current ethics review process, and an environmental scan of ethics review structures across our province.<sup>1</sup> Arising out of the findings from those components, this report has adopted an analytical framework referencing five key dimensions relating to the overarching goal of protecting the interests of human subjects involved in health research in British Columbia. Those dimensions represent areas of potential enhancement for current B.C. ethics review structures, and describe priorities for the access, capacity, consistency, efficiency, and quality of the ethics review process.

In seeking to better understand options for change, this report identifies a variety of models for reforming ethics review. We describe and categorize these options with the aim of providing a

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<sup>1</sup> The Michael Smith Foundation for Health Research. *Investigator Experience with Research Ethics Boards in British Columbia: Survey Findings*. Vancouver: MSFHR, 2007.  
The investigator survey was also informed by: The Michael Smith Foundation for Health Research. *The Ethics Review Process in British Columbia: An Environmental Scan*. Vancouver: MSFHR, 2007.

clearer understanding of the characteristics, challenges and opportunities inherent in each of them. We focus predominantly on models that are currently being explored or used as a streamlined or harmonized alternative to the system of independent, institution-based REBs. The models reviewed include both centralized and cooperative/collaborative approaches, with the latter representing mixed systems typically combining both centralized and institution-based features. To better illustrate our analysis of these approaches, two matrices were developed to relate various characteristics of the models and the dimensions of analysis to each other. The matrices also relate the models to the case studies documented in the report, presenting examples from numerous jurisdictions and model types.

While there have been many attempts to create the most accessible, effective, efficient, and uniform ethics review system, this research project has concluded that as yet, no single system has emerged as the most likely to succeed in reforming the system in a way that meets all stakeholders' goals and expectations. Irrespective of which of the mechanisms we looked at, to some extent they are all in transition, evaluating their own performance and seeking future options for increased regional, national and international harmonization. Informants often reported that their models are 'works in progress', continuing to adapt and improve based on experience and the changing demands of the global research environment.

There are many ways for harmonization of the administrative and deliberative functions of research ethics boards and we did not identify any single system that clearly addresses all the dimensions completely. The 'ideal' system typically envisioned is one accessible to researchers while at the same time highly protective of those who consent to bear research-related risk. Informants suggested that such a system would be characterized by consistent interpretation of ethical standards, administrative capacity, professional expertise and community and ethnic representation within the paradigms of a given context or jurisdiction. Hence, any effective plan to enhance processes for ethics review must address:

- the realities of the system to be served, in the light of contemporary international standards;
- the increasing volume of collaborative and multi-site studies requiring review;
- opportunities for efficiency and interactive communication offered by electronic systems; and
- the need for evidence-based mechanisms to monitor and assure performance quality.

In this context, and based on the findings of our scan, four overarching themes have emerged that appear to be important contributing factors in successful ethics review reform: leadership, information technology, trust, and accreditation.<sup>2</sup> With no system emerging as the panacea for ethics review, this project suggests that successful approaches to ethics review reform must incorporate 1) local context; 2) enhancements of challenges and weaknesses along the five dimensions (access, capacity, consistency, efficiency, and quality); and 3) contributing factors to success, reflected in the four themes (leadership, information technology, trust, and accreditation).

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<sup>2</sup> National Institute of Health, OHRP, Association of American Medical Colleges, American Society of Clinical Oncology, *Alternative Models of IRB Review: Workshop Summary Report*, November 17-18, 2005.

## 2. Introduction, Context and Notes on Methodology

Many stakeholders in B.C.'s health research community have expressed concern regarding the barriers that currently inhibit researchers from accessing effective and efficient ethics review across all types of research. An online survey conducted by MSFHR as part of this project<sup>3</sup> details the concerns about the current ethics review system in B.C. as expressed by investigators. In summary, there is considerable debate across the provincial research community about the current status of research ethics review and the system is described to have significant challenges: apparent inefficiencies; costly and time consuming processes; monitoring and enforcement structures; a lack of harmonization, leading to onerous duplication of efforts to achieve ethics approval for multi-centre research; and a lack of access to ethics review for community research. All these and other factors combined are seen as barriers with the potential to affect the competitiveness, quantity and quality of research performed in British Columbia.

While many agree that there is a clear need for a more coordinated provincial approach to ethics, it is not clear what potential approaches or solutions might be acceptable to stakeholders and feasible within the B.C. context. Options vary widely, from adoption of harmonized core guidelines and institutional review reciprocity to a single coordinated, shared, provincial ethics review body.

In early 2007, at the request of provincial health research stakeholders, and with the endorsement and support of the Ministry of Health and the Ministry of Advanced Education, the Michael Smith Foundation for Health Research agreed to facilitate a process to explore options in greater depth. One part of this process, resulting in the present report, sought to identify efforts undertaken in other jurisdictions to improve the effectiveness, efficiency and quality of the ethics review process. In addition to conducting research on these efforts in Canada, the U.S. and other countries, we conducted interviews with representatives from several of the organizations regarding their recent experiences.<sup>4</sup>

The purpose of this report is to present information on models designed to streamline and/or harmonize institutionally-based ethics review processes. In the course of the research and subsequent analysis, patterns and criteria for organizing the various models were identified. By describing and categorizing current ethics review models as they exist in the literature or in the 'real world', this report aims to offer a framework for future stakeholder discussions.

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<sup>3</sup> The other two parts of the process involved are:

- B.C. REB Scan: a description of mechanisms and structures for ethics review of research involving human subjects in various institutions across B.C., including identification of the issues and barriers related to ethics review and the opportunities to enhance or harmonize the B.C. system.
- B.C. Investigator Survey: an on-line survey of B.C. researchers with recent experience in the application process for ethics review to identify and prioritize the key barriers/areas of concern with respect to quality, access, consistency, efficiency and capacity for ethics review.

<sup>4</sup> List of interview partners, see Appendix A.

This report's presentation of a range of mechanisms and models from other contexts is designed to facilitate discussion around options for ethics review reform in B.C., by creating a common understanding of model characteristics and typical features. The categorization of the models is to a certain degree arbitrary and, in most cases, not distinct, but nevertheless provides a possible common starting point for the discussion.

Also arising from MSFHR's investigator survey and scan of ethics review structures in B.C., five dimensions were identified for analysis – each reflecting possible priority areas of system improvement. With the help of those dimensions, the various models and case studies identified in this report were linked to the concerns expressed by B.C. investigators. These dimensions are referenced in the present report to draw connections between current concerns and possible remedies for these concerns.

The report consists of the following sections, each addressing a different aspect of current ethics review mechanisms in theory and practice, including how they work, where they exist and how successful they are (according to our informants):

- Section two: Introduction, Context and Notes on Methodology
- Section three: Models of Ethics Review
- Section four: Selected Case Studies
- Section five and six: Analytic Summary Matrices (summarizing model features and relating models to five dimensions for analysis)
- Section seven and eight: Recurring Themes and Concluding Observations.

### **2.1 Terminology**

When discussing topics of ethics review and harmonization, terminology is not always clearly defined and agreed upon by all stakeholders and observers. The following is a brief guide to the use of key terminology in this report. We have attempted to follow the most common use of terminology and to be consistent in the application of terms.

*Reform:* Refers to any attempt to change the ethics review system with the goal of improvement (irrespective of the mechanism).

*Harmonization / Streamlining:* refers to attempts to improve on the current REB system by aligning existing processes and structures and developing new ones. Streamline is used in the same context. We did not make a clear distinction between 'harmonized' and 'streamlined' given that there are no clear criteria to distinguish between the two and too many complex models and case studies to allow for an accurate and discrete use of those terms.

*Cooperative/collaborative models:* For the same reasons as with ‘harmonization / streamlining’, the terms are used interchangeably. The term ‘hybrid’ is also at times used in reference to those models, due to their mixed centralized and decentralized features.

*Research Ethics Boards (REBs):* We use the predominant term in Canada to refer to ethics committees. In the U.S. the most common term is Institutional Review Board (IRB). Proprietary or country specific terms were used in reference to specific and discrete uses of terms: within case studies, in quotes or with respect to specific models.

*Multi-centre studies:* There is variation in the literature on the use of multi-centre versus multi-site studies. Often they are used interchangeably but may also define two different concepts of multiple research locations versus multiple collaborative researchers. Here we use the predominant term in Canada: multi-centre describes research that is conducted at more than one location or in more than one jurisdiction (which may be an institution, regional territory, or country) and may or may not involve multiple collaborative researchers at one or more locations.

## **2.2 Five Dimensions for Analysis**

As part of the consultative and research process undertaken by MSFHR in 2007, a survey was conducted seeking the views of B.C. researchers on their recent experiences with ethics review process at their respective institutions.<sup>5</sup> The results of this survey suggest that in British Columbia, the current institution-based approach to ethics review is viewed by many investigators as having room for improvement in several important areas, particularly in areas relating to consistency of review within and among REBs and efficiency of the review process.

For the purposes of the following analysis of the Research Ethics Board (REB) review process, the present report references a summary of the views of the investigators. Their responses were grouped into five key dimensions relating to priority components within the overarching goal of protecting the interests of human subjects involved in health research in British Columbia. In considering these dimensions (defined in Figure 1) it is important to note that they are a reflection of investigator perceptions at a point in time, and must therefore be considered in conjunction with the equally important perceptions and needs of other key stakeholders in the ethics review process..

In this section of the report, each of the dimensions defined on the next page is discussed in further detail. At the end of this report two matrices further relate this environmental scan and its component case studies to the five dimensions for analysis introduced in this section.

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<sup>5</sup> The Michael Smith Foundation for Health Research. *Investigator Experience with Research Ethics Boards in British Columbia: Survey Findings*. Vancouver: MSFHR, 2007.

**Dimensions of the Research Ethics Review Process  
Based on Investigator Perceptions**

**Capacity:**

This dimension relates to the perception that the REB has:

- sufficient expertise to assess applications across a spectrum of health research;
- sufficient frequency of meetings to respond in a timely manner;
- continuing access to sufficient numbers of willing and qualified board members to manage the demand for ethical review;
- sufficient resources to manage the ethics review process effectively.

**Consistency:**

This dimension relates to the perception that:

- the REB subscribes to a recognized standard of quality process, output and outcome;
- the ethics review process is of uniform quality across the province; and
- the same application would receive comparable review and outcome from any B.C. institution's REB.

**Access:**

This dimension relates to the perception that information is readily available to applicants in order that they may:

- have access to an REB, know to which REB to apply and how;
- have the skills and knowledge to prepare a high quality application;
- develop a clear sense of the REB processes, timelines, and decision rules;
- know how they can improve their chances of a successful outcome; and
- know when they can expect a decision from the REB.

**Efficiency:**

This dimension relates to the perception that REB processes are:

- clear;
- straightforward;
- concluded in a timely manner; and that
- REB application activities are not unnecessarily duplicated.

**Quality:**

This dimension relates to the perception that REB decisions are

- fair;
- well-informed;
- clearly justified to applicants;
- consistent with regulatory and legal obligations of all responsible parties;
- include annual recertification of ethics approval through the course of the approved research; and
- include site monitoring for compliance through the course of the approved research.

**Figure 1: Dimensions of the REB Process**

### 3. Models of Ethics Review

This section explores models of ethics review currently in use in other jurisdictions, with a particular focus on those models that have been described or used to enhance or reform the current institution-based ethics review system – primarily mechanisms characterized by centralization or cooperation/collaboration with local review boards.

The term ‘model’ is employed here in a wider rather than a narrowly descriptive sense: ‘models’ are presented as approaches to ethics review with specific common characteristics relevant to multiple REB situations. The purpose of identifying models of ethics review is to develop a structured understanding of the array of approaches that currently exist. The basis for this section is a review of literature and case studies.

The matrices in Section 5 relate those models to the case studies, which are described in more detail in Section 4. This approach aims to illustrate the conceptual characteristics of groups of approaches to ethics review (‘models’) and their manifestation in the ‘real world’ (case studies).

A number of options for improving the current system have been discussed in many diverse jurisdictions and in the literature and are described here.

The approach described above, asserts that any ethics review mechanism can be characterized by varying degrees of quality, consistency (uniformity), efficiency, accessibility, and capacity, two high level lenses were also applied in the preparation of this report to characterize the various existing and emerging ethics review models and describe their key features:

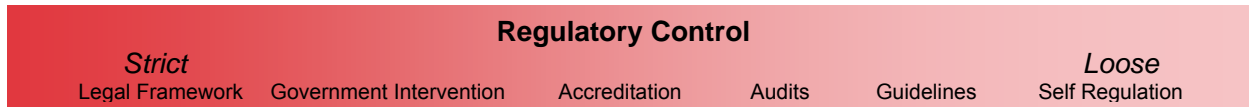
1. The degree of regulatory control
2. The degree of centralization

These two lenses discussed in further detail below are *not* mutually exclusive, but rather describe the various models and mechanisms from different perspectives.

#### **3.2 Regulatory Control**

Some of the more common efforts to improve efficiency and effectiveness aim to address the *quality* and *consistency* aspects of the ethics review process. Ethics review approaches with an emphasis on regulation typically address weaknesses in quality and consistency with tools such as guidelines. This may be supplemented with more or less formal interventions by various authorities that have accepted or been assigned a regulatory role in the ethics review process.

The ‘consensus system’ ethics review process, predominant in the western world, is based on peer assessment and review, rather than on administrative law (‘legal model’).<sup>6</sup> However, the range of ethics review systems is broad, reaching from fairly strict legislation to high level guidelines. Figure 2 below attempts to illustrate this range on a spectrum of exemplary listings (however it is not intended to represent a complete list of existing models and approaches to ethics review).



**Figure 2: Spectrum of Regulatory Control**

As illustrated, approaches dominated by regulatory control can cover a full spectrum from strict to loose regulatory control. However, it has been centralization, and not more regulatory control, which has been the most prominent feature of the initiatives addressing the all the challenges in current ethics review, including those related to quality and consistency. Consequently, this report will focus on models and case studies which are characterized by features visible through the centralization lens.

### 3.3 Centralization

Many recent efforts to address weaknesses in the institution-based ethics review system – predominantly but not exclusively – address the *efficiency*, *accessibility* and *capacity* aspects of the ethics review process. Models which typically address weaknesses in *efficiency* and *accessibility* are ‘streamlined<sup>7</sup> (centralized and cooperative/collaborative<sup>8</sup>) models’. These models vary in their degree or extent of centralization. Among the centralized and cooperative/collaborative approaches, the latter have recently received most attention as they also attempt to address some of the perceived weaknesses of centralization.

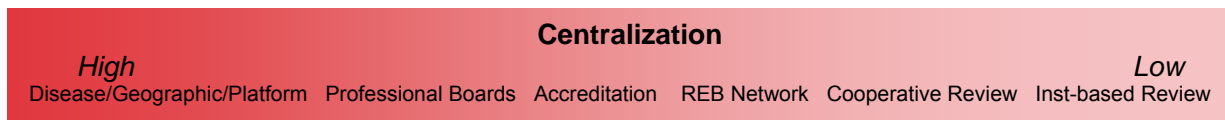
#### 3.3.1 Models characterized by Centralization

The models and review mechanisms described in this section are predominantly characterized by centralization features and to a lesser degree by regulatory characteristics. In summary, the models described below cover the whole spectrum from high to low levels of centralization, including models with collaborative features. The range of ethics review systems is broad, reaching from fairly strict legislation to high level guidelines. Figure 3 below attempts to illustrate this range on a spectrum of exemplary listings (however it is not intended to represent a complete list of existing models and approaches to ethics review).

<sup>6</sup> IMJ 2003, 33:188

<sup>7</sup> Also referred to as ‘harmonized’

<sup>8</sup> Also referred to as ‘hybrid’



**Figure 3: Spectrum of Centralization**

Some mechanisms, such as Central Review Boards and geographic or disease-specific ethics review structures are characterized by strong centralization. Other forms of ethics review reflect iterations of centralized models, with more emphasis on the ability to respond to specific institutional or disease-based needs. In this analysis they are primarily represented by examples of collaborative/cooperative structures.

### 3.3.2 Decentralized Models

In Canada, the responsibility for ethics in research involving human subjects lies primarily with institutional REBs, which follow and interpret sets of international and national guidelines, codes of ethics or policy statements. In British Columbia, this decentralized model provides the predominant mechanism for ethics review. MSFHR's environmental scan of ethics review structures in the province identified a total of 23 REBs that review human subjects research operating in B.C. as of 2007, the majority of them linked to academic institutions and health authorities. A minority are REBs established to meet special needs, including review of community-based research.

### 3.3.3 Central Review Boards

The benefits of centralized models for research ethics review are generally agreed to include:<sup>9</sup>

- cost savings
- improved efficiency
- reduced demand on limited human resources
- greater consistency of review
- more wide-scale data collection and analysis
- less concern about institutional conflicts of interest
- more options for unaffiliated investigators to obtain ethical reviews, and
- the ability to specialize more easily in a given research area.

<sup>9</sup> As stated in IRB May-June 2000, Vol.27, No.3:5

*Geographically-based or disease-based models* are common forms of centralized models where ethics review centralization occurs based on geography (e.g. a state or a province) or a specific disease, such as cancer. These models are typically designed to provide access to ethics review for all researchers, reducing the market for private or for-profit- ethics committees.<sup>10</sup> The major risks inherent in such models, if used exclusively, include a possible reduced ability to respond to local or regional differences in population, culture and other factors influencing study design and/or the review process.

To address such concerns, the U.S. Food and Drug Administration (the FDA) for example, requires adequate documentation of agreements between local and central review boards, delineating “specific responsibilities of the central IRB and the institution’s IRB for the initial and continuing review of the study” and urges central boards to consider “the ethical standards of the local community.”<sup>11</sup> The FDA explicitly encourages a centralized ethics review process for a “single multi-centre trial performed by a commercial or a publicly funded sponsor” and suggests that the various local boards “enter into agreements with a central IRB to rely on all or some of the review findings.”<sup>12</sup> Study sites without a board are allowed to rely fully on a central ethics review board for “all review responsibilities.”

Three suggested approaches for protecting local interests in a centralized system are: 1) site visits, 2) a database with information on investigation and research facilities and 3) good communication with local sources.<sup>13</sup>

Further potential advantages of the centralized model are described as follows<sup>14</sup>:

- A centralized group that meets frequently, with each member having time allotted to the review as a major part of job description, has the opportunity to develop “consistent ways of interpreting statutory language.”
- A centralized group, with professional leadership and relatively stable membership, could produce “uniform methods for measuring risks to humans that vary appreciably with scientific knowledge and circumstances.”
- A centralized group could be ‘politically insulated’ and less likely to experience conflicts of interest.

It has been argued that with respect to multi-centre studies one of the flaws of local review is its inability to influence protocol design: “Central review has a clear advantage, because a central board directly interacts with the principal investigators of the study and can negotiate protocol changes to

<sup>10</sup> European Journal of Health Law 2000, 7:269

<sup>11</sup> US Dept. of Health and Human Services, Federal Drug Administration, *Guidance for Industry: Using a Centralized IRB Review Process in Multi-centre Clinical Trials*, March 2006. accessed via <http://www.fda.gov/cber/gdlns/irB.C.intrial.pdf> ; also see US Code of Federal Regulations, 21 CFR 56.114

<sup>12</sup> ibid

<sup>13</sup> National Institute of Health et al. *Alternative Models of IRB Review: Workshop Summary Report*, 2005.

<sup>14</sup> Breyer S. *Breaking the Vicious Circle: Toward Effective Risk Regulation*. Cambridge: Harvard University Press, 1993.

enhance participant safety, reduce risk, and increase scientific validity.”<sup>15</sup> Advantages and disadvantages of centralized models are summarized in Figure 4.

### 3.3.4 Disease-Specific Ethics Review

With respect to first approval and continuing oversight, the benefits of centralized models<sup>16</sup>, such as geographically-based or disease-based models, are generally agreed to include:

- cost savings,
- improved efficiency,
- less demand on limited human resources,
- greater consistency of review,
- more wide-scale data collection and analysis,
- reduced concern about institutional conflicts of interest,
- more options for unaffiliated investigators to obtain ethical reviews, and
- the ability to specialize more easily in a given research area.

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<sup>15</sup> Pentz R, Khayat A, *The poster child for the need for central review of research protocols: the children's oncology group*, Cambridge Quarterly of Healthcare Ethics, 2004;13: 359-365

<sup>16</sup> As stated in IRB May-June 2000, Vol.27, No.3:5

<b>Characteristics of Centralized Systems                      (including Cooperative, Fully Centralized and Hybrid Boards)<sup>17</sup></b>	
<b>Administration</b>	<b>Deliberation</b>
<i>Advantages</i>	
One administrative body All committees under one management Interaction with local REBs centrally coordinated PI has: One contact point One application, filters for various fields One system to learn Lower administrative costs for one review Members accumulate knowledge of system Structured training and continuing education Workload efficiently distributed Tracking systems Potential for self-evaluation and outcomes study Centralized SAE reports and distribution	One committee review One request for revisions One decision Greater consistency/fairness Decisions Application of government standards Greater access to scientific experts in wide variety of disciplines Greater access to community and other lay representatives More likely to focus on core ethical issues than unimportant details due to uniformity in applications Protocol changes rapidly addressed Potential to enhance international collaboration
<i>Disadvantages</i>	
Higher per meeting cost Member fees Travel expenses Larger support staff Geographically remote for some parties Communications may seem more formal	Lay representatives from community and advocacy groups may feel uncomfortable in this setting. May be inconvenient for PI to attend meeting

**Figure 4: Administrative and Deliberative Characteristics of Centralized Systems**

In addition, geographically-based or disease-based models provide access to ethics review for all researchers, eliminating the market for private or for-profit- ethics committees<sup>18</sup>. The major downsides of such models, if used exclusively, are identified as:

- the lack of ability to respond to regional differences in population, culture and other factors influencing study design and/or the review process,
- the lack of beneficial redundancy in the safety net, the potential for increased bureaucracy,
- the need to re-evaluate current regulations, and
- the need for institutions to relinquish autonomy.<sup>19</sup>

<sup>17</sup> Fitzgerald MH, Phillips PA, *Centralized and non-centralized ethics review: a five nation study*, Accountability in Research. 2006; 13: 47-74.

<sup>18</sup> European Journal of Health Law 2000, 7:269

An example of category-specific collaboration is found in Ontario. The Ontario Cancer Research Network, in collaboration with Cancer Care Ontario and local Research Ethics Boards across the province, introduced the Ontario Cancer Research Ethics Board in December, 2003 to facilitate scientific and ethics review for multi-centre oncology trials. The Ontario Cancer Research Ethics Board (OCREB) flows from an extensive provincial consultation process over two years involving: REB chairs, regional cancer centres, host hospitals, investigators, bioethicists, research ethics coordinators and collaborating organizations such as the National Council for Ethics in Human Research, the Canadian Association of Research Ethics Boards, and the Canadian Institutes of Health Research. Several key issues were identified during this consultation process.

The primary goal of the Ontario Cancer Research Ethics Board is to reduce the current workload burden of local REBs, increase the quality and uniformity of reviews and simplify the initiation of multi-centre oncology trials in Ontario.<sup>20</sup> Twelve guiding principles were established to guide the development of the Ontario Cancer Research Ethics Board:

- local control
- roles and responsibilities,
- evaluation
- optimized workload
- better access to research
- phased development
- regulatory compliance
- clear accountability
- appropriate structure
- code of conduct
- scientific review process
- enhanced monitoring.

It must be acknowledged that the number of trials reviewed by OCREB is relatively small; hence, any conclusions from this example must be seen in that context.

In the United States the National Cancer Institute (NCI) and Office for Human Research Protection (OHRP) collaborated to develop a central institutional review board (CIRB) for federally funded oncology research. The initial driving force behind CIRB was the desire to increase patients' access to clinical trials supported by NCI. In 2002 the number of clinical sites participating in each trial ranged from 4 to 809. In a decentralized system this number of trials requires 3,000 initial reviews and 13,000 annual reviews in a one year time period.<sup>21</sup>

An ongoing debate with respect to disease-specific boards in general, and the CIRB in particular, is the distinction between scientific validity and scientific integrity, expressed in the following statement:

Some believe that the CIRB should address only safety and ethical issues, because all NCI-sponsored trials of cancer treatment pose reasonable designs or they would

<sup>19</sup> As stated in 4-IRB May-June 2000, Vol.27, No.3:5

<sup>20</sup> From the organization's website: [http://www.ocrn.on.ca/ethics\\_AboutOCREB.htm](http://www.ocrn.on.ca/ethics_AboutOCREB.htm), accessed Jun 8, 2006.

<sup>21</sup> Christian, M, Goldberg, J, Killen, J et al.. *A central institutional review board for multi-institutional trials*. New England Journal of Medicine. 2002; 18: 1405-1408.

not have survived the extensive scientific review to which they have already been subjected. Others argue that scientific merit and trial design are directly related to the risk-benefit assessment and are appropriate areas for review by either a local IRB or a CIRB. Although the CIRB should avoid imposing its views when dealing with issues about which reasonable people may disagree, the disease-specific scientific expertise of the board members increases the likelihood of controversies in the grey zone between safety and science.<sup>22</sup>

NCI has also developed a central board (PedCIRB) to review NCI-sponsored clinical trials conducted by the Children's Oncology Group (COG).<sup>23</sup> Prior to the creation of PedCIRB protocol activation required separate review by each local IRB and subsequent review of each amendment and each Serious Adverse Event (SAE). The potential for elimination of redundant reviews coupled with expertise in pediatric oncology and related disciplines among CIRB members should increase the availability of clinical trials to children with cancer.<sup>24</sup>

The NCI board system can also be characterized as one offering 'facilitated' or 'tandem' review (representing a collaborative rather than a purely centralized model). This is because each site's local REB retains the option to accept the CIRB review as final, to make modifications, or to conduct a full review of its own.<sup>25</sup> Figure 5 on the next page indicates the major division of several key responsibilities between CIRB and local boards.

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<sup>22</sup> Christian, M, Goldberg, J, Killen, J et al.. *A central institutional review board for multi-institutional trials*. New England Journal of Medicine. 2002; 18: at 1407

<sup>23</sup> The Children's Oncology Group comprises ~200 U.S. medical institutions.

<sup>24</sup> Anderson BD, Goldberg J, Adler J et al.. *The NCI pediatric central institutional review board (PedCIRB) initiative: Progress and impact*. Journal of Clinical Oncology. 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 6632

<sup>25</sup> www.ncicirb.org Accessed March 29, 2007

<b>Division of Key Responsibilities between CIRB and Participating Local Institutions<sup>26</sup></b>	
<b>NCI – Central IRB</b>	<b>Local Institutions</b>
<p>Perform initial reviews of new research studies, discuss any issues with the lead organization and Study Chair, and make a final decision of approval or disapproval of the study</p> <p>Maintain and make accessible to a designated local IRB the CIRB application, protocol reviews, letters to Study Chairs, approvals and disapprovals, and minutes of the CIRB meetings.</p> <p>Carry out Continuing Reviews, reviews of submitted SAEs, protocol amendments, DSMB reports and other documents submitted by the lead organization or Study Chair.</p> <p>Provide special expertise as needed from Board members or consultants to adequately assess all aspects of each study.</p> <p>Make available to the local institution the roster of CIRB membership</p>	<p>Ensure the safe and appropriate performance of the research at its institution.</p> <p>Provide a mechanism by which complaints about the research can be made to local study participants or others.</p> <p>For each study reviewed by the CIRB to be performed at the local institution, determine if there are any local context issues that must be addressed by the local IRB.</p> <p>Determine if the CIRB review is acceptable to the local IRB</p> <p>Decide whether to accept the CIRB review or conduct a separate local full board IRB review.</p> <p>As appropriate, add local restrictions, stipulations, or substitutions to CIRB approved informed consents.</p>

**Figure 5: NCI - CIRB Division of Responsibilities**

### **3.3.5 Geographically-based / Regional Ethics Review**

Over recent years, the overall increase in volume of clinical trials and the existence of complex and changing regulations have made ethics reviews more difficult and time consuming. In B.C. as in other jurisdictions with institutionally-based REB structures, many local REBs are faced with the challenge of maintaining sufficient review expertise and resources<sup>27</sup>. Under the local REB system, all research sites for a multi-centre trial complete a similar review, and it is widely acknowledged that this duplication can create inefficiencies.

Centralizing ethics review on a geographic basis (regional, provincial or national) has been adopted by some jurisdictions as a way to address the challenges inherent in local ethics review. One variation of geographically-based centralized models is ethics review in the form of Regional Ethics Boards (RegEBs) in the place of local, institution-based REBs. In one U.S. proposal, discussed at the President’s Council of Bioethics in 2002<sup>28</sup>, a RegEB would consolidate all activities related to

<sup>26</sup> “Division of Responsibilities between the Central IRB and Participating Local Institutions”, CIRB November 2005, accessed on CIRB website <http://www.ncicirb.org/> on October 25, 2007. This list is not exhaustive; there are additional responsibilities for central and locals boards listed in the document.

<sup>27</sup> Cross reference this finding to the MSFHR B.C. Scan.

<sup>28</sup> Wood, A., Grady, C., Emanuel, E.J. *The Crisis in Human Participants Research: Identifying the Problems and Proposing Solutions*. <http://www.bioethics.gov/background/emanuelpaper.html>, accessed September 25, 2006

human subjects protection for a given geographic region. A federal/central oversight body would coordinate, oversee, monitor, and compile data on all of the RegEBs.

The proposal suggests that each REB would be a relatively large organization composed of several divisions. One division would include Research Review Committees -- the actual panels that review research studies proposed by investigators. Another would be Ethics Policy Committees that propose ethics policies for the RegEB. A third would include liaisons between the RegEB and particular institutions and bodies conducting research in the geographic regions. At each major research institution, a single liaison would be dedicated to the institution; in other cases, one liaison may have responsibility for working with a number of medical practices or smaller institutions that conduct less research. The liaisons would have a coordinating function that encompasses submission of the research studies, education of the members of the institutions and the like. Under this 2002 U.S. proposal, each RegEB would have four main responsibilities:

1. conducting prospective review of every research trial in their geographic area;
2. monitoring these trials for adverse events and compliance with the protocol;
3. organizing the training of clinical researchers and their teams; and
4. developing and refining policies regarding major ethical issues in human participant research.

Numerous variations of geographically-based models exist, developed to meet specific geographic or other needs. In a number of European countries, for example, various iterations of geographically-based ethics review models were developed within the national context to address the specific situation of each country. Some of those models possess centralized supra-structures (details see Case Studies in Section 4).

The U.K. has adopted a multi-tiered system with various centralized features, with the goal of overcoming administrative, efficiency and quality challenges that resulted when researchers applied to multiple boards for approval of multi-centre studies. But because this system is administered through a branch of the National Health Service, at least one observer has noted that gaps still exist, for example, to meet the review needs of non-health related studies involving human subjects including educational and social services studies.<sup>29</sup>

Another form of a geographically-based model, a regional REB network, has been suggested in the literature. This model is characterized by loose central structures to facilitate more uniform ethics review (e.g., in developing countries) and to simplify REB procedures. But as with concerns for maintaining reference to local context within a provincial or state system, network of ethics boards with a wide geographic reach must take into consideration any cultural or national/regional

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<sup>29</sup> Personal Communication, Mrs. Margaret Shotter, September 2007.

differences. An REB network “could be regional or multinational and share common procedures and paperwork (with room for local modifications).”<sup>30</sup>

### 3.3.6 Professional Body Ethics Review (REB Platform)

Typically, REB Platforms (also known as Professional Body Ethics Review structures) are iterations of centralized models, often with some ability to respond to specific institutional or disease-based needs. Such platforms are established by an organization that is independent and without vested interest in the research to be assessed, but with sufficient expertise at hand that a high-quality ethics review can be performed. Frequently, this role is assumed by medical colleges that take on the role of centralizing the review process for their members.

The Canadian Medical Association (CMA) as well as many provincial medical colleges explicitly recognize the need for ethics review of research conducted by their members who may not be affiliated with institutions offering review board services.<sup>31</sup> In a number of Canadian provinces, the provincial medical colleges have policies in place to deal with issues around research ethics, including industry sponsored research or community-based research (e.g. Manitoba, New Brunswick, Ontario). In Alberta the provincial College of Physicians and Surgeons has taken active steps to ensure that there is “appropriate ethics review for practice-based research”, by establishing the Research Ethics Review Committee (RERC), a professional body ethics review platform.

In referring to the RERC, there are potential advantages of a professional body ethics review quoted in the literature:<sup>32</sup>

1. Research ethics review performed by a professional body is not associated with many of the institutional conflicts of interest that may be present within an institutional REB.
2. Institutions have a number of potentially conflicting goals, while the protection of the public interest is typically a main goal of a professional body. This, in theory, would ensure an ethics review that is mainly focused on protecting the public.

<sup>30</sup> Theoretical Medicine and Bioethics 1999; 20:pp162

<sup>31</sup> CMA Code of Ethics (update 2004), paragraph numbers 38, 39, 40; [http://www.cma.ca/index.cfm/ci\\_id/2419/la\\_id/1.htm](http://www.cma.ca/index.cfm/ci_id/2419/la_id/1.htm); accessed May 1, 2006. The CMA policy statement under the headline “research” reads as follows:

- Ensure that any research in which you participate is evaluated both scientifically and ethically and is approved by a research ethics board that meets current standards of practice.
- Inform the potential research subject, or proxy, about the purpose of the study, its source of funding, the nature and relative probability of harms and benefits, and the nature of your participation including any compensation.
- Before proceeding with the study, obtain the informed consent of the subject, or proxy, and advise prospective subjects that they have the right to decline or withdraw from the study at any time, without prejudice to their ongoing care.

<sup>32</sup> Three advantage of centralized REB taken from: The Journal of Law, Medicine & Ethics, 2004, Vol. 32, No. 2:366

3. The creation of a provincial or professional body REB has the potential to harmonize the review process in a given jurisdiction and to increase the geographic reach of an REB.
4. An REB platform would provide access to industry sponsored and community-based research that does not have access to an institutional REB.

### **3.3.7 Professional or Semi-Professional (Independent/Private) REBs<sup>33</sup>**

In the United States it is increasingly common for academic health centres to outsource ethics review to central ethics review boards, including the independent, for-profit boards such as the Western Institutional Review Board (WIRB). U.S. federal agencies, including the OHRP, the Food and Drug Administration<sup>34</sup> and the National Cancer Institute, have expressly approved outsourcing. The current situation in the U.S. is characterized as follows:

“Even institutions that still rely primarily on their local IRB may be increasingly open to accepting some aspects of central review. ... In fact, with the growth of central IRBs, the focus of the discussion may be shifting from whether to use them to how best to work with them.”<sup>35</sup>

Professional or semi-professional ethics committees potentially offer advantages with respect to efficiency and timeliness of review. Members of such committees are paid to spend part of their professional time on REB duty. A central office handles all administrative issues and manages the process. The implicit danger of a proliferation of various types of ethics review committees is the often quoted ‘forum shopping’ or ‘review shopping’.

Private ethics review boards exist in some jurisdictions, and while they typically have to adhere by national regulations (in the U.S.), they are widely perceived by their clients to outperform the institutional REBs in terms of higher efficiency and faster action. These private boards frequently take one of two forms:

1. the in-house REB, connected to a contract research organization or pharmaceutical company that conducts studies; or
2. the ‘for-hire’, independent, commercial REB comprised of independent contractors.

The primary advantage of independent REBs over institutional REBs is believed to be faster turnaround times. For example, whereas WIRB generally completes reviews in 10 days, estimates for many local REBs are 46 to 102 days.<sup>36</sup> Also, some independent REBs have developed the

<sup>33</sup> This section reflects excerpts from IRB May-June 2005, Vol.27, No. 3: p3. The original paper contains references.

<sup>34</sup> U.S. Dept. of Health and Human Services, Food and Drug Administration. *Guidance for Industry: Using a Centralized IRB Review Process in Multi-centre Clinical Trials*. March 2006.

<sup>35</sup> McNeil C. *Local or central? Debate over institutional review boards continues as alternative options emerge*. Journal of the National Cancer Institute. 2007; 99: 502-503, [jnci.oxfordjournals.org](http://jnci.oxfordjournals.org)

<sup>36</sup> Review time information based on IRB May-June 2005, Vol.27, No.3:3.

capacity to offer specialized review boards (e.g., pediatrics) that might not otherwise be achievable except at specialty centres. On the other hand, independent REBs may find it challenging to achieve critical mass of expertise in highly specialized areas.

While use of independent REBs raises certain conflicts of interest concerns, it can also eliminate those related to institutions that may have financial interests in protocol approval not unlike those of corporate sponsors. There are as yet few data available to assess the quality of either independent reviews or those performed at academic sites.

To prevent biases and 'forum shopping', administrative structures need to be in places that involve exclusive, mandatory jurisdiction, accreditation, and control.<sup>37</sup> Doug Kinsella, a leader in the effort to bring about the reform of Canadian governance for research involving humans,<sup>38</sup> suggested such a system for provincial REBs: Contract research organizations (CROs) and others would be required to pay a license fee for submitting protocols and they would have no direct financial or other link with REB members.<sup>39</sup>

### 3.3.8 Cooperative/Collaborative approaches

Centralization efforts in the context of addressing challenges with the existing local REB system do not always achieve the wide-reaching harmonization effects that were expected from them. As a result a number of hybrid models emerged.<sup>40</sup> These hybrid models are referred to in various ways, with 'cooperative' and sometimes 'collaborative' being the most commonly used terms. They capture the "best of both central and local processes"<sup>41</sup> to streamline the ethics review process and permit institutions to use joint review, rely on another qualified REB, or make similar arrangements to avoid duplication of effort for cooperative research."<sup>42</sup>

According to CentreWatch<sup>43</sup>, in the U.S. independent (centralized) REBs increasingly provide services for industry-sponsored trials and review an increasing amount of research sponsored by the U.S. Department of Health and Human Services (DHHS). However, many sites conduct full REB review regardless of whether an independent REB has previously reviewed the protocol. This

<sup>37</sup> Lemmens, T. *The Rise of Commercial Research Ethics Boards*.

<http://www.chrcrm.org/main/modules/pageworks/index.php?page=015&id=232>, (accessed April 11, 2006)

<sup>38</sup> Dr. Doug Kinsella was the founder of the National Council on the Bioethics of Research Involving Humans. He led the first (and only) systematic survey of the treatment of human subjects by those working in Canadian medical schools. He was a member of the Tri-Council Working Group on Ethics.

<sup>39</sup> Canadians for Health Research website, accessed June 8, 2006:

<http://www.chrcrm.org/main/modules/pageworks/index.php?page=015&id=232>

<sup>40</sup> McNeil C. *Local or central? Debate over institutional review boards continues as alternative options emerge*. *Journal of the National Cancer Institute*. 2007; 99: 502-503.

<sup>41</sup> IRB May-June 2005, Vol.27, No.3:1

<sup>42</sup> IRB May-June 2005, Vol.27, No.3:2

<sup>43</sup> CentreWatch is a Boston-based publishing and information services company and a business of The Thomson Corporation. The company provides information services used by patients, pharmaceutical, biotechnology and medical device companies, CROs and research centres involved in clinical research around the world.

duplication of review creates significant redundancy that could be reduced through more effective use of cooperative models.

Some concerns raised regarding structures for centralized ethics review relate to perceived legal liability by cooperating academic institutions regarding the ability to fully reflect and address local concerns.<sup>44</sup> Given the potential or perceived failure of centralized models to respond to regional differences, some jurisdictions have gone the route of cooperative ethics review by combining centralized and institution-based models (e.g. U.S. National Cancer Institute Central IRB<sup>45</sup>). This mixed system can respond to regional/cultural differences while making it easier for studies in a certain research area (e.g. cancer) to be evaluated by a centralized board.

A review of the relevant literature suggests there may be a trend toward adopting some form of mixed system (*cooperative/collaborative models*) to address the perceived weaknesses embedded in the institutional review and some of the alternative centralized systems. For example, in Europe the implementation of the European Directive on Clinical Trials<sup>46</sup> requires a 'single opinion' from each member state within a relatively short time frame for all industry-sponsored clinical trials. At the EU level, this policy decision is creating a drive toward collaborative and regional models for ethics review.<sup>47</sup>

In some cooperative/collaborative models, institutional ethics review boards at academic medical centres have entered into ongoing agreements in which their REBs have the option of accepting reviews by REBs at other centres when participating in a collaborative or multi-site trial. Participating boards may share information technology and other resources, such as uniform application forms and informed consent templates. Such reciprocal relationships are usually built on common past experience so that members of one board trust the quality of review and soundness of judgment of the other. For example, complex studies requiring expert opinion may benefit from such reciprocal relationships.

At a 2005 NIH workshop, eight options were identified as having some form of departure from traditional local review.<sup>48</sup> For consistency, these options are used in this report to inform the categorization of the collaborative/cooperative models discussed later in the Case Studies Section:

1. Local REBs share common materials and exchange information to facilitate work on multi-site studies (IRBNet)
2. An institution relies on the review of another institution's REB for a particular study

<sup>44</sup> IRB May-June 2005, Vol.27, No.3:3

<sup>45</sup> For examples of models for streamlines ethics review, see 4-IRB May-June 2000, Vol.27, No.3. Koski et.al., present examples of cooperative review, involving centralization (geographically and research area specific) and/or networking of ethics review mechanisms.

<sup>46</sup> For text of European Clinical Trials Directive (2001/20/EC), see: [http://eudract.emea.eu.int/docs/Dir2001-20\\_en.pdf#search=%22clinical%20trials%20directive%202001%2F20%2FEC%22](http://eudract.emea.eu.int/docs/Dir2001-20_en.pdf#search=%22clinical%20trials%20directive%202001%2F20%2FEC%22); accessed September 25, 2006

<sup>47</sup> IRB May-June 2005, Vol.27, No.3:1

<sup>48</sup> National Institute of Health, OHRP, Association of American Medical Colleges, American Society of Clinical Oncology. *Alternative Models of IRB Review: Workshop Summary Report*. November 17-18, 2005.

3. A single independent REB conducts a review on behalf of one or more sites, either for single or multi-site studies (examples include the Western IRB and Chesapeake Research Review, Inc.)
4. A local REB participates in a facilitated review for a multi-site study; following review by a central REB, the local REB accepts, modifies, or reviews its findings (an example is NCI's Central IRB process)
5. A national and regional REB review the same protocol concurrently (an example is the model used by the Indian Health Service)
6. Sites form a consortium and use the REB of one of the sites to review a collaborative protocol (an example is the Multi-centre Academic Clinical Research Organization (MACRO))
7. Sites form a consortium and a new entity is created for review purposes (an example is the Biomedical Research Alliance of New York (BRANY))
8. Multiple REBs review research at a single foreign site (an approach that has been used by the National Institute of Allergy and Infectious Diseases (NIAID))

This scan identified a number of theoretical approaches/models that are reflected in practical approaches or case studies of ethics review systems reforms pursued in various jurisdictions to enhance processes for ethics review of research involving human subjects. Analysis indicates that most ethics review harmonization efforts are either based on centralization alone or show some elements of centralization combined with collaborative features (i.e. having some relationship with local REBs). Within the cooperative/collaborative models, there are various degrees of centralization, ranging from networks of REB collaboration to facilitated review systems with fixed centralized supra-structures.

### **3.4 Tools for System Modification**

In conjunction with efforts to harmonize ethics review by developing new mechanisms and processes, in most jurisdictions parallel efforts have been pursued to improve existing or develop new review guidelines and to enhance ethics education. The following is a high level description of some of these initiatives.

#### **3.4.1 Ethics Education**

In many jurisdictions, authorities have determined that one important contributor to improving the current system of ethics review is to enhance ethics education. This approach does not replace or significantly alter the structure of a given ethics review system, but it is understood to have the potential to contribute to quality improvement and review consistency across Boards.

The current guideline-driven institution-based system does not depend on a legal framework with clear criteria for the assessment of research misconduct or detailed prescriptions for situations in which unethical research behaviour occurs. Such a system relies to a large degree on the ethical and moral conscience of each individual researcher, and thus a common understanding of the issues is a key contributor to consistent, high quality reviews.

In the research community, there is generally a high level of ethical behaviour. When research misconduct occurs it is often understood to arise from a lack of knowledge and or an investigator encountering new areas of ethical challenge, rather than from any unethical or malevolent intent. For researchers, ethics education is seen as one way to achieve a common denominator understanding of what constitutes ethical or unethical conduct.

In Canada, the TCPS describes the process of a continuing ethics review “as a collective responsibility, to be carried out with a common interest in maintaining the highest ethical and scientific standards. Research institutions should strive to educate researchers on the process of a continuing ethics review through workshops, seminars and other educational opportunities”.<sup>49</sup>

In December 2000, U.S. the Office of Research Integrity (ORI) issued the Public Health Service (PHS) Policy on Instruction in the Responsible Conduct of Research (RCR). This policy, which has not yet been approved, would have required mandatory ethics training for all research staff receiving PHS funds (including Administration for Children and Families, Centres for Disease Control and Prevention, Indian Health Service, and the National Institutes of Health).<sup>50</sup> The ORI continues to develop ethics resources and training opportunities that guide research with human participants and some government agencies have integrated education into their funding requirements. The NIH requires all applicants for grants and all REB members to certify that they had received ethics education with respect to research involving human subjects.<sup>51</sup>

### 3.4.2 Guideline Development

Ethics guidelines provide the framework for current ethics review systems. Consequently, gaps in guidelines can contribute to variations in quality and uniformity of reviews. Our literature review revealed evidence of gaps in current international and national guidelines.

Ethics review in most countries is based on a system of national and international guidelines alone; today, there is no international legal regulatory framework governing research with humans. Most national and international guidelines are believed to reflect weaknesses and gaps in addressing the current and evolving needs for ethics review. Given that current ethics guidelines need to support various systems and be applicable to a wide spectrum of context, there are some inherent gaps in

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<sup>49</sup> TCPS, Article 1.13

<sup>50</sup> Online Research Ethics Course [http://ori.hhs.gov/education/products/Montana\\_round1/research\\_ethics.html](http://ori.hhs.gov/education/products/Montana_round1/research_ethics.html); Introduction (accessed April 11, 2006)

<sup>51</sup> The Journal of Legal Medicine, 25: 138

the system and room for improving existing guidelines. The challenges range from lack of consensus on the interpretation and implementation of the widely accepted, and fundamental, national and international guidelines for REBs, to a lack of enforcement mechanisms and a limitation of guidelines to certain aspects of the ethics review process and certain types of ethical issues (such as autonomy and 'non-maleficence', but not, for example, justice and the needs of the community).

Developing provincial/regional or organizational ethics guidelines can address some of those shortcomings by meeting the specific requirements of a jurisdiction or by responding to issues existing in the context of a defined scope for a given ethics review system (geographical or functional). For example, options for guideline improvement can include introducing legislation that creates a more stringent legal framework or drafting of joint guidelines with other jurisdictions to supplement existing national guidelines.

Regulatory steps taken to changes to the current ethics review system vary widely and depend on the context within which ethics review reform occurs, as well as the entity (e.g. jurisdiction, funding organization, or institution) responsible for the ethics review process.

## 4. Selected Case Studies

This section presents further information regarding selected examples that may have particular relevance to efforts designed to enhance mechanisms for the ethics review of human subjects research in B.C. The information in this section is based on a literature review to identify relevant case studies and interviews with selected key informants of representative models to gather information regarding how these models function in the real world of academic health centres and other human subjects research environments across Canada and in the United States, the European Union and Australia.

### 4.1 *Canada*

In Canada ethics review is framed by both federal and provincial regulations. Given that the federal guidelines are broad and leave much room for interpretation at the provincial or institutional level, each province has pursued different approaches to ethics review to meet the specific needs and goals discretely relevant to each jurisdiction.

#### 4.1.1 **Alberta**

In Alberta we found a combination of local boards, cooperative agreements, non-institutional boards and several non-governmental agencies working towards a harmonized system.

##### **College of Physicians and Surgeons of Alberta**

The College of Physicians and Surgeons of Alberta has a Research Ethics Review Committee (RERC), established in 1998, to accommodate physicians who are ineligible for ethics review of research projects at major academic or health institutions and who wish to conduct research involving human subjects.<sup>52</sup> The RERC is constituted following the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans and the Medical Research Council (MRC) standards for review of proposals for research by physicians, to assure that scholarly standards, scientific validity and ethical integrity are achieved. The REB website assists the preparation submissions to the RERC by providing Informed Consent templates for standard and genetic studies and a template for Disclosure of Health Information as well as a wealth of other information.<sup>53</sup>

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<sup>52</sup> College of Physicians and Surgeons of Alberta Research Ethics Review Committee (“RERC”): for multi-centre studies, the first investigator whose application is received at the College for RREB review of a study is designated the “Lead Investigator” and investigators at other sites who submit subsequent applications for the same study are designated “Additional Investigators.” Rev. May 2005. [www.cpsa.ab.ca](http://www.cpsa.ab.ca) Accessed 6/2/07

<sup>53</sup> [http://www.cpsa.ab.ca/collegeprograms/research\\_ethics.asp](http://www.cpsa.ab.ca/collegeprograms/research_ethics.asp)

Unaffiliated researchers other than physicians are supported by the Community Research Ethics Board of Alberta (see AHFMR below).<sup>54</sup>

The University of Calgary and Calgary Regional Health Authority (Calgary RHA) share a Health Research Ethics Board ('Conjoint Health REB' or 'CHREB'),<sup>55</sup> which has become the subject of a reciprocity agreement for multi-centre research entered into among the College of Physicians and Surgeons of Alberta, the Alberta Cancer Board and the University of Alberta (Biomedical Panel)<sup>56</sup> For example, Alberta Cancer Board Ethics Committee will accept the approval of the CHREB for protocols which have investigators at both the Cross Cancer Institute in Edmonton and the Tom Baker Cancer Centre in Calgary.<sup>57</sup>

### **Alberta Heritage Foundation for Medical Research**

The Alberta Research Ethics Community Consensus Initiative (ARECCI), created in 2003, is a joint project of Alberta Heritage Foundation for Medical Research (AHFMR), the Provincial Health Ethics Network (PHEN), the Regional Health Authorities and Alberta Health and Wellness. ARECCI's initial focus was on ethical issues related to quality assurance and the question of whether such research requires ethical review. Now in Phase III, ARECCI's objectives include developing a "consensus amongst participating REBs, health authorities and other stakeholders on what constitutes a quality ethics review".<sup>58</sup> Along with this consensus they strive to increase the clarity, consistency, transparency, and efficiency of ethics screening and review processes and provide tools to implement their recommendations with the hope of influencing health regional, provincial and federal policy related to ethics review processes.

In addition, AHFMR supports the Community Health Ethics Research Review Committee, established to provide researchers who are not registered physicians and without access to a recognized REB the opportunity for ethics reviews of proposed health research.<sup>59</sup> PHEN holds an annual Regional Ethics Representative Forum and promotes ongoing discussion of bioethics.

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<sup>54</sup> Hirtle, M. *Provincial and Territorial Legislation and Regulatory Frameworks on Research Involving Humans, prepared for Ethics and Governance Division*. Health Canada, 2003

<sup>55</sup> The University of Calgary has two REBs, one for the Faculties of Medicine, Nursing, Kinesiology, and the Calgary Health Region ("CHREB") and one for all other faculties ("CFREB")  
<http://www.phen.ab.ca/ecommittees/research.asp#CHERRC> Accessed 10/2/07

<sup>56</sup> The University of Alberta REB has separate Panels for invasive ("biomedical") and non-invasive health research.  
<http://www.phen.ab.ca/ecommittees/research.asp#CHERRC> Accessed 10/2/07

<sup>57</sup> <http://www.phen.ab.ca/ecommittees/research.asp#CHERRC> Accessed 10/2/07

<sup>58</sup> ARECCI Phase III Update (newsletter), February 2007

<sup>59</sup> Hirtle, M. *Provincial and Territorial Legislation and Regulatory Frameworks on Research Involving Humans, prepared for Ethics and Governance Division*. Health Canada, 2003

## 4.1.2 Ontario

### Ontario Cancer Research Ethics Board

In 2003, the Ontario Cancer Research Network (OCRN), in collaboration with Cancer Care Ontario, established The Ontario Cancer Research Ethics Board (OCREB) to meet the urgent need for centralized provincial review of adult oncology multi-site clinical trials, enabling therapeutic improvements to reach patients in a more timely fashion. OCRN studied precedents in the U.S. and the U.K. and conducted an extensive provincial consultation process over two years involving REB chairs, regional cancer centres, host hospitals, investigators, bio-ethicists, research ethics coordinators and collaborating organizations such as the NCEHR, CIHR, and the Canadian Association of Research Ethics.

Originally, OCREB operated as a facilitated review process, allowing full local review where requested but the system has evolved so that OCREB now has authority “to approve, reject, propose modifications to, put on hold or terminate the research project at its sole discretion.”<sup>60</sup> OCREB saw significant increase in the number of multi-centre oncology studies it reviewed within the first two years.<sup>61</sup> Again in 2006 they saw the number of new protocols submitted increase from 31 to 56 and the number of clinical trials submitted more increase from 21 to 54.<sup>62</sup>

OCREB launched three initiatives in 2007 to reduce the workload of investigators and their staff at the local level, enhance patient protection and strengthen communication through: 1) a centralized system for receiving and tracking the myriad reports of external Serious Adverse Events (SAEs), 2) a standardized consent form template, and 3) a monthly open dialogue [teleconference] with local centres. These initiatives will incorporate the Ontario oncology research community and national partners such as the Clinical Trials Group of the National Cancer Institute of Canada, which OCREB reports will “demonstrate the collaborative nature of OCREB’s operations and reflect a strong emphasis on continuous communication.”<sup>63</sup> This is likely partly enabled by the relatively small number of reviews (see above).

OCREB’s streamlined format, which enables more rapid initiation of multi-centre trials, was an important prerequisite for launching the Ontario Institute for Cancer Research in December 2005. OICR’s new centre of excellence in cancer research will require the uniform and efficient system for ethics review of applications from multi-disciplinary and multi-institutional teams that OCREB now provides. One advantage of OCREB is the ongoing monitoring of trials, with SAEs sent from sponsors to OCREB for distribution to sites and notice of actions required at the local level.

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<sup>60</sup> Board of Record Study Agreement [www.oicr.on.ca/OCRN/OCREB\\_Board\\_of\\_Record\\_Study\\_Agreement.DOC](http://www.oicr.on.ca/OCRN/OCREB_Board_of_Record_Study_Agreement.DOC) Accessed 9/20/07

<sup>61</sup> Ontario Cancer Research Ethics Board, Annual Report 2005

<sup>62</sup> [http://www.oicr.on.ca/OICR\\_AR\\_06\\_07.pdf](http://www.oicr.on.ca/OICR_AR_06_07.pdf) Accessed September 17, 2007.

<sup>63</sup> [http://www.oicr.on.ca/OICR\\_AR\\_06\\_07.pdf](http://www.oicr.on.ca/OICR_AR_06_07.pdf) Accessed September 17, 2007.

With mounting evidence of the quality of OCREB's reviews, trust has been established at the local level. OCREB is currently the research ethics board for multi-centre oncology clinical trials in 14 cancer treatment centres in Ontario (out of a total of 29).

### The Toronto Academic Health Sciences Council

The Toronto Academic Health Sciences Council (TAHSC) oversees the partnership arrangement among the University of Toronto and affiliated teaching hospitals. In 2002 TAHSC established several working groups to address diverse health policy issues, including the ethical conduct of research, in general, and “enhanced processes” for review of research involving human subjects.<sup>64</sup> The TAHSC has developed “Harmonized Core Application Guidelines” (shared tools) for all applications involving TAHSC institutions, either directly or through staff acting as investigators at external sites.

### 4.1.3 Quebec

Historically, the province of Quebec has had two kinds of local REBs (designated<sup>65</sup> and non-designated) and a central REB<sup>66</sup> for the review of research involving the participation of minors and legally impaired adults in the absence of an institution with a designated REB. Currently, the Province has more than 100 REBs, of which 50% are designated (plus several private review boards).

The Quebec Ministry of Health has developed a strategic plan — Ministerial Action Plan on Research Ethics and Scientific Integrity (MSSS) — scheduled to go into effect in April 2008 which will apply to research to be conducted at two or more places. Under this plan the Ministry will designate one REB as the primary review board to which the dedicated Principal Investigator for the study will apply. This REB will ensure that the application is reviewed by an REB in each place the study will be conducted under. All necessary revisions from the local REBs will be reviewed and brought forward to the Principal Investigator by the primary REB. Once the study is approved, the primary REB is now responsible for the ongoing monitoring (including SAEs) and periodic renewals of ethics for the research. To bring this concept to fruition it was necessary to negotiate with the Ministry of Education for the right to govern human subjects research conducted at Quebec universities.

The Ministry of Justice has been working on a modification of the sections of the Civil Code defining privacy rights and the duty of confidentiality to include human subjects research with a particular

<sup>64</sup> Ferris, L.E., Singer, P.A., Naylor, C.D. *Better governance in academic health sciences centres: moving beyond the Oivieri/Apotex affair in Toronto*. Journal of Medical Ethics. 2004; 30: 25-29.

<sup>65</sup> McGill University has five REBs. There is currently a reciprocal agreement between McGill and the University of Montreal with respect to multi-centre clinical trials. McGill's Clinical Trials Research Group (CTRG), founded in 1990, investigates ethical and legal questions in human research, including REB responsibilities.

<sup>66</sup> Article 21 of the Civil Code of Quebec

provision that will formalize the centralized system for multi-site review. Research conducted in private medical offices by unaffiliated investigators is not covered by the new centralized system. Before rolling out the new system the Ministry will prepare a roadmap to guide REBs and pharmaceutical sponsors through the multi-site application and review process.

The Fonds de la Recherche en Santé du Québec (FRSQ) is a non-profit funding agency created in 1964 by the Ministry of Development, Innovation and Export Trade and is supported by 19 health research centres. The organization had proposed approaches to centralizing ethics review of multi-centre trials in recent years and in 2005 the FRSQ described its role as “a bridge between the MSSS and the research community”. FRSQ may promote harmonization by creating a model of standardization that may include the development of software for MSSS, standards,<sup>67</sup> uniform applications and common forms for Informed Consent, and research ethics training.<sup>68</sup> Their role will be further defined with a report that they expect to be published in Quebec in the fall of 2007.

An Advisory Group reporting to the FRSQ found a recurring theme of reconciliation between the social value of health research and the protection of human subjects: “We do not believe that scientific advancement and basic rights protection are necessarily opposed.”<sup>69</sup>

### 4.1.4 Newfoundland

The province of Newfoundland and Labrador has four regional Health Authorities: Eastern, Central, Western and Labrador-Grenfell. The Health Care Corporation of St. John’s administers the hospitals and health care facilities within the Eastern Regional Health Authority,<sup>70</sup> including the Health Sciences Centre (i.e. Memorial General Hospital), Janeway Health Sciences Centre (pediatric), St. Clare’s Mercy Hospital and Waterford Hospital (psychiatric). Each of the other three health authorities administers smaller hospitals and health care facilities.

In 2000, the Newfoundland and Labrador (NL) Health Ministry formed an Advisory Working Group comprised of hospital, government and academic representatives. Over a 5 year period, a consensus was reached about how to structure a comprehensive, centralized provincial system for more precise control of human subjects research.<sup>71</sup> Bill 23 was drafted and, in December 2006 an

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<sup>67</sup> In 1994 FRSQ created a Research Ethics and Scientific Integrity Committee, which developed a set of Standards, adopted in 2001 and proposed for inclusion in the Civil Code.

<sup>68</sup> The FRSQ and Research Ethics: Perspectives and Issues, October 2005. Also, see Advisory Group on the Governance Framework for Data Banks and Bio-banks used for Health Research, Report, December 2006

<sup>69</sup> Fonds de la Recherche en Santé du Québec. *Advisory Group Final Report on a Governance Framework for Data Banks and Biobanks Used for Health Research*. 2006.

<sup>70</sup> In 1995 the Health Care Corporation of St. John’s united the hospitals and health care facilities operating in the provincial capital. The Corporation’s Board of Trustees is appointed by the provincial government.

<sup>71</sup> Pullman, D. *Research governance, bio-politics and political will: recent lessons from Newfoundland and Labrador*. *Health Law Review*. 2005; 13: 75-79.

Act to Establish a Health Research Ethics Authority for the Province (Figure 6) was approved by the legislature.<sup>72</sup>

<b>Newfoundland and Labrador Health Research Ethics Authority Act (SNL 2006 Chapter H-1.2, scheduled to be proclaimed August 2008)</b>	
<p><b>Health Research Ethics Authority (“Authority”)</b></p> <p>Authority will be established as a non-profit corporation administered by the Minister appointed under the NL <i>Executive Council Act</i> for purposes of Chapter H-1.2, with power to ensure that health research involving human subjects is conducted in an ethical manner and responsibility to enhance public awareness of the ethical dimension of health research involving human subjects. Authority will be governed by a Board of Directors appointed as follows :</p> <ul style="list-style-type: none"> <li>• Minister appoints 4 directors: (1) person to represent Memorial University (upon consultation with University president, (2) person to represent the Eastern Regional Health Authority (upon consultation with Eastern CEO, (3) person employed in the Minister’s department presided over by the; and (d) person chosen to represent the public</li> <li>• Minister, upon consultation with Memorial University president and Eastern CEO appoints one of the directors as chairperson.</li> <li>• REB chairperson is a member of the Authority but shall not vote at its meetings.</li> <li>• Director appointed for a 3 year term, eligible for second term.</li> </ul> <p>Authority shall, within 2 business days of its receipt, refer an application to the Health Research Ethics Board (HREB) or another REB approved by the Authority</p>	<p><b>Health Research Ethics Board</b></p> <p>Authority, upon consultation with Minister, the president of the Memorial University and Eastern CEO and with reference to TCPS criteria, will appoint Health Research Ethics Board members (10-person minimum).</p> <ul style="list-style-type: none"> <li>• Men and women, and at least 2 persons with experience in the conduct of health research involving human subjects, 1 person knowledgeable in ethics; one person knowledgeable in the law related to health research involving human subjects; and one person to represent the general public.</li> <li>• Authority appoints one of the REB as Chairperson</li> <li>• REB members appointed for 3-year term, eligible for reappointment</li> </ul> <p><b>Other REBs</b></p> <p>Authority may approve other REBs which are (a) not-for-profit and (b) established in conformity with the TCPS.</p> <p>HREB or other approved REB shall consider an application within 30 days of receiving it and may either (a) approve the application; (b) approve the application subject to the changes the board or other body may require; or (c) refuse to approve the application.</p> <p>REB considering an application shall apply one or both of TCPS and ICH-GCP plus other guidelines or standards approved by the Authority and, subject to Authority’s approval and where appropriate, may vary or substitute a standard or rule contained in the TCPS.</p>
<p><b>A person (or corporation) shall not engage in health research involving human subjects without approval for the research from the HREB or another research ethics body approved by the Authority.</b></p>	

**Figure 6: Review of Human Subjects Research in Newfoundland and Labrador**

A transition team and Human Investigation Committee (HIC) are currently in place. When Bill 23 becomes law in the summer of 2008 the Health Research Ethics Authority, a non-profit corporation, will create the Newfoundland and Labrador Health Research Ethics Board (NL-HREB) to replace the HIC. The NL-HREB will be empowered to review all health-related human subjects research and it will have *exclusive* jurisdiction for the review of clinical trials and genetic studies. The HREB will

<sup>72</sup> SNL2006 Chapter H-1.2

have discretion to create sub-committees for medical subspecialties and behavioural research. Funding will come from Memorial University Faculty of Medicine and user fees from commercial sponsors, with any budgetary shortfall to be filled by the provincial government.

Existing TCPS-compliant REBs retain the right to review health research that does not fall within the HREB's exclusive purview. There is currently discussion to develop an accreditation process for these REBs. Regional Health Authorities retain the right to conduct facilities reviews for all research.

The NL legislation subjects all private sector research to the same requirements as research conducted in the public domain or by investigators employed by public institutions. As compensation, sponsors will be allowed to submit applications directly.

The leadership in NL has been working with their counterparts in New Brunswick, Nova Scotia and Prince Edward Island. Their current focus is the development of uniform applications and informed consent documents, but they are considering the consolidation of some areas of review such as oncology.

### 4.1.5 Saskatchewan<sup>73</sup>

The Saskatchewan Academic Health Sciences Network (SAHSN) was formed in 2002 to foster increased coordination between the academic and health service sectors in the province of Saskatchewan. It includes the Saskatoon Health Region, the University of Saskatchewan, Regina Qu'Appelle Health Region, other provincial Health Regions, and the Province of Saskatchewan. The ethical review process for research with human participants has been brought to the attention of the SAHSN Board on many occasions. Improved coordination, streamlined, and expedited approaches to the research ethics review process and among Research Ethics Boards (REBs) have been some of the issues identified. In particular, multi-site reviews, jurisdictional considerations, and liability concerns are paramount to a coordinated approach.

In Saskatchewan, the *Health Information Protection Act* (1999) states that for research purposes, use and disclosure of personal health information can occur if the research project has been approved by a Minister-approved REB. There are several REBs in the province of which four have been Minister-approved. In addition, national developments and inter-provincial initiatives will impact the REBs' mandates, processes, and coordination in Saskatchewan. The SAHSN has recently initiated a Provincial Working Group, with representatives from more than ten different organizations, to develop a collaborative approach to the research ethics review process for health research undertaken in Saskatchewan.

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<sup>73</sup> Information in this section provided by Dr. Susan Blum, Director of Finance and Administration for the Saskatchewan Health Research Foundation.

## 4.2 Canada and the United States: Private Ethics Review Boards

In the United States, as well as Canada, there are numerous independent Research Ethics Review Boards (i.e. venture boards that are independent of organizations that conduct research and are often for-profit). CentreWatch, a U.S. based service provider to the clinical research industry, states that independent REBs may provide services for as much as 40 percent of the market for industry-sponsored trials.<sup>74</sup> While the trend toward private ethics review is stronger in the U.S., independent for-profit ethics boards also exist in Canada. The highly centralized method of review is common to private REBs and may provide greater accessibility for researchers who are not affiliated with a major institution, and for industry sponsored research. They may also be able to provide quicker turnaround times for multi-centre research, particularly when the research is being conducted in more than one state, province or country.

**Institutional Review Board Services (IRBS)**<sup>75</sup> is an example of a well known private review board. The Institutional Review Board (The IRB) of IRBS is constituted and operated according to the rules and regulations as detailed in the Canadian Food & Drug Regulations, Division 5 (Clinical Trials), ICH GCP E6, the Canadian TCPS, U.S. CFR Title 21 Parts 50 and 56, and CFR Title 45 Part 46. IRBS also holds a Federal Wide Assurance with the U.S. Office of Human Research Protections.

Reviews are provided for both American and Canadian multi-centre research, with investigators located in most provinces and states; in Asia as a Central IRB; and elsewhere as an "oversight" IRB to ensure compliance with FDA standards. The IRB reviews hundreds of protocols annually, sponsored by both industry and government. Public sponsors include the NIH, VA, and CIHR. Committee members are compensated on a consulting basis and none of the voting members holds any other financial or other vested interest in IRBS, and as an independent company, IRBS has no financial interest in research projects it is asked to review - all reviews are strictly at arms length.

The genesis of Contract Research Organizations (CROs) may be traced to 1981 when the FDA issued regulations requiring all research under its oversight to receive IRB review, including research conducted by pharmaceutical companies, private offices and institutions too small to have an IRB. For more than a decade after passage of the FDA regulations, the U.S. Office for Protection from Research Risks (OPRR) refused to accept independent ethics review. The OPRR's major objection (which many people still find valid) had to do with the profit incentive of the CRO, which arguably creates a conflict of interest. In 1996 OPRR changed its policy in this regard and OPRR's successor the Office for Human Research Protection (OHRP) not only allowed review by CROs but, in some cases, have encouraged it.<sup>76</sup>

Established in 1996, the REB services offered by 'ethica' are part of a non-profit division of **ethica Clinical Research Inc.**, a Contract Research Organization (CRO).<sup>77</sup> All profits arising from the

<sup>74</sup> CentreWatch 2002, 9 (4): 1. 5-10; quoted in: IRB May-June 2005, Vol.27, No.3:2

<sup>75</sup> <http://www.irbservices.com/>

<sup>76</sup> Forster, D. *Independent institutional review boards*. Seton Hall law Review. 2002; 32:513-523.

<sup>77</sup> <http://www.ethicaclinical.ca/>

services of the REB are re-invested into research subject protection initiatives. They are committed to being an experienced, independent and transparent REB. They are also AAHRPP accredited.<sup>78</sup> Their services include extensive consultation in protocol and form development.

### 4.2.1 The Western Institutional Review Board<sup>79</sup>

The Western Institutional Review Board (WIRB) was created in 1968 as a non-profit board by an unaffiliated scientist in the state of Washington, who needed ethics review to comply with the terms of an NIH grant. Technically, it is not an 'institutional' review board because it is not affiliated with a health care or academic institution engaged in research. The board later reviewed a variety of research for other investigators in the local community, and WIRB was incorporated in 1977 and in 1981 it was reorganized as a for-profit organization. With the changing regulatory environment of the late nineties, WIRB extended its institutional services to several large university REBs and other local REBs.

Headquartered in Olympia, WA, WIRB has been accredited by AAHRPP for five years. It typically reviews protocols for international clinical trials that comply with FDA regulations and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. Its clients include the University of Washington, the Gates Foundation and Johns Hopkins University. WIRB has a streamlined administrative system consisting of 'smart' technology for applications and associated forms and a highly-trained staff with specialized review skills. Depending on the complexity of a protocol, as many as six persons may review an application before sending it to a full Board review.

The deliberative process is also streamlined. WIRB has several conference rooms so that panels can meet simultaneously. Each panel reviews up to six protocols per day. Panel members may be full-time or part-time employees. Three days prior to a scheduled review, each member of the assigned panel receives a CD containing the application for review on a home computer. One member is appointed to give special attention to the consent form. The CD is carried to the meeting and inserted in the laptop available at each member's seat around a conference table. A local representative may be invited to join the discussion.

Voting takes place in a three-tiered process that determines: 1) whether the application is complete, meaning the contents match the items on a checklist; 2) whether the consent form is adequate, as presented by a member, and 3) whether the principal investigator is qualified to conduct the study.

One of WIRB's strengths is its ability to monitor trials both by providing central review of SAEs and site visits. It performs 2500 site visits annually. Every site is visited at least once in 3 years, sites with

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<sup>78</sup> Originally incorporated in Massachusetts under the auspices of Founding Member Public Responsibility in Medicine and Research (PRIM&R), and later incorporated as a non-profit organization in Maryland in 2001, the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) offers accreditation to organizations that conduct or review research with humans. [www.aahrpp.org](http://www.aahrpp.org).

<sup>79</sup> <http://www.wirb.com>

high-risk protocols as often as every six months. It has access to expert consultants and may refuse to do a review if it does not have sufficient expertise (e.g. pediatric oncology, ophthalmology). It is knowledgeable about global health care systems.

In response to Canada's revised research review requirements, WIRB established a panel to review research conducted in Canada, located in Vancouver, B.C. The Panel, whose standing members are Canadian nationals, held its first review meeting in October 2001. When research is found approvable by a U.S. panel, but a site based in Canada submits, the submission is reviewed by WIRB's Canadian panel, which reviews and modifies consent forms according to Health Canada regulations. Language in consent forms approved by the Canadian panel may differ from the language in the approvable consent form as approved by a WIRB U.S. panel. Sponsors of research involving multiple Canadian locations may benefit from requesting an 'approvable' review by WIRB's Canadian panel prior to submitting Canadian investigators for review. WIRB provides services to a growing number of institutions, while continuing to serve independent researchers around the world.

### **4.3 The United States**

In the United States, the predominant mechanism for ethics review is the institution-based ethics review where the local REB's primary function is consideration of local context and oversight of local performance of studies. The local Institution must have a current Federal Wide Assurance (FWA), an Assurance of Compliance approved by the Office for Human Research Protections (OHRP).<sup>80</sup> This mechanism, an equivalent of which does not currently exist in Canada, is a federal harmonization effort striving to achieve consistent quality in ethics review. At the same time, there are numerous attempts in the United States to further harmonize the ethics review system by means of developing and implementing centralized and cooperative/collaborative ethics review mechanisms. These efforts are largely driven by the volume of research occurring in the U.S. and the highly competitive environment for industry sponsored research.

#### **4.3.1 Partners Health Care System**

The Partners Health Care System (Partners) is a private corporation based in Boston. Founded by Massachusetts General Hospital (MGH) and Brigham and Woman's Hospital (BWH), it is one of the world's leading biomedical research organizations, with more than half of its annual research budget funded by NIH.<sup>81</sup> In addition to its two academic medical centres, the Partners also include community hospitals, community health centres, and a physician network.<sup>82</sup> Each institution under Partners has its own REB. The Partners Human Research Committees (PHRC or REB) are responsible for all human subject research ethics review conducted under BWH or MGH.

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<sup>80</sup> See also Section 7.4 "Accreditation".

<sup>81</sup> <http://www.infoed.org> Accessed 9/20/07

<sup>82</sup> <http://www.partners.org/>

In 2004, the Human Research Protection Program for MGH and BWH received full accreditation from the AAPHRPP and provided the incentive for harmonization among REBs within the Partners system. Currently, four hospitals have collaborated: BWH, MGH, Faulkner Hospital (FH) and the Dana-Farber Cancer Institute (DFCI). BWH and MGH have a reciprocal agreement, whereby either REB may serve as the Board of Record for the other. The agreement among BWH, MGH, FH and DFCI requires all adult oncology trials to be reviewed at DFCI on behalf of the other hospitals. The Harvard School of Public Health (HSPH) has entered an agreement with PHRC to accept their review on a case by case basis, particularly wherein investigators collaborate between the institutions, but do not carry out the study at HSPH. Newton Wellesley Hospital has a similar agreement with PHRC. The Shriners Hospital for Children has an “Inter Institutional Amendment” to accept the review of the MGH IRB, and the Spaulding Rehabilitation Hospital has an Inter Institutional Amendment to accept review from MGH, BWH, DFCI and McLean Hospital.

Partners is currently developing software with the potential to serve the needs of a unified system. Each hospital will have the option of adopting the new software program whether they are participants in the harmonized process or not.

### **4.3.2 MACRO**

The Multi-centre Academic Clinical Research Organization (MACRO) had its beginnings at Washington University’s Centre for Clinical Studies in St. Louis, MO. In 2000 MACRO was created through an alliance of five academic health centres with an agreement to cooperate on the REB process for the review of clinical trials protocols through a policy of “limited reciprocity”, meaning that institutions within MACRO can accept the reviews of other MACRO institutions while also addressing local concerns. In practice, one primary reviewing institution shares information with the other trial participants who can perform a local administrative review to assess any local concerns.

MACRO was designed as a distributed network model with standardized operating procedures and performance indices. However, it would still rely on its existing local Research Ethics Review Committees and was therefore dependent upon their schedules. The lead Research REB would still be responsible for ongoing review of trials. The hope was to prove that the MACRO review process would save money and time by reducing redundancy.

The plan was designed to attract commercial sponsors of clinical trials by achieving competitive advantage over larger academic health centres: industry sponsors and Contract Research Organizations (CROs) have access to investigators at leading academic centres with a reciprocal REB approval process authorized by the Office for Human Research Protections (OHRP), via cooperative amendment to its Multiple Project Assurance for compliance with DHHS Regulations. Originally the medical schools at Washington University, Vanderbilt University, the University of Pennsylvania, Baylor College and the University of Alabama at Birmingham agreed to collaborate. The plan was to rotate REBs of record every two years.

After voluntary collaboration for several years, the actual use of MACRO by the participating institutions was limited. Based on the sources accessible to us (interviews and literature search), we were not able to identify sufficient explanation for this phenomenon. Furthermore, to our knowledge there are yet no performance indices clearly measuring the quality of the MACRO review or its efficiency. While MACRO still exists as an entity it now has only two member institutions: Washington University and Vanderbilt University. These institutions are determined to pursue their initial vision with some modifications. In the meantime the Centre for Clinical Studies maintains a staff of 30 employees, including research assistants and data coordinators, who are available to assist investigators (for a fee), and it has entered into a cooperative venture agreement with a major pharmaceutical company.

### 4.3.3 Biomedical Research Alliance of New York (BRANY)

BRANY is one of the largest alliances of research sites in the world. BRANY was started in 1998 through the New York Academy of Medicine and currently includes more than 200 institutions and practice settings.<sup>83</sup> Most BRANY centres are situated in New York State, but it includes centres in 36 other states as well as 10 international centres.

BRANY offers a central REB that is AAHRPP accredited and holds an OHRP Federalwide Assurance (FWA).<sup>84</sup> It is a unique, independent review board that is owned and operated by academic medical centres. It will perform review for any site able to use an independent or central REB as well as for academic sites under BRANY. They advertise increased efficiency through a centralized Board, but sensitivity to and knowledge of local context. A local representative takes part as a guest in the REB meeting if necessary and an REB member may serve as the local representative whenever possible. Members are drawn from participating institutions, and Chairs have usually participated at the REBs of their home institution. BRANY prides itself on having members with diverse and quality expertise. REB members do not receive remuneration.

Services of the REB include assigned project managers, compliance audits by certified staff, weekly REB meetings resulting in notice of decisions within 48 hours of the meeting. BRANY tracks relevant metrics monthly and performs audits to ensure investigator GCP compliance and to educate research staff.

BRANY offers numerous standard form templates, however many are samples and are not required for use. They have also recently introduced a web-based tool for investigators to track their REB applications and monitor their continuing review, to report SAEs and to generate custom forms (e.g. COI declarations, amendment submissions).

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<sup>83</sup> <http://www.brany.com/>

<sup>84</sup> Further details can be found at: <http://www.hhs.gov/ohrp/humansubjects/assurance/filasurt.htm>

The success of delegation of REB review to BRANY by so many institutions is attributed to the diverse institutional representation and leadership, numerous accreditations including modified FWAs and excellent communication.<sup>85</sup>

### 4.3.4 National Cancer Institute Central IRB

The Central IRB Initiative (CIRB) was created to help reduce the administrative burden on local IRBs and streamline multi-centre cancer treatment trials while continuing a high level of protection for human research participants.<sup>86</sup> The CIRB Initiative is sponsored by NCI in consultation with the Department of Health and Human Services Office for Human Research Protection (OHRP).

The initiative began in 1999 as a pilot program for phase III multi-centre trials. Today, the CIRB is composed of two Boards, one for adult and one for pediatric oncology studies.

The Adult CIRB began reviewing studies in January 2001 and has reviewed and approved over 116 Phase 3 adult trials. The Pediatric CIRB began reviewing studies in November of 2004 and has reviewed 63 studies.

An investigator submits directly to the CIRB via the NCI's Clinical Trials Cooperative Group Program.<sup>87</sup> The facilitated review process allows the REB from the investigator's institution to accept the CIRB review of a study while providing concerns related to the local context. Typically, consideration of the CIRB review is conducted by the local REB Chair. The REB may opt to reject the CIRB and continue review with its own Board if necessary. Once the CIRB review is accepted by the local REB, it takes responsibility for the study and conducts all continuing and SAE reviews. The local REB is still responsible for reviewing SAEs at its site and for oversight of local conduct of the study.

Through this process the CIRB aims to enable local REBs to rapidly approve NCI sponsored multi-centre trials, provide consistent standards of review and promote collaboration among local REBs and the investigators that use their services.

An investigation of CIRB efforts noted that as of March 2002, the majority of CIRB protocols were subject to full, rather than facilitated, review by local REBs.<sup>88</sup> As of December 2006, 4,318 reviews were submitted to the CIRB. As reported above, 179 of these (4%) actually received approval indicating that the remainder (96%) received local REB review. There are over 300 'signatory' institutions participating in the initiative, but roughly 50% of these have accepted a CIRB review.

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<sup>85</sup> Koski et al. *Cooperative Research Ethics Boards*. IRB. May-June 2005, Vol.27, No. 3: Hastings Centre.

<sup>86</sup> [www.nciirb.org](http://www.nciirb.org)

<sup>87</sup> Cooperative Groups include researchers, cancer centres, and community physicians throughout the US, Canada, and Europe. The Cooperative Group Program involves more than 1,700 institutions that contribute patients to group-conducted clinical trials. More information is available at: <http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group>

<sup>88</sup> IRB May-June 2005, Vol.27, No.3:pp3., Koski et.al.

The major goal of the CIRB is to decrease the time taken to obtain ethics approval. The system avoids multiple applications for multiple REBs, and aims to improve adverse event review. This may allow non-affiliated investigators such as community physicians, greater access to participation in trials; allow more streamlined collaboration and therefore the opportunity for a greater number of trials with large numbers of sites, including those that involve rare diseases. However, if REBs continue to choose to proceed with full reviews in the majority of cases, the CIRB system could be unnecessarily duplicative and perhaps as burdensome or more than the current REB review process.

### 4.3.5 IRBNet

IRBNet is a set of online communications and documentation collaboration tools created by Dartmouth College and the Children's Hospital of Philadelphia to support the design, management, review and oversight of research involving human subjects.<sup>89</sup> Started in 2001 with a grant from NIH, IRBNet seeks to streamline the exchange of information among researchers, REBs, and sponsors, thereby facilitating the review and oversight process when multiple centres are involved with a single protocol.<sup>90</sup>

By creating an easily accessible and secure medium to assist researchers in the development of a study and allow REBs to communicate within their Board or with other REBs, IRBNet promotes the efficiencies of centralization and electronic communication with the quality afforded by the diverse scientific and ethical expertise of individual REBs. Resources created by experts in various fields of research intend to help a researcher create a protocol and consent forms that will meet federal regulations but allow adaptation to local needs. Researchers can then distribute these forms to multiple research sites easily and with an accessible forum for review. REBs are able to review the status of either local or multi-centre studies, and communicate with other REBs about decisions relating to a common protocol.

IRBNet aims to standardize among REBs as much as possible and lessen the strain on limited REB resources, but still allow variation in local presentation and formatting. Cooperative review is, however, dependant on the willingness of various sites and REBs to use the technology.

## 4.4 European Union

The European Clinical Trial Directive (EU-CTD) was adopted in 2001 and became the law of member countries in 2004. It was designed to simplify and harmonize the regulation of clinical trials in countries belonging to the European Union, consistent with Good Clinical Practice (GCP). GCP is an international ethical and scientific quality standard drafted in 1996 by the International

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<sup>89</sup> [www.IRBNet.org](http://www.IRBNet.org)

<sup>90</sup> Koski, G. et al. *Cooperative Research Ethics Review Boards: A Win-Win Solution?* IRB Ethics and Human Research. Volume 27, No3. 2005: The Hastings Centre

Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) through a consultative process and with consideration of the current good clinical practices of the European Union, Japan, the United States, Australia, Canada, the Nordic countries, and the World Health Organization (WHO) and subsequently accepted by virtually all countries involved in clinical trials.<sup>91</sup> Compliance with the Directive challenged member countries to review current practices and the period of re-evaluation that ensued resulted in much debate and many positive changes.<sup>92</sup>

Research Ethics Boards across the European Union have implemented the EU-CTD to promote a more efficient and effective process. While some such as Denmark, have had some degree of harmonization prior to the EU-CTD, countries such as Hungary, Portugal, Sweden, the U.K. and the Netherlands have adopted new harmonization practices in many different ways. There are some common themes across these countries such as standardizing procedures and application processes and centralizing the oversight and political decisions for REBs. One of the most significant changes in the process is the responsibility of the clinical trial sponsor to apply for ethics approval, an activity that is currently the responsibility of the principal investigator. Another significant regulation that is being adopted by many systems requires an ethics committee to provide a decision within 60 days of receipt of a valid application. This period is suspended if the committee is awaiting response from the applicant on a request for information.

### 4.4.1 Sweden

In January 2004, under a government imposed statute, institution-based ethics committees in Sweden were replaced by six Regional Ethics Committees (RECs) and one central committee, established as independent government bodies.<sup>93</sup> Each of the six RECs is divided into sub-committees (departments) that make independent decisions for the REC on specific fields of research. Each REC is required to have at least one sub-committee specifically for medical research. The administrative leadership, chairpersons and board members are all appointed by the government.

All RECs are designed to be self-financed, and a fee is charged for each application. REC members are provided with a small sum in remuneration for their service.<sup>94</sup> The secretariats for each REC are run from the University associated with its geographical location. The RECs are expected to meet 10 to 12 times a year and all applications to be decided on within 60 days (as per the EU-CTD)

The secretariat for the central committee resides with the Swedish Research Council and is responsible for overseeing the conduct of RECs as well as reviewing specific types of research involving biobanks. The secretariat for the central committee is also responsible for the organization

<sup>91</sup> U.S. Federal Drug Administration, Guidance for Industry, E6 Good Clinical Practice Consolidated Guidance, 1996.

<sup>92</sup> European Forum for Good Clinical Practice: Examining the Value and Impact of the EU Clinical Trial Directive, Brussels, Belgium, May 2005.

<sup>93</sup> <http://www.epn.se/eng/start/index.aspx>

<sup>94</sup> Journal of Medical Ethics 2006;32:483-486:pp483

of the authority and participation in EU work.<sup>95</sup> It may also act as an appeal board for RECs. The Swedish Research Council nominates appropriate Board members to the government for appointment.

For both RECs and the central committee, the Chair and a scientific secretary, who is selected by and from the board members, are responsible for processing applications and dealing with them. The scientific secretary presents each application to the Board at meetings.

For multi-centre studies, only one application for ethics approval from the major research body is required to the REC that is primarily responsible for that jurisdiction.

### 4.4.2 Denmark

Since 1980 Denmark has had a system of research ethics committees with eight regional committees and a national committee: The Danish National Committee on Biomedical Research Ethics. In 1992, the system of review became regulated by law: the Act on the Biomedical Research Ethics Committee System. According to the law, all research projects in Denmark involving human beings or any kind of human tissue, cells etc. require permission from an ethics committee. For clinical trials involving medical devices, the Principal Investigator must also receive approval from the Danish Medicines Agency. It is always the investigator and not the sponsor of research who must apply to the regional ethics committee.

In the case of multi-centre trials, the investigator must only apply for approval from one regional committee, i.e. the regional committee in the area, where the principal investigator carries out the research project. If the project is a multi-national trial, permission from a Danish committee is always required.<sup>96</sup>

The Danish National Committee on Biomedical Research Ethics is composed of members nominated from the Minister of Interior and Health, the Minister of Science, Technology, and Innovation, and two representatives from each regional committee. Their responsibility is to coordinate the regional committees by providing standard guidelines, acting as an appeals committee for every regional committee, and providing recommendations to the government on issues in ethical research. In 2006, recommendations led to an amendment to the Act that will provide greater protection to vulnerable populations.

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<sup>95</sup> Ministry of Education and Cultural Affairs. Statute 2003:617 containing instructions for the Central Ethical Review Boards. October 9, 2003: Stockholm.

<sup>96</sup> See the Danish National Committee on Biomedical Research Ethics: <http://www.cvk.im.dk/visArtikel.asp?artikelID=1537>, accessed September 25, 2006

### 4.4.3 Hungary<sup>97</sup>

Hungary has three levels of ethics review: national, regional and local (institutional). Different categories of research are reviewed on different levels. Legislation implementing the European Clinical Trials Directive has been in place since July 2002, removing the rights of the Hungarian Regional Ethics Committees (RECs) to review certain types of research. Three National Ethics Commissions (NECs): the Scientific and Research Ethics Commission (TUKEB), the Clinical Pharmacology Ethics Commission (KFEB) and the Human Reproduction Commission are independent bodies supervised by the Ministry of Health. RECs review research protocols that do not fall under one of these NECs (e.g. epidemiological studies, research based on biological materials). Many of the members of the NECs are prominent members of regional RECs and receive a quarterly payment for their work as experts.

The Clinical Pharmacology Ethics Commission (KFEB) reviews all clinical trials involving medicinal products. In 2003, over 250 clinical trial studies were reviewed. A study protocol must first be submitted to the National Institute of Pharmacology (NIP), which reviews the regulatory professional and scientific merit issues pertaining to the study. It provides the protocol to the KFEB, which conducts the ethics review of the protocol in parallel to this administrative review, however the NIP must submit its recommendations to the KFEB prior to their meeting and ethical decisions. The NIP is responsible for bringing concerns to the researchers or sponsor and then ultimately grants approval for a study upon completion of the KFEB review. In line with the EU-CTD, the approval process adheres to a 60 day timeframe.

Once approved by either an NEC or REC, the institutional Ethics Committee (EC) evaluates the protocol for feasibility (e.g. appropriate resources such as adequate personnel and medical equipment) and upon approval takes on the responsibility of monitoring the trial and reviewing reported SAE's. If the research is carried out at more than one health care institution, each institution's ethics board has to review the protocol. All ECs report ultimately to the NEC or REC that provided approval.

### 4.4.4 Portugal

Until 2005, institution-based health ethics committees (HECs) had a dual role, acting both as REBs (reviewing research protocols and having the legal power to prevent a trial from taking place in a particular hospital), and as advisory clinical ethics committees, in the case of complex medical issues.<sup>98</sup>

As a result of the EU-CTD, the Ethics Committee for Clinical Investigation (CEIC) as well as the CEIC executive (made up of committee members) was created under the Minister of Health.

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<sup>97</sup> Sandor, J. et al. *National Regulations on Ethics and Research in Hungary*. European Commission, 2003: Brussels.

<sup>98</sup> This section directly informed by: *Journal of Medical Ethics* 2006;32:483-486:p485

Originally the role of CEIC was to oversee HEC operation by providing resources and support, ensuring quality review, and enforcing the 60 day limit for approval. They also assessed clinical trial applications to determine the most appropriate HEC to handle the application. The National Institute of Pharmaceuticals and Medicines, established in 1993, continues to approve and authorize the use of pharmaceuticals and medical products including those used in clinical trials. In practice, the CEIC is now a centralized committee that assesses all clinical trials in Portugal. The 34 members of the CEIC, some of whom are members of existing institutional review committees, were nominated by the government, and include several medical doctors and academics, dentists, pharmacists, nurses, civil servants working for the general health service, jurists, a finance specialist, an economist and a priest. The CEIC acts as the major ethics reviewer, but consults with REBs for local context.

Although there has been a significant increase in clinical trials conducted in Portugal since the CEIC was created, the system has been criticized for lack of increased efficiency.<sup>99</sup>

### 4.4.5 United Kingdom

In the U.K., there are two types of research ethics committees: Local RECs (geographic area equals the catchment of one Strategic Health Authority) and centralized Multi-Centre MRECs (catchment is the whole of the U.K.). The Central Office for Research Ethics Committees (COREC) was established in 2000 by the National Patient Safety Agency (which is part of the National Health Services) to provide help and leadership for Research Ethics Boards in England and the REB system by co-ordinating the development of operational and infrastructure arrangements in support of their work. The concept was to centralize the major part of the review and defer local issues to local boards. In practice, local boards still conducted full reviews so that the initial challenges to the REB system were exacerbated.

After implementation of the EU-CTD in May 2004, REBs in the U.K. became legally accountable to a new government body, the United Kingdom Ethics Committee Authority. (see intro, Section 4.4). With the EU-CTD and the implementation of Standard Operating Procedures (SOPs) for U.K. REBs in March 2004, the U.K. system was overhauled to effectively incorporate these standards and address the problems as identified by an Ad Hoc Advisory Group<sup>100</sup> to increase efficiency in the ethics review process. Reform propositions included reduction of number of local research ethics committees, linking all committees with the central office, elimination of fees for privately-sponsored research, creation of a uniform computerized application and customized software which identifies types of research and leads applicant to relevant questions.

In April of 2007 the National Patient Safety Agency incorporated the COREC and the Research Ethics Committees into the National Research Ethics Service (NRES). There are currently around 190 NHS REBs in the U.K. The purpose of the NRES is to coordinate the REBs in England under

<sup>99</sup> Carvalho, F.L.. *Regulation of Clinical Research and Bioethics in Portugal*. Bioethics. Volume 21, No. 5, pp290 – 302. June 2007: Blackwell Publishing

<sup>100</sup> Department of Health. *Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees*. June 6, 2005: United Kingdom.

the NHS and provide quality oversight to the system; provide a training program for both the REB members and coordinators in England; develop and implement standard operating procedures for REBs across the U.K.; work closely with counterparts in Northern Ireland, Scotland and Wales in discussing issues in research ethics, to create a U.K.-wide framework and explore the implementation of the EU-CTD across the U.K.

The NRES has provided a more streamlined application/review procedure as follows:

- The PI completes application by following instructions that guide the applicant to pertinent sections. A Central Allocation Office informs the PI, upon request, as to which committees are geographically convenient, are suited to that particular field of research (no specialty boards) and have available time to take on new applications (about 120 total number of committees).
- The PI's application indicates their preferred REB to review. Site specific assessments (SSAs) may be required for multi-site research if the procedures are not routine or not low-risk. There is an electronic submission system, but a signed hard copy must accompany applications.
- The NRES performs application validation (checking for omissions or errors) and if necessary, contacts the PI for corrections, or otherwise assigns application to an REB. There are four possible types of REBs that the application can be assigned to: either an authorised REC or one of three types of 'recognised' REBs, which are:
  - Type 1: for Phase 1 clinical trials in healthy volunteers only.
  - Type 2: for single-site or single domain clinical trials that do not fall under type 1.
  - Type 3: for multi-site clinical trials or other research anywhere in the U.K.
- Assigned committee schedules review time and invites the PI to attend. Deliberative process follows ICH-GCP rules even if not considering a clinical trial and the crucial initial question is: has the study been adequately peer-reviewed?
- Decisions must be rendered within 60 days in accordance with the EU-CTD. The final decision options are: 1) favourable, 2) provisional with set of questions, 3) peer review not adequate and 4) unfavourable

In general, there is no expedited review (public health emergency would be an exception) but a pilot project is underway for review when two screeners find "no material ethical issues." At the end of 2007, the NRES will report on the "Fast Track" pilot to develop a screening process for identifying applications which could benefit from early advice to applicants where the submission is unlikely to gain REB approval due to possible incompleteness or poor presentation, studies that were submitted inappropriately, and where a study may require a more in depth expert review.<sup>101</sup>

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<sup>101</sup> <http://www.nres.npsa.nhs.uk/applicants/about/develop.htm>

Plans for the future include further reduction in the total number of committees, evaluation and accreditation of committees, training programs and audits, a system to utilize mock proposals as a quality measurement tool.

Three factors helped make this reform successful: 1) standard operating procedures already formulated by the EU-CTD, 2) software design and 3) budget for the central office staff. The decision to retain local committees was partly due to resistance but also to give PIs the chance to attend and help recruitment of volunteer members.

One of the key differences between the North American and U.K. systems for ethics review is their ultimate accountability/affiliation. In the U.K., Research Ethics Committees are entirely independent of the researcher and the organizations funding and hosting the research. REBs are 'endorsed' by being either recognized or authorized. REBs are recognised by the United Kingdom Ethics Authority by the class of research and geographical area of the REB. Although this avoids potential conflict of interest between an REB and a parent institution, non-health (particularly non-clinical trials of investigational medicinal products) research does not fall under the recognised REB classifications, and many of these types of studies do not require any ethical review. There is not common regulation for research that falls outside of GafREC<sup>102</sup> as the responsibility of ensuring ethical compliance lies with the organisation where the research will take place.

### 4.4.6 The Netherlands

From the 1970's institutional REBs in the Netherlands conducted ethics reviews of research proposals. However, in 1999 Human Subjects Research legislation created The Central Committee on Research involving Human Subjects (CCMO) and also established an accreditation agency. Of the more than 100 committees, 80 applied for accreditation, and resulting approvals caused a rapid decrease in the number of functional committees. Local review boards provide 'Standing Orders' to the CCMO, declaring an area of competence. The CCMO became officially subject to the EU-CTD in March 2006.

The CCMO is responsible for review of specific categories of medical research such as gene therapy, vaccines, and non-therapeutic research with minors and incapacitated subjects (most studies are still reviewed by institutional REBs), maintaining a comprehensive research data base, accreditation of local Medical Research Ethics Committees (MRECs) and promulgation of legally binding directives for MRECs. It also serves as an appeal board for MRECs, provides training to its members, and develops standard procedures and application templates across all boards.

In 2006, a total of 1816 research applications were reviewed. Seventy percent were reviewed by MRECs in academic institutions, 12% by MRECs in hospitals, 17% by non-institutional MRECs and

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<sup>102</sup> This document provides the standards framework for NHS including requirements for ethical approval of research: Department of Health. *Governance arrangements for NHS Research Ethics Committees*. August 3, 2001: United Kingdom.

only 1% by the CCMO. In accordance with the EU-CTD, various documents must be reviewed exclusively by one central body and ethical and scientific review must be handled together with MRECs. Implementation of the EU-CTD required making a determination of available expertise among the members of the CCMO and the need to seek external advice when necessary. The government is committed to re-evaluating the system every four years.

The CCMO accreditation process ensures that an MREC has the appropriate membership, and member training, sufficient resources (including an electronic system of process and communication for committees and applicants and a central tracking database), and participation in CCMO education. The CCMO hosts meetings for MREC Chairs every six months and workshops for staff three or four times per year. The CCMO may also utilize mock research proposals for quality assurance and is willing to withdraw accreditation if MRECs do not comply with ongoing accreditation standards. It is noted that maintaining an accredited committee has positive economic and political implications for hospitals, and therefore they take pride and care in abiding by CCMO standards.

Despite the existence of the CCMO, the system in The Netherlands is characterized as decentralized. There are 32 accredited MRECs but approval of a multi-centre proposal by any one of the MREC's covers all institutions within the country.

Feasibility review by facilities is also required and this can become problematic. For each trial, directors must sign a Feasibility Declaration, but many hospitals still want to do a full review. It is up to the research director to limit this process by submitting only the pertinent portions of the file to the director. To increase transparency, build trust and reduce duplicative efforts, the CCMO hosts meetings for REBs, administration and research bodies involved in the ethics review process on a regular basis.

### **4.5 Australia**

The Australian National Health and Medical Research Council (NHMRC) issued a Statement on Human Experimentation in 1966. A decade later the policy became law and it was eventually extended to research in the humanities or social sciences<sup>103</sup> and restated as The National Statement on Ethical Conduct in Research involving Humans. In 2000 the Strategic Review addressed large multi-centre trials and recommended a uniform application process, an accountability system, central data base and training for ethics committee members.<sup>104</sup> There is currently a National Ethics Application Form to facilitate collaboration at different locations throughout Australia.

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<sup>103</sup> Fitzgerald MH, Phillips PA. *Centralized and non-centralized ethics review: a five nation study*. *Accountability in Research*. 2006; 13:47-74.

<sup>104</sup> Australian Government National Health and Medical Research Council website lists numerous local ethics review committees. <http://www.nhmrc.gov.au/ethics/human/ahec/history/index.htm> Accessed 9/20/07

#### 4.5.1 New South Wales Health

On July 1<sup>st</sup> 2007, NSW Health implemented a system of single ethics and scientific review of research proposals in public health organisations. Key stakeholders rejected reciprocity in favour of a 'Lead Committee' model. One of the factors influencing this choice was the demographics of Australia (geographically vast with low population density). A current multi-centre research proposal conducted within NSW need only obtain approval from one accredited Lead Health Research Ethics Committee (HREC) (local RECs may not be used as the 'lead' if they are not formally accredited to fulfill the lead role). This lead HREC will conduct a single review of multi-centre research on behalf of all sites within the NSW public health system at which a research project is to be conducted, thereby eliminating the need for each local HREC to conduct its own review.<sup>105</sup> A Site Specific Assessment must be conducted by each site involved in the research to approve the conduct at that site. This SSA involves consideration of such matters as resources, staff, and patient availability and may be submitted in parallel to the Lead HREC application. Non-government or academic institutions are not required to follow this single system, but are open to choose to accept the ethical approval of a lead HREC.

The NSW Health Research Ethics Database allows track the number of applications each lead HREC receives, and how long it takes to approve each application. This will assist in ensuring a sufficiently high and uniform standard throughout NSW. The HREC's efficiency and timeliness in measured within a 60 day time frame similar to the EU-CTD (see Section 4.4).

#### 4.5.2 Cancer Institute of New South Wales

The Cancer Institute of New South Wales (CI-NSW) was established by legislative Act in 2003 in recognition of the importance of accelerating improvements in cancer control in NSW and following an ongoing debate about the need to address critical relationships between local ethics boards and research sponsors.<sup>106</sup> This Act requires CI-NSW to provide a system that facilitates expeditious ethical approval for multi-centre clinical trials and other cancer related research.

Prior to the creation of CI-NSW, protocols in New South Wales were reviewed by the Population and Health Services Research Ethics Committee. As of July 2007, the CI-NSW Clinical Research Ethics Committee is also available for review of oncology studies. Applicants may choose another board accredited by the NSW Government of Health as a Lead Committee for an oncology trial but the expectation is that eventually all adult oncology review will be handled by CI-NSW.

Establishing these Research Review Committees is the first step to meet the proposed program of the NSW Cancer Plan 2007-2010 to achieve "high quality single scientific and ethical review of multi-

<sup>105</sup> As described by the NSW Health, <http://www.health.nsw.gov.au/healthethics/researchers.html>

<sup>106</sup> Act No. 14, 2003, repealed the New South Wales Cancer Council Act 1995, described the constitution, objectives and functions of the Cancer Institute (NSW) and provided for registration of the New South Wales Cancer Council as a company.

site cancer research in NSW, and to meet international benchmarks for quality and timeliness of review.”<sup>107</sup> Many of the oncology trials reviewed are international, industry-sponsored and may have been previously approved somewhere else in the world. Plans for pediatric oncology and customized software are underway. Compensation to committee members is also under consideration. The CI-NSW is committed to addressing key barriers to moving forward in streamlining the ethics review process.

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<sup>107</sup> NSW Cancer Plan 2007 – 2010. *Accelerating the Control of Cancer*. June 2006, Cancer Institute New South Wales,

## 5. Matrix: Predominant Ethics Review Models (Decentralized, Centralized and Cooperative/collaborative)

The following matrices relate various features of the models described in Section 3, to each other, and to the five dimensions for analysis (Figure 2). The examples shown in the table below illustrate the use of each type of model, however the examples are not exhaustive and often an application may fall under more than one type of model, particularly when involving collaborations or a combination of central and local review processes. Additional Features of Harmonization describes the other mechanisms in place to facilitate the review model. Often these related closely with other types of models listed and further details about each example may be found under the referenced page. Additional features assume some form of standard application procedure for central review bodies. There are additional models that have been suggested in the literature but have not been explored here through our case studies.

Model Type		Key Characteristics	Potential Effects of the Model - for Consideration (listed are the most specific effects for each model, list is not exhaustive)	Example(s) (not necessarily exclusive to one model type)	Additional Features of Harmonization Example (samples, not exhaustive)	See Rep. page
Decentralized	Institution-based ethics review (local REB review)	Institution-based, local REBs. Decentralized structure.. Exist in institutional context	<ul style="list-style-type: none"> <li>At times inconsistent levels of regulatory control across and between jurisdictions.</li> <li>The status of ethics committees is complex and often ill-defined.</li> <li>Board composition in Canada and elsewhere varies widely.</li> <li>ERCs may not always have sufficient information about potential conflicts of interest or other information relevant to the research to be evaluated.</li> <li>Accountability structures (including monitoring and sanctioning functions) are often ill- defined.</li> <li>Responsibilities for ensuring ethical research are often not clearly assigned.</li> <li>The ERC system can be costly and absorb substantial human resources (staff, faculty, investigators, etc.).<sup>108</sup></li> <li>Institution-based models often require multiple submissions to the various institutional ethics committees, which may result in time delays and administrative inefficiencies, particularly for multi-centre studies.</li> <li>Research performed by industry, or community-based research not governed by public body guidelines and thus falls outside of existing national regulations.</li> <li>It can be difficult for community researchers or privately funded researchers to access an independent ERC and few such committees exist outside major metropolitan areas.</li> </ul>	British Columbia	May share common tools and forms with other institutional REBs.	See footnote <sup>109</sup>

<sup>108</sup> JAMA, September 21, 2005, Vol. 294, No.11:1368

<sup>109</sup> For more information regarding the ethics review process in B.C., please see: The Michael Smith Foundation for Health Research. *The Ethics Review Process in British Columbia: An Environmental Scan*. Vancouver: MSFHR, 2007.

Model Type		Key Characteristics	Potential Effects of the Model - for Consideration (listed are the most specific effects for each model, list is not exhaustive)	Example(s) (not necessarily exclusive to one model type)	Additional Features of Harmonization Example (samples, not exhaustive)	See Rep. page
<b>Centralized Models</b>	<b>Centralized</b>	<p>Research ethics review is conducted by a single, central review board. Principal Investigators have one contact point and one application.</p> <p>Often a central board is responsible for all research of only a specific field or disease within a geographic area, while local or regional boards continue to monitor single site research.</p> <p>Frequently structured training and continuing education.</p> <p>Tracking/monitoring systems are common.</p> <p>One committee review, one request for revisions, one decision.</p>	<ul style="list-style-type: none"> <li>• Lower administrative costs for one review and less demand on limited human resources (improved efficiency).</li> <li>• Greater consistency of review,</li> <li>• Members accumulate knowledge of system.</li> <li>• Improved access to scientific experts in wide variety of disciplines and to community and other lay representatives.</li> <li>• More likely to focus on core ethical issues than details due to uniformity in applications.</li> <li>• Potential to enhance international collaboration.</li> <li>• The lack of beneficial redundancy in the safety net, the potential for increased bureaucracy; larger support staff.</li> <li>• The need to re-evaluate current regulations, and the need for institutions to relinquish autonomy.</li> <li>• Geographically remote for some parties. May be inconvenient for PI to attend meetings.</li> <li>• Lay representatives from community and advocacy groups may feel uncomfortable in this setting.</li> <li>• If used exclusively, may create lack of ability to respond to regional differences in population, culture and other factors influencing study design and/or the review process.</li> </ul>	<p><b>Newfoundland and Labrador (Canada):</b> A Central Health Research Ethics Board (HREB) established to review all health related research including clinical trials and genetic studies. Allows access for industry-sponsored studies. Note: In practice 2008.</p>	<ul style="list-style-type: none"> <li>• Existing local REB continues low-risk or non-health related human subjects ethics review.</li> <li>• Possible subcommittees under central HREB for subspecialties.</li> <li>• Development of accreditation system for local REBs.</li> <li>• Application of government standards.</li> </ul>	27
				<p><b>Portugal:</b> Central EC reviews all clinical trials in the country.</p>	<ul style="list-style-type: none"> <li>• Consultation with local Health Ethics Committees (HECs) if necessary for local context.</li> <li>• Central EC provides oversight and standard guidelines to HECs.</li> </ul>	40
	<b>Professional Body</b>	<p>Iteration of centralized model, but with more ability to respond to specific institutional or disease-based needs.</p> <p>An organization that is independent and without vested interest in the research to be assessed, but with sufficient expertise at hand that a high-quality ethics review can be performed, takes on the role of centralizing the process.</p> <p>Frequently, this role is assumed by medical colleges.</p>	<ul style="list-style-type: none"> <li>• Not associated with many of the institutional conflicts of interest that may be present within an institutional REB.</li> <li>• Protection of public interest is typically a main goal of a professional body. In theory, this would ensure an ethics review that is mainly focused on protecting the public.</li> <li>• May provide greater access for non-affiliated researchers and physicians.</li> </ul>	<p><b>The Canadian Medical Association:</b> CMA and provincial medical colleges increasingly take responsibility for ethics review. Some provincial colleges have policies to deal with issues around research ethics, including industry sponsored research or community-based research (e.g. Manitoba, New Brunswick, Ontario).</p>		17
				<p><b>The College of Physicians and Surgeons (Alberta, Canada):</b> Research Ethics Review Committee for non-affiliated physicians in Alberta.</p>	<ul style="list-style-type: none"> <li>• Standard applications</li> <li>• Templates for different types of informed consent and Disclosure of Health Information.</li> </ul>	24
			<p><b>Alberta Heritage Foundation for Medical Research:</b> Community Health Research Review Committee for non-affiliated, non-physician researchers.</p>		25	

Model Type	Key Characteristics	Potential Effects of the Model - for Consideration (listed are the most specific effects for each model, list is not exhaustive)	Example(s) (not necessarily exclusive to one model type)	Additional Features of Harmonization Example (samples, not exhaustive)	See Rep. page
<b>Professional or Semi-Professional</b> (Independent/Private)	Typically, there are two separate forms of private REBs: 'in-house' REB, which is connected to a contract research organization or pharmaceutical company that conducts studies; and for-hire, independent, commercial REB made up of independent contractors.  Members of such committees are paid to spend all or part of their professional time on REB duty. Typically, a central office handles all administrative issues and manages the process.	<ul style="list-style-type: none"> <li>• Potential for faster turnaround times and often higher efficiency.</li> <li>• May raise certain conflicts of interest concerns, but can also eliminate those related to institutions that may have financial interests in protocol approval.</li> <li>• Independent/private REBs have developed the capacity to offer specialized review boards (e.g., pediatrics) that might not otherwise be achievable except at specialty centres.</li> <li>• The implicit danger of a proliferation of various types of ethics review committees is the often quoted 'forum shopping'.</li> <li>• Independent REBs may find it challenging to achieve critical mass of expertise in highly specialized areas.</li> <li>• There are as yet few data available to assess the quality of either independent reviews.</li> </ul>	<b>WIRB (US/Canada):</b> Central Board for all single or multi-centre research.	<ul style="list-style-type: none"> <li>• Canadian REB provides regional Canada specific REB services such as ensuring Canadian regulation adherence and translation services.</li> <li>• Local study representative invited as guests to REB meetings if necessary.</li> </ul>	32
<b>Disease-specific</b>	Research ethics review conducted by a single, central review board for a specific disease. This is most often utilized for oncology research.	<ul style="list-style-type: none"> <li>• Enhanced expertise in the disease area likely improves review quality</li> <li>• More wide-scale data collection and analysis potential</li> <li>• May provide access to ethics review for all researchers in that area, eliminating the market for private or for-profit- ethics committees.</li> </ul>	<b>OCREB (Ontario, Canada):</b> Central Board for multi-centre oncology studies in Ontario. Acts as the REB for these studies at 14 of a possible 29 research centres in Ontario.	<ul style="list-style-type: none"> <li>• Consultation with REBs at local sites when needed.</li> </ul>	26
<b>Geographically-based</b>	REBs responsible for a specific geographic area.	<ul style="list-style-type: none"> <li>• Allows considerable local context consideration.</li> <li>• Researchers may access REB more easily.</li> <li>• REB may access local knowledge more readily.</li> <li>• Depending on the size of the geographic region may be challenging for some investigators to attend meetings.</li> <li>• Potential to provide easier access for investigators in centres over those in rural and remote areas.</li> </ul>	<b>IRBS (Canada/U.S.):</b> IRBS in Ontario, Quebec, B.C. and Florida provides regional review service, but allows for coordinated central REB for multi-centre trials. It is an independent, private company that does not contract or conduct any clinical research.	<ul style="list-style-type: none"> <li>• Conducted under the central oversight of the NSW Health review system.</li> <li>• Development of custom software</li> </ul>	45
			<b>NSW Health:</b> 'Lead Committee' Model allows a multi-centre study to be reviewed at the main location of research only. Site specific assessments are conducted locally.	<ul style="list-style-type: none"> <li>• Accreditation</li> <li>• Central database tracks activities of all Lead REBs.</li> </ul>	44
<b>Regional Ethics Review</b>	Form of geographically-based ethics review. Each Regional REB would consolidate all activities related to human subjects protection for a given region, while a federal/central oversight body, would coordinate, oversee, monitor, and compile data on all of the Regional Ethics Boards.  Regional Ethics Committees may be composed of several divisions including Research Review Committees, Ethics Policy Committees, and liaisons between institutions/bodies.	<ul style="list-style-type: none"> <li>• Allows considerable local context consideration.</li> <li>• Researchers may access REB more easily.</li> <li>• REB may access local knowledge more readily.</li> <li>• If regions are too small (i.t.o. number of institutions and/or population) there is the risk of lack of REB expertise in all relevant research areas.</li> </ul>	<b>Denmark:</b> Each Regional EC (REC) provides ethics review and a central committee provides oversight. For multi-centre studies, only the REC where the study is being predominantly conducted conducts ethics review.	<ul style="list-style-type: none"> <li>• Central EC acts as appeal board for RECs.</li> <li>• Standard guidelines for all RECs.</li> <li>• Independent central EC monitors.</li> <li>• RECs and provides recommendations to government.</li> </ul>	31
			<b>NRES (U.K.):</b> Applications are fielded by a central body and are then distributed to regional REBs. The regional REBs provide ethics review and the central committee provides oversight.	<ul style="list-style-type: none"> <li>• RECs are 'recognized' by the NRES and are therefore approved to review specific types of research (e.g. Clinical Trials).</li> <li>• Multi-centre studies reviewed by a single recognized REB that works nationally.</li> <li>• Shared Standard Operating Procedures (SOPs) and software among REBs.</li> </ul>	41

Model Type	Key Characteristics	Potential Effects of the Model - for Consideration (listed are the most specific effects for each model, list is not exhaustive)	Example(s) (not necessarily exclusive to one model type)	Additional Features of Harmonization Example (samples, not exhaustive)	See Rep. page	
<b>Cooperative/ collaborative Models</b>	<b>Facilitated (tandem) Review of Single or Multi – centre Studies</b>	A local REB participates in a facilitated review (typically for a multi-site study); following review by a central REB, the local REB accepts, modifies, or reviews its findings.	<ul style="list-style-type: none"> <li>• Potential for elimination of redundant reviews coupled with expertise in specific disease areas, such as pediatric oncology, should increase the availability of clinical trials specific patient groups.</li> </ul>	<p><b>National Cancer Institute and OHRP (U.S.):</b> A central institutional review board (CIRB) for federally funded oncology research. Central REB facilitates the review process for multi-centre studies but allow local input. PedCIRB: NCI has also developed a central board to review NCI-sponsored clinical trials conducted by the Children’s Oncology Group.</p>	<ul style="list-style-type: none"> <li>• Local REB may choose to not use the CIRB system for any study (single or multi-centre).</li> <li>• Increase patient access to clinical trials supported by NCI.</li> </ul>	36
				<p><b>Quebec (Canada):</b> Primary REB designated as single point of application and review for multi-centre trial, but each local REB provides input. Primary REB responsible for ongoing review. Single centre studies continue to be reviewed by the local REB. NOTE: in practice April 2008</p>	<ul style="list-style-type: none"> <li>• FRSQ provides system oversight, consultation and education for this approach under the government.</li> <li>• Development of standard applications and Informed Consent forms underway.</li> </ul>	27
				<p><b>Hungary:</b> Three levels of cooperative review: National level for specific types of research, regional REBs, and institutional REBs to review feasibility.</p>	<ul style="list-style-type: none"> <li>• National administrative review for clinical trials works in tandem with the related national REB.</li> <li>• Institutional REB takes on continuing review once approved by national or regional REB.</li> </ul>	39
	<b>REB Network</b>	A network of regional / national REBs characterized by loose central structures. REBs have a wide geographic reach and share common procedures and paperwork (with room for local modifications)	<ul style="list-style-type: none"> <li>• May facilitate more uniform ethics review (in literature proposed for developing countries) and to simplify REB procedures.</li> <li>• Must take into consideration any cultural or regional differences.</li> </ul>	<p><b>MACRO (U.S.):</b> Agreement among participating institutions allows ‘limited reciprocity’ where an REB may accept another’s multi-centre review but can review for local concerns and regarding facilities. Possibility of a rotating Board of Record among the REBs.</p>	<ul style="list-style-type: none"> <li>• Shared SOPs and performance indices.</li> <li>• ‘One Board of Record’ and ‘Lead REB’ responsible for ongoing review.</li> </ul>	36
	<b>Shared Tools or Resources</b>	Several REBs share common application forms, templates or other tools.	<ul style="list-style-type: none"> <li>• More streamlined administrative process.</li> <li>• May not capture local context.</li> </ul>	<p><b>TAHSC (Toronto, Ontario, Canada):</b> Academic institutions and hospital REBs under the TAHSC share “Harmonized Core Application Guidelines”.</p>	<ul style="list-style-type: none"> <li>• None known.</li> </ul>	27
	<b>REB Cooperation (multi-centre)</b>	Local REBs share common materials and exchange information to facilitate work on multi-site studies.	<ul style="list-style-type: none"> <li>• More streamlined administrative process.</li> </ul>	<p><b>IRBNet (U.S.):</b> Shared documentation and communication tools for multi-centre studies that may be utilized by an REB or investigators.</p>	<ul style="list-style-type: none"> <li>• Protocol preparation assistance for PIs.</li> </ul>	37
	<b>REB Cooperation (Institution relies on another institution’s review)</b>	An institution relies on the review of another institution’s REB for a particular study.	<ul style="list-style-type: none"> <li>• Access to disease or research area expertise for small or local REBs.</li> </ul>	<p><b>NCI CIRB (U.S.):</b> Another institution may accept the CIRB review.</p>	<ul style="list-style-type: none"> <li>• Case by case basis of acceptance..</li> </ul>	36
<b>Consortium</b>	Sites form a consortium and a new entity is created for review purposes. May outsource REB review and study monitoring.	<ul style="list-style-type: none"> <li>• Greater trust among collaborative bodies as they each contribute.</li> <li>• Less demand on site specific resources.</li> <li>• Greater access to scientific experts across a range of disciplines.</li> </ul>	<p><b>BRANY (U.S.):</b> REBs at several institutions share resources with the BRANY REB that acts as a central REB for either single or multi-centre studies.</p>	<ul style="list-style-type: none"> <li>• Accreditation.</li> <li>• Institutions may opt to use local REB.</li> <li>• Web-based application and monitoring for investigators</li> <li>• Standard forms.</li> <li>• Local representative a guest to REB meetings if necessary.</li> </ul>	35	

Model Type	Key Characteristics	Potential Effects of the Model - for Consideration (listed are the most specific effects for each model, list is not exhaustive)	Example(s) (not necessarily exclusive to one model type)	Additional Features of Harmonization Example (samples, not exhaustive)	See Rep. page
<b>Reciprocity</b> (Single or multi-site)	In this cooperative model institutional ethics review boards at academic medical centres have entered into ongoing agreements in which their REBs have the option of accepting reviews by REBs at other centres when both centres are participating in a collaborative or multi-site trial.  Sites may form a consortium and use the REB of one of the sites to review a collaborative protocol.  Participating boards may share information technology and other resources, such as uniform application forms and informed consent templates.	<ul style="list-style-type: none"> <li>Reciprocal relationships are often built on common past experience so that members of one board trust the quality of review and soundness of judgment of the other.</li> <li>Particularly useful for complex studies requiring expert opinion.</li> </ul>	<b>MACRO:</b> Limited reciprocity allows acceptance of another REB's review within the agreement.	<ul style="list-style-type: none"> <li>Shared SOP's and performance indices.</li> <li>'One Board of Record' and 'Lead REB' responsible for ongoing review.</li> </ul>	36
			<b>Alberta, Canada:</b> Approval from any REB within agreement for a multi-site study is accepted by U of Calgary, Calgary RHA, the College of Physicians and Surgeons, U of Alberta, Alberta Cancer Board, and affiliated research centres.	<ul style="list-style-type: none"> <li>U of Calgary and Calgary RHA share a Conjoint Health REB used by both institutions.</li> </ul>	24
			<b>Partners Health Care (MA, U.S.):</b> Several hospitals have agreement to accept the reviews of the other hospital REBs on a case by case, or absolute basis.	<ul style="list-style-type: none"> <li>Shared Board (Partners Human Research Committee) between Brigham and Woman's Hospital and Massachusetts General Hospital.</li> <li>Agreement between hospitals for one to act as the primary oncology specific REB.</li> <li>Development of shared software available to all REBs under Partners.</li> </ul>	33

## 6. Matrix: Five Dimensions for Analysis of Current Ethics Review System

### 6.1 Access

Dimension - Access	Key Challenges related to the Dimension (primarily based on report – other challenges may exist)	Selected Models and Tools to address challenges		Example / Selected Relevant Case Studies	Selected ways in which models address challenges (examples, not exhaustive and not exclusively addressing only one dimension)
<p>This dimension relates to the perception that information is readily available to applicants in order that they may:</p> <ul style="list-style-type: none"> <li>• have access to an REB, know to which REB to apply and how;</li> <li>• have the skills and knowledge to prepare a high quality application;</li> <li>• develop a clear sense of the REB processes, timelines, and decision rules;</li> <li>• know how they can improve their chances of a successful outcome; and</li> <li>• know when they can expect a decision from the REB.</li> </ul>	<ul style="list-style-type: none"> <li>• Institution-based models do not typically enable harmonized or reciprocal regional or national review.</li> <li>• Research that is performed by industry, or community-based research not governed by public body guidelines and may fall outside of existing national regulations (e.g. the Tri-Council Policy Statement on Research Ethics, to which Canada's major research universities are signatory).</li> <li>• It can be difficult for community researchers or privately funded researchers to access an independent REB and few such committees exist outside major metropolitan areas.</li> <li>• The pressures of commercialization and globalization create a climate that increasingly requires accelerated REB approval, causing companies performing clinical trials to favour jurisdictions with the most favourable regulatory environment.<sup>110</sup></li> </ul>	Centralized	Professional or Semi-professional Review (Independent Ethics Boards)	WIRB ethica Institutional Review Board Services (IRBS) Canada	<ul style="list-style-type: none"> <li>• While independent/private ethics boards typically adhere by national regulations, they often outperform the institutional REBs in terms of speed and efficiency. However, no common standards exist, and thus the implicit danger of a proliferation of various types of ethics review committees is the often quoted phenomenon of researchers going 'forum shopping'.</li> </ul>
				Professional Body Ethics Review (REB Platform)	The College of Physicians and Surgeons of Alberta Research Ethics Review Committee (RERC)
		Collaborative	Facilitated (with disease specific features)	NIH National Cancer Institute Central IRB Initiative (CIRB)	<ul style="list-style-type: none"> <li>• The facilitated review process allows the REB from the investigator's institution to accept the CIRB review of a study while providing concerns related to the local context. Through this process the CIRB aims to enable local REBs to rapidly approve NCI sponsored multi-centre trials, provide consistent standards of review and promote collaboration among local REBs and the investigators who use their services.</li> </ul>

<sup>110</sup> Widener L. Symp. J. 31, 2001-2002: pp41

## 6.2 Quality

Dimension - Quality	Key Challenges related to the Dimension (primarily based on report – other challenges may exist)	Selected Models and Tools to address challenges		Example / Selected Relevant Case Studies	Selected ways in which models address challenges (examples, not exhaustive and not exclusively addressing only one dimension)
<p>This dimension relates to the perception that REB decisions are</p> <ul style="list-style-type: none"> <li>• fair;</li> <li>• well-informed;</li> <li>• clearly justified to applicants;</li> <li>• consistent with regulatory and legal obligations of all responsible parties;</li> <li>• include annual recertification of ethics approval through the course of the approved research; and</li> <li>• include site monitoring for compliance through the course of the approved research.</li> </ul>	<ul style="list-style-type: none"> <li>• In the current system, discrepancies between the perceptions of principal investigators and the opinions of REB members and chairs about the quality of the application and review process are not uncommon.</li> <li>• REBs are often overburdened by the volume of research coming before them, a strain that is compounded by concerns about training of REB members and possible conflicts of interest.</li> <li>• The constantly changing nature of research challenges existing notions about what constitutes risks and potential benefits.<sup>111</sup></li> </ul>	Centralized	Disease-specific	NCI has central board (PedCIRB) to review NCI-sponsored clinical trials conducted by the Children's Oncology Group (COG)	<ul style="list-style-type: none"> <li>• Models typically have critical mass of expertise in highly specialized areas.</li> </ul>
		Centralized	Facilitated (with geographic features)	U.K. National Research Ethics Service (NRES)	<ul style="list-style-type: none"> <li>• The NRES has provided a more streamlined application/review procedure and plans for the future include further reduction in the total number of committees, evaluation and accreditation of committees, training programs and audits, a system to utilize mock proposals as a quality measurement tool.</li> </ul>

<sup>111</sup> Prologue: Protecting research participants — a time for change. Report and recommendations of the National Bioethics Advisory Commission. Ethical and Policy Issues in Research Involving Human Subjects. Bethesda: MD, 2001, 288pp

### 6.3 Efficiency

Dimension - Efficiency	Key Challenges related to the Dimension (primarily based on report – other challenges may exist)	Selected Models and Tools to address challenges	Example / Selected Relevant Case Studies	Selected ways in which models address challenges (examples, not exhaustive and not exclusively addressing only one dimension)	
<p><b>Efficiency:</b> This dimension relates to the perception that REB processes are</p> <ul style="list-style-type: none"> <li>• clear;</li> <li>• straightforward;</li> <li>• concluded in a timely manner; and that</li> <li>• REB application activities are not unnecessarily duplicated.</li> </ul>	<ul style="list-style-type: none"> <li>• Generally, there are no clear benchmarks for speed and responsiveness of ethics review committees, nor do common efficiency metrics exist. However, the general notion exists that the ethics review process is too long and does not meet all the needs of researchers and industry.</li> <li>• Accountability structures (including monitoring and sanctioning functions) are often ill-defined.</li> <li>• Responsibilities for ensuring ethical research are often not clearly assigned.</li> <li>• The REB system is tends to be costly and may absorb significant human resources (staff, faculty, investigators, etc.).</li> <li>• Institution-based models often require multiple submissions to the various institutional ethics committees, which may result in time delays and administrative inefficiencies, particularly for multi-centre studies.</li> <li>• Ethics committees are often overworked, and characterized by a duplication of processes, and a lack of clear structures and guidelines. Some rely on voluntary participation of academics who are already taxed by teaching, research, administrative and peer-review duties.</li> </ul>	Centralized	REB Consortium	BRANY	<ul style="list-style-type: none"> <li>• The BRANY REB is an independent review board owned and operated by academic medical centres. It is able to review research projects for U.S. or Canadian sites. Its members include experienced academicians from several premier institutions. The BRANY REB mechanism has a number of quality enhancing features, including a OHRP Federalwide Assurance (FWA), personalized attention for sponsors and investigators, assigned Project Managers, compliance audits conducted by certified staff, REB members and consultants from several geographic locations.</li> </ul>
			Collaborative	REB Reciprocity	MACRO
		REB Cooperation		IRBNet	<ul style="list-style-type: none"> <li>• By creating an easily accessible and secure medium to assist researchers in the development of a study and allow REBs to communicate within their Board or with other REBs, IRBNet promotes the efficiencies of centralization and electronic communication with the effectiveness afforded by the diverse scientific and ethical expertise of individual REBs.</li> </ul>

### 6.4 Capacity

Dimension - Capacity	Key Challenges related to the Dimension (primarily based on report – other challenges may exist)	Selected Models and Tools to address challenges		Example / Selected Relevant Case Studies	Selected ways in which models address challenges (examples, not exhaustive and not exclusively addressing only one dimension)
<p>This dimension relates to the perception that the REB has</p> <ul style="list-style-type: none"> <li>sufficient expertise to assess applications across a spectrum of health research;</li> <li>sufficient frequency of meetings to respond in a timely manner;</li> <li>continuing access to sufficient numbers of willing and qualified board members to manage the demand for ethical review; and</li> <li>sufficient resources to manage the ethics review process effectively.</li> </ul>	<ul style="list-style-type: none"> <li>REBs often face heavy workloads.</li> <li>REB membership is often characterized by a broad range of familiarity with research methodologies and uneven education levels.</li> <li>In today's highly specialized research environment, there are many areas of research, such as genetics and stem cells, where only few scientists are sufficiently well-versed to evaluate ethical implications.</li> <li>The evaluation of risks and benefits in new fields of research may require legal and ethical scholarship in addition to technical expertise.<sup>112</sup></li> </ul>	<b>Centralized</b>	Disease-specific	Ontario Cancer Research Ethics Board (OCREB)	<ul style="list-style-type: none"> <li>Primary goal of OCREB is to reduce the current workload burden of local REBs, increase the quality and uniformity of review and simplify the initiation of multi-centre trials in Ontario. OCREB operated as a facilitated review process, allowing full local review where requested but the system has evolved so that OCREB now has authority to approve, reject, propose modifications to, put on hold or terminate the research project at its sole discretion. OCREB launched three initiatives in 2007 to reduce the workload of investigators and their staff at the local level, enhance patient protection and strengthen communication through: 1) a centralized system for receiving and tracking the myriad reports of external Serious Adverse Events (SAEs), 2) a standardized consent form template, and 3) a monthly open dialogue (teleconference) with local centres.</li> </ul>
			Geographically-based / regional ethics review	Sweden	<ul style="list-style-type: none"> <li>Institution-based ethics committees in Sweden were replaced by six Regional Ethics Committees (RECs) and one central committee, established as independent government bodies. The secretariats for each REC are run from the University associated with its geographical location. The RECs are expected to meet 10–12 times a year and all cases to be decided on within 60 days. For multi-centre studies, only one application for ethics approval from the major research body is required to the REC that is primarily responsible for that jurisdiction.</li> </ul>

<sup>112</sup> Downie J, McDonald F. *Revisioning the oversight of research involving humans in Canada*. Health Law Journal; 2004, 12:159-181.

### 6.5 Consistency

Dimension - Consistency	Key Challenges related to the Dimension (primarily based on report – other challenges may exist)	Selected Models and Tools to address challenges		Example / Selected Relevant Case Studies	Selected ways in which models address challenges (examples, not exhaustive and not exclusively addressing only one dimension)
<p>This dimension relates to the perception that</p> <ul style="list-style-type: none"> <li>the REB subscribes to a recognized standard of quality process, output and outcome;</li> <li>the ethics review process is of uniform quality across the province; and</li> <li>that the same application would receive comparable review and outcome from any B.C. institution's REB.</li> </ul>	<ul style="list-style-type: none"> <li>The current ethics review systems tend to be affected by inconsistent levels of regulatory control across and between jurisdictions.</li> <li>The status of ethics committees – be it legal, administrative or moral – is complex and often still ill-defined.<sup>113</sup></li> <li>Board composition in Canada and elsewhere varies widely<sup>114</sup> and that there is often a discrepancy between the prescribed composition of REBs and reality<sup>115</sup></li> <li>REBs may not always have sufficient information about potential conflicts of interest or other information that may be “crucial to the validity of the research”.<sup>116</sup></li> <li>There is often a lack of comprehensive and detailed guidelines and/or review criteria.</li> </ul>	Centralized	Disease-specific (currently with some collaborative features, but moving toward centralization)	Cancer Institute of New South Wales	<ul style="list-style-type: none"> <li>'Lead Committee' model - One of the factors influencing this choice was the demographics of Australia (geographically vast with low population density). The lead HREC conducts a single review of multi-centre research on behalf of all sites within the NSW public health system at which a research project is to be conducted, thereby eliminating the need for each local HREC to conduct its own review. The NSW Health Research Ethics A central database allows tracking of the number of applications each lead HREC receives, and how long it takes to approve each application. This will assist in ensuring a sufficiently high and uniform standard throughout NSW.</li> </ul>
		Centralized/Regulatory	Accreditation	Netherlands Central Committee on Research involving Human Subjects	<ul style="list-style-type: none"> <li>The CCMO is responsible for review of specific categories of medical research such as gene therapy, vaccines (most studies are still reviewed by institutional REBs), maintaining a comprehensive research data base, accreditation of local Medical Research Ethics Committees (MRECs) and promulgation of legally binding directives for MRECs.</li> <li>The CCMO accreditation process ensures that an MREC has the appropriate membership, member training, sufficient resources (including an electronic system of process and communication for committees and applicants and a central tracking database), and participation in CCMO education.</li> </ul>

<sup>113</sup> European Journal of Health Law 2000, 7:269

<sup>114</sup> J Med Ethics 2006; 32:53 studies have shown that, despite clear TCPS guidelines, board composition in Canada varies widely and that there is often a discrepancy between the prescribed composition of REBs and reality. Scientists are usually well represented, but shortcomings are mainly in the area of ethics and legal representation.

<sup>115</sup> IRB March-April 2005, Vol. 27, No 2:13 Studies in Canada and the U.K. have shown that over three quarters of RECs do not have a statistician (U.K., 85%; Canada, 78%).

<sup>116</sup> Brooklyn Journal of International Law, 2004-05: 790

## 7. Recurring Themes

Based on the findings of our research, four themes emerged that appear to be important contributing factors to successful ethics reform along the five dimensions that frame this analysis: leadership, information technology, trust, and accreditation. Comments related to these themes were repeatedly made by interview subjects with respect to critical elements of a successful ethics review harmonization and could also be identified through our literature review. Each of these themes is discussed briefly below.

### 7.1 Leadership

At a meeting in Ottawa in 2004 the Leaders Forum, convened by the Council for Health Research in Canada, noted the increasingly important role of research in the formulation of evidence-based health care policy.<sup>117</sup> With that principle in mind most health researchers and policy-makers feel a sense of urgency to include the coordination of research ethics review as a priority item in federal, provincial and private sector plans to increase support for clinical research.

Ethics review is an important part of human subjects protection within a complex system of health care delivery, academic medicine, public grants and commercial sponsorship. Leadership is required not only to create consistency and efficiency among institutional REBs but also to assure the quality of oversight throughout the health care system. At the 2005 NIH workshop, from which options were identified that represent a departure from traditional local review (see Section 3.3.8.), some relevant leadership strategies were developed as well:<sup>118</sup>

- Quality
  - Identify independent indicators
  - Provide performance data
  - Provide evidence of benefit
  - Provide training and continuing education
- Coordination with local institutions
  - Ensure all policies and procedures are transparent
  - Conduct site visits
  - Invite reciprocal visits
  - Negotiate agreements that recognize local interests
  - Clearly define division of roles and responsibilities

<sup>117</sup> Steering Committee of the Leaders' Forum for Health Research in Canada. *Strengthening the Foundation of Canada's Health Research Enterprise: A Background Report*. 2004

<sup>118</sup> National Institute of Health, OHRP, Association of American Medical Colleges, American Society of Clinical Oncology. *Alternative Models of IRB Review: Workshop Summary Report*. November 17-18, 2005.

- Consider local representation on central Board
- Develop means for accessing and using local information
- Communicate effectively

Leadership is cited as a critical element in the success of the Biomedical Research Alliance of New York (BRANY) (see Section 5.3.3).

### **7.2 Information Technology (IT)**

Facilitated by the availability of appropriate and affordable technology, the automation of the ethics review process is a fairly recent but increasingly common development. There are currently numerous academic health centres that have developed compatible electronic systems, either through their own resources or through an external software vendor. In Newfoundland information technology was adapted from the Faculty of Medicine's admission's software. In creating the MACRO network Washington University received software from Johns Hopkins University. Partners Healthcare and the University of New South Wales are both customers of InfoEd<sup>119</sup> which is used for grant submissions as well as ethics review.

In our case studies we have found that a state-of-the-art software system, customized and fine-tuned to meet the needs of the environment for which it is intended, is an essential ingredient in any harmonization strategy. A fully automated application and communications system frees administrative and professional time to focus on important substantive issues.

IRBNet was developed through a cooperative venture of Dartmouth College and The Children's Hospital of Philadelphia and funded under the NIH program for Human Subjects Research Enhancement Awards (see Section 4.3.5). The IRBNet software seeks to leverage the scientific and ethical expertise of individual IRBs by creating an environment for cooperative (or facilitated) review of multi-site research protocols.<sup>120</sup> This software is designed as a 3-phase process: 1) study design, 2) study distribution and 3) ethics review. IRBNet is designed for multi-centre review. "[T]he initial and any subsequent IRB reviews can be shared with other IRBs who have reviewed the same study. When viewing the study details, an IRB Administrator will see if a study has been submitted to other IRBs, the status of those IRB reviews, and whether there are IRB comments available for review." IRBNet has the potential to provide the framework for a national computer database of all multicentre protocols.<sup>121</sup>

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<sup>119</sup> [www.infoed.org](http://www.infoed.org) Accessed 9/20/07

<sup>120</sup> [www.irbnet.org](http://www.irbnet.org) Accessed 9/20/07.

<sup>121</sup> Jansen L. *Local IRBs, Multi-centre Trials, and the Ethics of Internal Amendments*. IRB: Ethics and Human Research. 2005; 27:7-11

The University of British Columbia also uses an electronic application platform called the Researcher Information Services (RISe). It used by four REBs associated with the University to allow online submission, tracking, renewal and amendment of ethics applications.<sup>122</sup>

A commercial software vendor, ClickCommerce,<sup>123</sup> describes the potential capabilities of an electronic ethics review administrative system as follows:

- Submission of Study Data:

PI and study team members collaborate in completing application and required forms for new studies, modifications, SAEs and continuing review. Software intelligently uses PIs responses to particular application questions to guide applicant through the right set of forms, according to whether a study is biomedical, behavioural, cancer-related or one of many other specialties, and prompts the PI or Study Coordinator for missing information such as such as biosafety, radiation, and gene therapy forms. Administrators can include help text and web links to answer researchers' questions in the application process. Upon submission application is automatically routed to designated persons.

- Agenda Construction and Meeting Minutes

Administrators tag a study as expedited, full review, exempt or 'other' and system schedules the study, notifies members of the complete agenda and provides reviewers with links to studies they'll be responsible for presenting in the next meeting. Administrators, Committee Chairs and Primary and Secondary Reviewers have ability to provide feedback to the PI team. After a meeting the system helps administrator to process stipulations and prepare and distribute minutes. System automatically notifies PI teams of meeting results and timing for study clarifications, changes or approval reviews.

- Integrated and Secure Management Reporting and Audit Trail

Entry into system is password protected and each user sees only specific kinds of information. All study information is contained in a secure Study Workspace. Confidential data remains in the server.

While this description of technology use in ethics review is not representative or exhaustive, it provides an example of the potential process enhancing implications of technology for all dimensions: access, quality, efficiency, capacity and consistency.

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<sup>122</sup> For more information please see: The Michael Smith Foundation for Health Research. *The Ethics Review Process in British Columbia: An Environmental Scan*. Vancouver: MSFHR, 2007.

<sup>123</sup> [www.clickcommerce.com](http://www.clickcommerce.com) Accessed 9/20/07.

### 7.3 Trust

In the debate of harmonizing the ethics review process, one question that ranks at the meta-level of the discussion, is whether, a priori, researchers should be trusted or controlled. This somewhat sensitive issue is directly linked to (or, it could be argued, must precede) decisions around which ethics review model is preferable within a jurisdiction.

Whether, for example, a more regulatory position is taken that embeds ethics committees in to the legal system of a country, or whether a guideline system is favoured that leaves the interpretation of guidelines and managing of the details of the ethics process in the hands of institutions, depends on the overall philosophical view of ethics review.

The concept of 'trust' assumes that researchers will do their utmost to ensure ethical research and that the process of scientific dialogue (through peer review) will ensure sufficient guidance and control over new and ongoing research.

The 'control' concept assumes that the system cannot be self-regulatory and that clear and detailed regulations are the best way to ensure ethical research. The trust concept tends to enable research first and then address potential unethical behaviour. The control (danger of stifling research but preventing unethical research) tends to focus on protecting research subjects first and within that allow research to happen.

While in essence the two concepts are not far apart there is, however, an important philosophical difference in these two approaches that, depending on which one is taken, frames the discussion around ethics review in a diametrical way.

The accountability of public or private bodies involved in ethics review is toward the individual participants of a study, to society as a whole, which "provides the resources for research and will be ultimately be affected by the results", and toward the researchers.<sup>124</sup>

An expert in administrative law suggests that "trust in institutions arises not simply as a result of openness in government, responses to local interest groups, or priorities emphasized in the press ... but also from those institutions' doing a difficult job well."<sup>125</sup> Others compare institutional review with hands-on professional and personal responsibility:

"The responsibility for ensuring [ethical human research] ... falls primarily to those who propose and conduct the research ... One of the most serious flaws in the current system for human subjects research is a direct but unintended consequences of the implementation of the institutional review board review process, namely that

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<sup>124</sup> BMC Medical Ethics 2002, 3:7

<sup>125</sup> Breyer S. *Breaking the Vicious Circle: Toward Effective Risk Regulation*. Cambridge: Harvard University Press, 1993.

investigators have been allowed to delegate their personal responsibility for the ethical considerations of their work to the institutional review board. ...

“Even when proposed research is extensively vetted within the scientific community and approved by an institutional review board, questions may arise regarding the adequacy of the design of studies on both scientific and ethical grounds. Indeed, responsible scientists have an obligation to question their own work and the work of others.”<sup>126</sup>

Goodyear-Smith et. Al. suggest that “The preferable focus should be the promotion of ethical research, but not the prevention of unethical research, which inevitably results in researchers being impeded from doing their work.”

Overall, for a coordinated system to work effectively, efficiently and with high quality results, there needs to be trust among individuals (investigators, patients, board chairs, members and administrators, academics, physicians, ethicists and lawyers) and among institutions and communities (government agencies, academia, hospitals, various REBs, vulnerable populations and ethnic groups). Clearly, a centralized or co-operative model is fundamentally contingent upon the trust that each institution has in the central REB or in the REBs of the other institutions cooperating in the network. Without that trust, institutions will be unwilling to cede responsibility for ethical review to another body or each other.

### **7.4 Accreditation**

Accreditation has been a catalyst in many efforts to streamline ethics review and is a key element in some of the plans to develop harmonized systems.

In Canada formal accreditation of institutional ethics review boards does not currently exist. However, there are a number of efforts to develop a national ethics review board accreditation mechanism.

In the face of international pressure for national regulations consistent with global standards for the conduct of clinical trials,<sup>127</sup> Health Canada and leading health research organizations had recognized the need for more systematic governance of research involving humans. As a result, in June 2003, the House of Commons Standing Committee on Health discussed the absence of a regulatory framework for REBs and recommended that Health Canada develop an REB accreditation process relative to clinical trials.<sup>128</sup>

<sup>126</sup> Koski, G. *Ethics, science, and oversight of critical care research*. The Office for Human Research Protections, American Journal of Respiratory Critical Care Medicine. 2004; 169: 982-986

<sup>127</sup> Hirtle, M. *Provincial and Territorial Legislation and Regulatory Frameworks on Research Involving Humans*. prepared for Ethics and Governance Division, Health Canada, 2003

<sup>128</sup> Lemmens, T. *Federal regulation of REB review of clinical trials: A modest but easy sep towards an accountable REB review structure in Canada*. Health Law Review. 2005, 13: 39-50.

In the same year, the National Council on Ethics in Human Research (NCEHR) mandated a task force to develop an accreditation system.<sup>129</sup> NCEHR is a national organization mandated to advance the protection and well-being of human participants in research and to foster high ethical standards for the conduct of research involving humans.<sup>130</sup>

The organization is currently working toward an accreditation process.<sup>131</sup> The NCEHR Task Force on Accreditation was established to make recommendations for the development of an accreditation system for human research protection programs. According to its final report<sup>132</sup>, the Task Force has, based on broad consultations, described the characteristics of a system of accreditation for Programs Ensuring Ethical Research with Humans (PEERH), which include recommendations for the establishment of a voluntary accreditation mechanism, as well as a set of standards defining performance expectations, structures and processes for ethics review.

The three proposed standards relate to a program ensuring ethical research with humans; research ethics board composition and operations; and research ethics board review methods and processes. The Task Force has described a proposed cycle of accreditation, involving a period of guided self-study by the organization seeking accreditation, a site visit by peers, a draft report to which the organization responds and the issuance of a final report to the accrediting entity, which determines the accreditation status. Accreditation would be for a limited term. The report describes a proposed organization for the accrediting entity, to be located within NCEHR, but independently funded.

Building on the NCEHR Task Force recommendations, another initiative to develop an accreditation system comes from the Sponsors Table for Human Research Participant Protection in Canada, ([www.hrppc.pphrc.ca](http://www.hrppc.pphrc.ca)). The Sponsors Table is a group of organizations which share a common interest in promoting research that meets the highest standards in excellence and ethics. An Experts Committee established by the Sponsors Table to provide independent analysis and recommendations met for the first time in September 2006 and submitted a draft report in August 2007.<sup>133</sup> The report discussed accreditation models in Canada and the United States and proposed a new Canadian oversight system for research involving humans.

The Experts Committee Report proposes the creation of a *Canadian Council for the Protection of Human Research Participants* with three interrelated functions: policy, education, and accreditation. Implementation would require all research involving humans conducted in Canada or by Canadians to receive prospective ethical review and ongoing oversight from an REB following the Canadian Policy Statement on Research Involving Humans (CPSRIH) and operating within the accredited

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<sup>129</sup> [www.ncehr-cnerh.org](http://www.ncehr-cnerh.org) Accessed 6/1/07

<sup>130</sup> [www.ncehr-cnerh.org](http://www.ncehr-cnerh.org)

<sup>131</sup> For the Final Report of the NCEHR Task Force on Accreditation: *Promoting Ethical Research with Humans*, see: [http://www.ncehr-cnerh.org/english/task\\_force.php](http://www.ncehr-cnerh.org/english/task_force.php).

<sup>132</sup> For Final Task Force Report "Promoting Ethical Research with Humans, March 2006, see: [http://www.ncehr-cnerh.org/english/task\\_force.php](http://www.ncehr-cnerh.org/english/task_force.php)

<sup>133</sup> Sponsors Table, *Moving Ahead: Draft Report of the Experts Committee for Human Research Participant Protection in Canada*, August 15, 2007

Programs for Ensuring Ethical Research with Humans (PEERH). Stakeholder consultation on the report is ongoing at the present time; if adopted, the recommended changes have the potential to influence research ethics review in Canada and in B.C.

The discussion of ethics board accreditation in Canada precedes the founding of NCEHR. The Canadian Council on Health Services Accreditation (CCHSA) is a national accrediting body established in 1958. In 2003 CCHSA presented its strategies for measuring and improving quality at an international REB forum held in Quebec:<sup>134</sup>

- Define ‘quality’ and specify dimensions linked to standards
- Build QI into standards
- Establish indicators and monitoring
- Build accreditation into day-to-day activities
- Establish a regular accreditation cycle
  - Self-assessment
  - Site visits by surveyors
  - Survey reports
  - Survey recommendations; it stated that 83% of its recommendations had been implemented and 62% of respondents believed the accreditation process helped improve quality. In the conference report CCHSA shared its

Furthermore, in 2007 the Provincial Health Ethics Network (PHEN), an Alberta non-profit organization which provides resources on addressing ethical issues related to health, solicited feedback from its members and others interested in health ethics concerning the CCHSA’s draft ethics-related accreditation program.<sup>135</sup>

“Participants commended CCHSA on its effort to further strengthen the complex role of ethics in Canadian health care. Health care organizations are increasingly using the CCHSA’s Accreditation Programme as a guide for incorporating the consideration of ethical issues into their organizations’ cultures. It was felt that the pervasiveness of ethical issues in the delivery and planning of health systems was well recognized within this new Draft Programme as evidenced by the many standards containing references to the need for ethical reflection and action. While numerous participants felt that the Programme was successful in more comprehensively incorporating ethical considerations into the standards, a significant number commented that the picture of ethics used throughout the documents was

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<sup>134</sup> International Conference on Canadian and American Perspectives on Quality Improvement and Performance Evaluation in Systems of Human Research Protection, Montreal, October 2003

<sup>135</sup> Provincial Health Ethics Network, Review of Canadian Council on Health Services Accreditation (CCHSA) Draft Accreditation Programme 2008, Submitted July 2007

narrower than justified. For the most part, the standards address values, frameworks, principles, guidelines, codes of conduct and policies, which are part of the ethical life of people and organizations, but are not the only important considerations. It was suggested that the Programme also consider ways of cultivating appropriate attitudes, habits, virtues, cultures, and environments within health organizations. In this way, participants felt that the standards echoed a somewhat bureaucratic or managerial view of ethics that focused more on compliance and less on how to foster an ethical culture within an organization that enables people to put values into practice.”<sup>136</sup>

Notably reflected in the comments received from the PHEN survey is the notion of addressing the cultural context around ethics review at the system level, not merely at the individual level, to support regulatory and process based efforts to harmonize ethics review. This notion is closely linked to the findings summarized under the headline ‘trust’, above.

Contrary to the situation in Canada, in the U.S. the majority of medical schools (80%) are accredited or are working toward accreditation for their human research protection programs (including REBs). The accreditation process assesses the REBs against rigorous national standards set by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).<sup>137</sup> Incorporated as a non-profit organization in Maryland in 2001, AAHRPP offers accreditation to organizations that conduct or review research with humans.

Parallel to accreditation in the United States another mechanisms exists that assures standards and common understanding of rules and responsibilities in conducting research with humans: Under the Department of Health and Human Services (DHHS) human subjects protection regulations (at 45 C.F.R. 46.103), every institution engaged in human subjects research that is funded or conducted by DHHS must obtain an Assurance Of Compliance approved by the Office for Human Research Protections (OHRP). This “Assurance of Compliance”, when granted, is called a Federalwide Assurance (FWA). Both awardee institutions and collaborating "performance site" institutions must file Assurances. The awardee is responsible for ensuring that all collaborating institutions engaged in the research hold an OHRP approved Assurance prior to their initiation of the research.

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<sup>136</sup> *ibid*

<sup>137</sup> JAMA. September 21, 2005, Vol. 294, No. 11:1368; and: Association for the Accreditation of Human Research Protection Programs, Inc. [www.aahrpp.org](http://www.aahrpp.org), accessed April 11, 2006

## 8. Concluding Observations

This research project has found a wide array of models for ethics review. Any potential efforts to reform or revise the current, predominantly institution-based ethics review system in B.C. will necessarily have to balance the need to support and facilitate research while at the same time ensuring protection of research subjects. Both in the current ethics review literature, and as reflected in the scan and survey undertaken by MSFHR for this initiative, it would appear that some important characteristics of an accountable, effective and efficient system include:

- Quality processes that ensure highest levels of ethical research conduct;
- Uniform, harmonized and reciprocal processes across/between jurisdictions;
- Transparent and clear guidelines and processes;
- Clear accountability structures;
- Administratively effective and cost-efficient processes (e.g. reciprocity to eliminate or reduce requirements for multiple submissions for single study; effective review mechanisms for highly-specialized, disease-specific studies);
- Broad accessibility (for studies outside the current institutional review system, e.g. community based research); and
- Responsiveness to different/local research environments (geographic, ethnic, cultural, populations, etc.).

Most of the models described in the literature also exist in some form in the 'real world'. While there have been many attempts to create the most accessible, effective, efficient, and uniform ethics review system, no one system has emerged as the most likely to succeed in achieving the above goals.

Naturally, the contexts within which ethics review occurs are as diverse as the models and mechanisms that have been developed. Which of the systems or combination of systems could work in a given jurisdiction would likely depend on factors such as:

- Number and nature of research institutions involved
- Predominant types of research to be reviewed, and range of types
- Geographic distribution of participating research institutions
- Level and nature of lack of access to ethics review in participating jurisdictions
- Opinions and interests of the research community
- Opinions and interests of research managers (stakeholders)

- Legal and institutional contexts

A thorough analysis of stakeholder interests as well as a detailed assessment of the research infrastructure in a given jurisdiction can provide critical support to any decision-making on adopting new models for ethics review.

Hence, any effective plan to enhance processes for ethics review must address the realities of the system to be served, in the light of contemporary international standards; the increasing volume of collaborative and multi-site studies requiring review; opportunities for efficiency and interactive communication offered by electronic systems; and the need for evidence-based mechanisms to monitor and assure performance quality.

In this context and based on the findings of our scan, four overarching themes emerged that appear to be important contributing factors in successful ethics reform: leadership, information technology, trust, and accreditation.

In considering the themes, accreditation and information technology can be likely be capitalized on more effectively for the purpose of creating an increasingly efficient system, if supported by the two remaining themes: strong and collaborative leadership in conjunction with a culture that nurtures and develops trust among all participating parties.

## Appendix A Participants in an Environmental Scan of Ethics Review Processes

<b>International Survey of Harmonized Ethics Review MSFHR Telephone Interviews: July — October 2007</b>		
<b>Organization</b>	<b>Governance</b>	<b>Location</b>
Alberta Research Ethics Community Consensus Initiative (ARECCI)	Non-Profit - Alberta Heritage Foundation for Medical Research	Edmonton
Cancer Institute of New South Wales	Public Health System	Australia
Central Committee on Research Involving Human Subjects (CCMO)		The Hague, Netherlands
Fond de la Recherche en Santé Québec	Ministry of Development, Innovation and Export Trade	Montreal
Multi-centre Academic Clinical Research Organization (MACRO)	Private Network: Washington University and Vanderbilt University	St. Louis
National Research Ethics Service	U.K. - National Health Service	London
Newfoundland and Labrador HIC		St. John's
Ontario Cancer Research Ethics Board		
Partners Health Care System	Harvard University School of Medicine Teaching Hospitals	Boston
Saskatchewan	Public Health System	Saskatoon
Western Institutional Review Board (WIRB)	For-profit Contract Research Organization	Olympia and Vancouver
<b>Thanks also to Dr. Greg Koski of the MGH Institute of Health Policy and Dr. Michael McDonald of the UBC Centre of Applied Ethics for sharing their insights.</b>		

## Appendix B Acronyms and Abbreviations

AAHRPP	Association for the Accreditation of Human Research Protection Programs(U.S.)
AHFMR	Alberta Heritage Foundation for Medical Research
ARECCI	The Alberta Research Ethics Community Consensus Initiative
B.C.	British Columbia
BRANY	Biomedical Research Alliance of New York
BWH	Brigham and Woman’s Hospital
CCMO	Central Committee on Research involving Human Subjects (Netherlands)
CIHR	Canadian Institutes for Health Research
CI-NSW	Cancer Institute of New South Wales (Australia)
CIRB	Central Institutional Review Board (U.S.)
CMA	Canadian Medical Association
COG	Children’s Oncology Group (NCI, U.S.)
COREC	Central Office for Research Ethics Committees (England)
CRO	Contract Research Organization
DFCI	Dana-Farber Cancer Institute
DHHS	Department of Health and Human Services (U.S.)
DSMB	Data Safety and Monitoring Board
EU-CTD	European Union Clinical Trials Directive
FDA	Food and Drug Administration (U.S.)
FRSQ	Fonds de la Recherche en Santé Québec
FWA	Federal-wide Assurance (U.S.)
HEC	Health Ethics Committee
HIC	Human Investigation Committee (Newfoundland)
HREB	Human Research Ethics Board
HSPH	Harvard School of Public Health
ICH – GCP	International Conference on Harmonization – Good Clinical Practice
IRB(s)	Institutional Review Board(s) (U.S.)
IRBS	Institutional Review Board Services
LREC	Local Research Ethics Committee
MACRO	Multi-centre Academic Clinical Research Organization
MGH	Massachusetts General Hospital
MRC	Medical Research Council
MREC	Multi-centre Research Ethics Committee (U.K.) or Medical Research Ethics Committee (Netherlands)

MSFHR	Michael Smith Foundation for Health Research
MSSS	Ministerial Action Plan on Research Ethics and Scientific Integrity (Quebec)
NCEHR	National Council on Ethics in Human Research
NCI	Nation Cancer Institute
NEC	National Ethics Committee
NHMRC	National Health and Medical Research Council (Australia)
NIAID	National Institute of Allergy and Infectious Disease (U.S.)
NIH	National Institute of Health (U.S.)
NL	Newfoundland and Labrador
NRES	National Research Ethics Service (England)
NSERC	Natural Sciences and Engineering Research Council
NSW	New South Wales (Australia)
OCREB	Ontario Cancer Research Ethics Board
OCRN	Ontario Cancer Research Network
OHRP	Office of Human Research Protection (U.S.)
OPRR	Office for Protection from Research Risks (U.S.)
ORI	Office of Research Integrity (U.S.)
PHRC	Partners Human Research Committees
PHS	Public Health Service (U.S.)
PI	Principal Investigator
PRE	Interagency Advisory Panel on Research Ethics
RCR	Responsible Conduct of Research
REB	Research Ethics Board
REC	Research Ethics Committee
RegEB	Regional Ethics Board
RERC	Research Ethics Review Committee
RHC	Regional Health Authority
SAHSN	Saskatchewan Academic Health Sciences Network
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SSA	Site Specific Assessment
SSHRC	Social Sciences and Humanities Research Council
TCPS	Tri-Council Policy Statement for Research Involving Human Subjects
WHO	World Health Organization
WIRB	Western Institutional Review Board



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