Background Paper for Health Canada

International and Canadian Activities Related to the Ethical Review of Clinical Trials

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Background Paper

International and Canadian Activities Related to the Ethical Review of Clinical Trials

1. Introduction

1.1. Purpose and Scope

The intent of this background paper is to describe the range of accreditation systems that have been established in other countries as well as the provincial initiatives that have been implemented to promote high quality clinical research with improved protections for human research participants. Consistent with Health Canada's mandate, the focus will be on biomedical clinical trials involving health products.

1.2. Background

1.2.1. Historical Perspectives on Good Clinical Practices

Any history of research ethics begins with the Nuremberg Code and the Declaration of Helsinki as definitive documents that introduced the concepts of voluntary participation, informed consent and ethical review of research. The ethical principles that are fundamental to scientific research with humans were developed in parallel in Canada[1], the United States[2] and elsewhere through the 1970s. Many countries introduced or strengthened laws, regulations and guidelines related to research involving regulated health products in response to tragedies involving regulated products (e.g., thalidomide in Europe) or publicly funded research (e.g., the Tuskegee syphilis experiment in the United States).

By the late 1980s, pharmaceutical companies were implementing global strategies for obtaining market approval of their products and found the technical requirements across countries to be onerous, time-consuming and often duplicative. This led to the initiation of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 1990, with the goal of promoting the harmonization of regulatory requirements by a joint regulatory-industry initiative. To date, ICH has developed over 50 harmonized guidelines as well as the Common Technical Document for regulatory submissions and the Medical Dictionary for Regulatory Activities Terminology.[3] Health Canada has been an official Observer of the ICH Steering Committee and has adopted most of the ICH guidelines.

The ICH E6: Good Clinical Practice: Consolidated Guidelines (ICH GCP) was adopted by Health Canada for the conduct of clinical trials involving drugs in 1997. At the same time, the Tri-Council Policy Statement on the Ethical Conduct of Research Involving Humans (TCPS) was being developed by the three federal granting Councils. Unfortunately, when the TCPS was released in 1998, it was not consistent with the ICH GCP guidance and Research Ethics Boards (REBs) in Canada have had to deal with inconsistent requirements regarding the review of clinical trials. The release of the 2nd edition of the TCPS (referred to as TCPS2)[4] in 2010 resolved most of these inconsistencies.

Over the past decade, the World Health Organization has also provided several guidance documents related to ethics committees, building on the WHO *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*, which many consider to also be an internationally accepted GCP.[5] WHO guidance documents include operational guidelines for ethics committees[6], a complementary guideline on surveying and evaluating ethical review practices[7] as well as a *Handbook for Good Clinical Research Practice (GCP).*[8] In 2011, the World Health Organization released *Standards and operational guidance for ethics review of health-related research with human participants* that it designed to serve as a basis upon with ethics committees can develop their own practices and written procedures and benchmark their achievements.[9]

Finally, the regulations and guidance of US Food and Drug Administration (FDA) address the responsibilities of sponsors, investigators and Institutional Review Boards (IRBs)[A] as well as human subject protection.[10] FDA refers to these US requirements collectively as GCPs.

1.2.2. Regulatory Frameworks in Canada

There are two research oversight processes in Canada: one for federally funded research and one for regulated research, as clarified below.

The three federal granting agencies in Canada (i.e., Canadian Institutes for Health Research, Social Sciences and Humanities Research Council, and National Science and Engineering Research Council) have the responsibility for oversight of research that they fund. Institutions that receive funding from the three Agencies are accountable for all expenditures.[11] An institution that receives federal research grants must sign a Memorandum of Understanding (MOU) committing the institution to adhere to the TCPS2 for all research conducted under its auspices. Representatives of the Agencies visit research institutions periodically to perform financial monitoring of accounts, including a "…review of the effectiveness of procedures, systems and controls in place at the institution…".[12]

[A] In this paper, the local term for an ethics committee is utilized as appropriate to the context, for example, REB is used in the Canadian content and IRB is used in the US content.

In December 2011, the three Agencies launched a new Tri-Agency Framework: Responsible Conduct of Research that replaced previous policy statements and processes related to research integrity. The new Framework identifies the processes to be used when there is an allegation of a breach of an Agency policy.

Health Canada is responsible for regulatory oversight of clinical trials involving drugs, natural health products and medical devices. After extensive consultation, Health Canada published regulations about drugs for clinical trials involving human subjects in 2001 that adopted internationally recognized good clinical practices and these regulations are known as the clinical trial regulations (Division 5 of the Food and Drugs Regulations: Drugs For Clinical Trials Involving Human Subjects).[13] Although the regulations do not explicitly refer to the ICH GCP document, this is the only GCP document that Health Canada has adopted and so ICH GCP forms the basis for the conduct of drug research in Canada.

Under the clinical trial regulations, all research involving investigational drugs requires prior authorization by Health Canada and may be subject to regulatory inspection. Sponsors are required to provide information to Health Canada regarding clinical trial sites and their Research Ethics Boards (REBs) (via the Clinical Trial Site Information Form). While phase IV clinical trials (i.e., post-marketing studies conducted according to product labeling) do not need prior authorization, Health Canada has regulatory authority over these trials and may inspect them.

Following the implementation of the clinical trial regulations, the Health Product and Food Branch Inspectorate (HPFBI) developed an inspection program for clinical trials involving drugs. Under the Food and Drugs Act and regulations, HPFBI has the authority to inspect sponsors and investigators but not REBs, since they are defined in the regulations as bodies that are independent of the sponsor.

Similar regulations related to natural health products were promulgated in 2003 which require the research involving natural health products to be conducted according to GCPs.[14] In contrast, the Medical Device regulations and guidance related to clinical trials have not been updated since 1999 and refer to the Medical Research Council Guideline[15] that preceded the first edition of the TCPS. Health Canada has adopted an ISO standard (ISO 14155: Clinical Investigation of Medical Devices for Human Subjects), however, this document must be purchased and hence it not widely known to REBs in Canada.

1.2.3. Past Attempts to Improve the Oversight of REBs

Health Canada helps Canadians to maintain and improve their health by providing access to safe, high quality drugs, medical devices and other health products. Since market approval by Health Canada of new and innovative health products is based on the results of clinical trials involving humans, Health Canada has been interested

in improvements to the Canadian system of governance of human subject research, including the development of an accreditation system.

The National Council on Bioethics in Human Research (later renamed the National Council on Ethics in Human Research or NCEHR) is a non-governmental organization that was established by Health Canada, the Medical Research Council of Canada and the Royal College of Physicians and Surgeons of Canada in 1989 with the mission "to advance the protection and promotion of the well-being of human participants in research and to foster high ethical standards for the conduct of research involving humans". Since there was no oversight mechanism of REBs in Canada, NCEHR developed a program of voluntary site visits to Canadian research organizations. Data obtained from the early site visits were summarized in a report that identified many shortcomings regarding compliance with the TCPS.[16] In order to address this further, NCEHR established a Task Force to Study Models of Accreditation for Research Ethics Boards in 1999.

This first NCEHR Task Force reviewed different models of oversight taking into account developments from other countries, most notably the report of the Institute of Medicine[17] that presented an accreditation model. The Task Force recommended that NCEHR "affirm the need for a nation-wide oversight process for the ethics review of research in humans based on standards" and that this accreditation program be conducted by an arms-length non-governmental organization.[18]

The Forum for IRBs/REBs in Canada and the United States (FOCUS) held its first invitational conference on the topic of quality improvement and performance evaluation in systems of human research protection. During this workshop, existing systems from the Canadian Council on Health Services Accreditation (CCHSA, now Accreditation Canada), the US Office for Human Research Protections (OHRP), and the Association for the Accreditation of Human Research Protection Programs (AAHRPP) were reviewed. Specific recommendations emerged from this workshop regarding the need for clear standards for the accreditation of REBs, equivalence of standards between countries and for a national, voluntary accreditation program.[19]

NCEHR established a new Task Force for the development of an accreditation system for human research protection programs in 2003 in response to concerns by others and from those within Council.[20] In its final report, the Task Force recommended "that NCEHR, by working with appropriate stakeholders, add to its services to the communities of research organizations and researchers an accreditation function…" and that NCEHR develop standards and other documents for the assessment of organizations through a site visit process.[21] An accreditation process with an iterative process for the development of accreditation standards, implementation and review was proposed. A sub-committee of the Task Force proposed a list of nine proposed standards and developed the elements of three of these standards.

This report introduced the concept of accreditation of Programs Ensuring Ethical Research with Humans (PEERH). The PEERH of an organization would include the REB, researchers, research participants and those responsible for education, resources, and administration aspects of research with humans. The acronym, PEERH, was chosen to reflect the educational nature of an accreditation process based on peer review. While evaluation of an REB by itself was considered, the Task Force recognized that REBs exist within organizations and so the REB and the researchers are subject to organizational policies and procedures. Based on experiences from the NCEHR site visit program, the members of this Task Force felt strongly that an organization's entire program for conducting research involving humans should be evaluated as part of an accreditation process.

The NCEHR Task Force had considered other types of oversight, not only accreditation:

- Certification focuses on the competence of individuals and usually involves an assessment against standards that have been established by a professional organization. Examples of certification programs include the Certified Physician Investigator (CPI) certification by the Academy of Pharmaceutical Physicians and Investigator, Certified Clinical Research Professional by the Society of Clinical Research Associates and the certification programs for clinical research associates, clinical research coordinators, principle investigators by the Association of Clinical Research Professionals.
- Licensure is normally issued by a government authority to individuals who have met certain standards or competence.
- Public assurance system, such as the system in place for US federally funded research by the Office for Human Research Protections (OHRP), relies on an organization committing to conduct research according to established standards.

While these alternative types of oversight were considered by the Task Force, they were not pursued because these systems were not based on peer review and did not address the broader PEERH of an organization.

During the consultations conducted by NCEHR during the development of the second Task Force report, a new group of interested organizations met in 2005 and became known as the Sponsors' Table with members of the Royal College of Physicians and Surgeons of Canada, the Association of Universities and Colleges in Canada, Health Canada and the three federal granting agencies. Over several meetings, the membership of this group was broadened and objectives were developed. The main objective of the Sponsors' Table was to establish an Experts Committee with the mandate "to provide expert advice on the development of a system for human research participant protection in Canada, considering accreditation and alternative models…".

The Experts Committee built upon the work of the previous Task Forces and evaluated a public assurance system, the NCEHR model of accrediting an organization's PEERH as well as a variety of existing accreditation models including that of the Canadian Council for Animal Care (CCAC), AAHRPP and CCHSA. The Experts Committee recommended the establishment of a Canadian Council for the Protection of Human Research Participants with the responsibility for the inter-related functions of accreditation, policy and education similar to the model that had already been developed for the oversight of animal research by the CCAC. [22]

Similar to the earlier Task Forces, the Experts Committee strongly believed that the accreditation process should address all aspects of an organization's program (or PEERH) and should not be limited to the REB. Primarily this was because the REB does not function as an isolated entity but shares responsibility of the safety and welfare of human research subjects with the organizations, researchers, and sponsors of research.

Although the term "accreditation" is used in many other countries, the authority and accountability of accrediting entities over ethics committees is varied. Some countries have implemented programs that may be best characterized as a system of registration or designation of ethics committees. Other countries have established processes to monitor the activities of ethics committees with varying degrees of oversight. It is the intent of Part 2 of this background paper to summarize some of the international models of accreditation that have been developed and implemented.

1.2.4. Standards for Stakeholders in PEERH

"Accreditation is based on continuously evolving standards derived from guidelines, regulations, policies and best practices. It is a self-assessment and peer-assessment process used by organizations to accurately assess their level of performance in relation to established standards and to implement ways to continuously improve the system."[23]

There are Canadian standards in place or under development for some of the stakeholders involved in a PEERH:

- REBs: In 2007, Health Canada sponsored an initiative with the Canadian General Standards Board (CGSB) to develop a National Standard of Canada to be issued by the Standard Council of Canada. The intent was to develop a voluntary standard for REBs reviewing biomedical clinical trials regulated by Health Canada. The National Standard has gone through various drafts and consultations and it is hoped that it will be finalized in 2012.
- Sponsors and Investigators: Health Canada's Food and Drug Act and Regulations, as well as ICH GCP, contain detailed requirements for sponsors and investigators regarding clinical trial conduct.

- Organizations that have signed a MOU with the three federal granting agencies must comply with the TCPS2 and the *Tri-Agency Framework: Responsible Conduct of Research*.

Currently, there are no Canadian standards addressing the overall PEERH in an organization addressing activities including, but not limited to:

- Governance and maintenance of the effectiveness of an organization's PEERH
- Policies and procedures related to resource management and administrative aspects of research involving humans
- Educational requirements and activities for investigators and their staff
- Activities that an organization undertakes to monitor the quality and integrity of clinical trial activities conducted under its auspices
- Organizational policies regarding research participants, including outreach activities and complaint handling
- For organizations that have not signed a MOU with the three granting agencies (i.e., in the private sector), policies and procedures to manage conflicts of interest

1.2.5. Research Landscape in Canada

There are two main funders of clinical trials in Canada; the Canadian Institutes of Health Research (CIHR) provides public funding and the pharmaceutical industry provides private funding of clinical trials.

The research investment by CIHR for 2010-2011 was $966 million of which $129 million (13%) was spent on clinical research.[24] One of the key areas that CIHR's Strategy for Patient-Oriented Research has targeted is overcoming the challenges involved in conducting multicenter clinical trials by supporting "thematically organized clinical research networks" providing national platforms to undertake clinical trials.[25] The first network, a national imaging clinical trials network, was launched as recommended by CIHR and NSERC jointly to address alternative means of producing radioactive isotopes to support research.

A model clinical trial template agreement was proposed by members of the Association of Canadian Academic Healthcare Organizations (ACAHO) and Canada's Research-Based Pharmaceutical Companies (Rx&D) and developed with funding by CIHR.[26] The model agreement is being piloted between October 1st, 2011 and March 31, 2012 for phase II and III clinical research.

The pharmaceutical industry R&D expenditures are monitored and reported by he Patented Medicine Prices Review Board (PMPRB).[27] In 2010, total R&D expenditures in Canada by reporting companies was $1,178 million that was a decrease of 12.1% from 2007 expenditures (see Figure 1). Of the members of Rx&D, R&D expenditures were $1,000 million in 2010, a decrease of 11.7% over 2009.

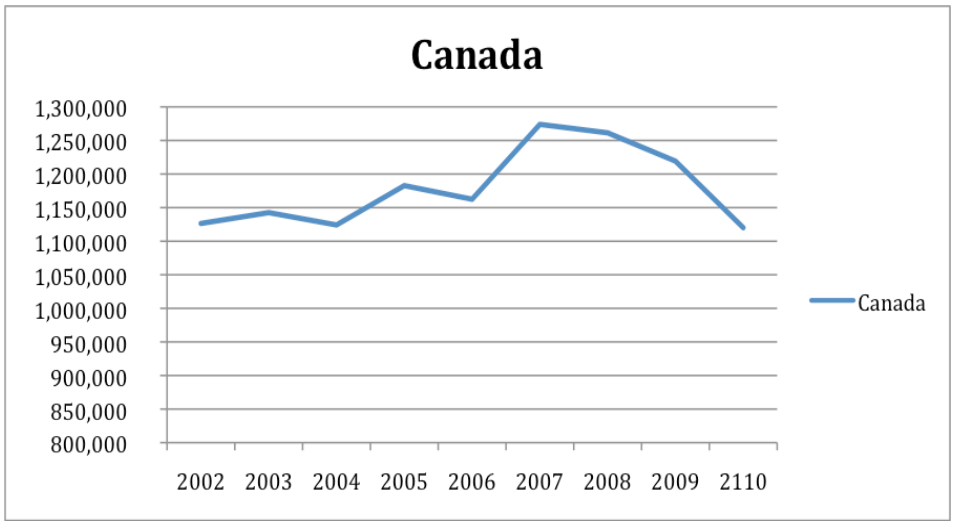

Figure 1: Patentee R&D Expenditure in Canada by Year[28]

R&D expenditure by type of phase of clinical trial in 2010 was $33.9 millions for phase I, $113.3 millions for phase II and $317.8 millions for phase III clinical trials. These data underestimate the R&D investments by the pharmaceutical industry because they do not include expenditures that do not qualify for tax credits[29], including but not limited to:

- Phase IV clinical trials, observational studies, non-interventional studies or pharmacovigilance research studies
- Salaries of Canadian personnel directly engaged in eligible work outside Canada
- Administrative, supervisory and operational personnel
- Equipment utilized in R&D activities
- University Chair endowments
- Charitable or other donations, grants or sponsorships directed toward R&D in Canada

Table 1: 2010 R&D Expenditure by Patentees by R&D Performer

Type of Research	R&D Expenditures 2010($millions)
Intramural/Patentees	575.1
Universities and hospitals	160.9
Other companies [B]	241.7
Others	142.2
Total	1,120.1

Research that is conducted by universities and hospitals comprise 14.4% of the total 2010 R&D expenditures (see Table 1). There is some variation between companies

[B] Other companies is defined by PMPRB as corporations, resident in Canada, undertaking research on behalf of the reporting patentee, or research in the same class of business as the reporting patentee. Corporations carrying out the research do not have to be at arm's length from the reporting patentee.

in how the extramural expenditures are reported. For example, expenditures listed under "other companies" may include contract research organizations (CROs), including phase I clinics, as well as site management organizations (SMOs). CROs are contracted by sponsors to manage the conduct of clinical trials at research sites and often their responsibilities include payments to the investigators who are conducting the research. Therefore, it is difficult to accurately ascertain the ratio of research conducted at public institutions (listed as "universities and hospitals") versus private organizations (which would consist of "others" plus part of "other companies").

In 2010, industry R&D activities took place in all provinces but there was none in the territories (see Table 2). Consistent with previous years, 85.9% of the 2010 R&D expenditures were in Ontario and Quebec. Note: these expenditures include both intramural and extramural expenditures.

Table 2: 2010 R&D Expenditure by Industry by Province/Territory

Province	Expenditures (all patentees) ($000)	Regional Share (%)
Newfoundland and Labrador	4,667	0.4
Prince Edward Island	96	0.0
Nova Scotia	11,163	1.0
New Brunswick	2,134	0.2
Quebec	461,212	41.2
Ontario	500,163	44.7
Manitoba	7,460	0.7
Saskatchewan	3,339	0.3
Alberta	77,624	6.9
British Columbia	52,223	4.7
Territories	0.0	0.0

Compared to the PMPRB´s seven comparator countries, Canada´s 2008 R&D-to-sales ratio was second lowest at 8.1%, just ahead of Italy. Ratios in all other comparator countries were well above Canada´s, with the United States at 19.4% and the United Kingdom at 42.3%.

Another source of information about clinical trials conducted in Canada is clinicaltrials.gov, which is a registry for federally and privately supported clinical trials conducted in the United States and worldwide. A total of 646 clinical trials were registered in 2011 that involved Canadian sites, of which 399 studies were funded by the pharmaceutical industry and an additional 24 studies were funded jointly by the pharmaceutical industry and the National Institutes of Health. The remaining studies were funded by health charity organizations, such as the Heart and Stroke Foundation. The distribution of clinical trials across the provinces for those clinical trials that were registered in 2011 is provided in Table 3. Please note that many clinical trials take place in more than one province.

Table 3: Number of clinical trials registered in clinicaltrials.gov in 2011, by funding source and by Province

	BC	Alberta	Sask	Man	Ont	Que	NB	NS	PEI	Nfld
Industry	121	108	19	42	264	190	22	48	2	32
Industry +NIH	125	109	20	43	284	197	22	49	2	0
All sources	155	138	24	50	393	245	23	62	2	33

Industry sponsored clinical trials in 2011, with sites in Canada, are being conducted at 9088 clinical trial sites worldwide of which Canada has 863 sites. Many Canadian sites are involved in more than one clinical trial. Of the clinical trial sites in Ontario, approximately 69% are private sites versus public sites (e.g., hospitals and universities).[30]

There are no published data on the nature of research sites in Canada and metrics associated with various types of sites. One major pharmaceutical company graciously shared their data from 203 clinical trials, conducted at 1563 research sites in Canada, which ended subject recruitment between 2005 and 2011. Of these research sites, 62% were private sites (i.e., physicians in private practice) rather than public sites (i.e., universities and hospitals). The proportion differs by therapeutic area, for example, oncology and infectious disease research are typically conducted at public sites whereas as cardiovascular and pain/inflammation research are more often done at the point of care (i.e., private sites). The average time between approval of the clinical trial agreement and the first patient's first visit, a measure of the efficiency of clinical trial start up, was 171 days for private sites as compared with 264 days for public sites.

1.2.6. Multi-center research

Since the late 1990s, it has been internationally recognized that there are the problems associated with multiple ethics reviews for multi-center research.[31 32 33] The redundancy of having each participating institution perform an ethics review of multi-center research is thought to be time-consuming and a waste of human resources.

In the European Union, the Clinical Trial Directive of 2001 introduced the requirement for EU countries to develop a procedure for the adoption of a single ethics opinion for multi-center research. Each country in the EU has developed their own system for ethics review – a sub-group of the European Forum for Good Clinical Practice tackled the challenge of identifying the differences and similarities between member countries and maintains current information on their website.[34]

In the US, the Food and Drug Administration (FDA) issued guidance on the use of a centralized IRB review process in multicenter clinical trials.[35] Further to the FDA guidance, the Office for Human Research Protections clarified that they take into consideration whether a single central IRB was responsible for the review of

research. [36] In 2011, the US Department of Health and Human Services gave advance notice of proposed rulemaking regarding human subject protection that included proposed provisions for the streamlining of IRB review of multi-site studies.[37]

In Canada, the TCPS2 has a chapter dedicated to multi-jurisdictional research and sets out options, procedures and considerations.[38] The adoption of alternative review models is an institutional responsibility, however, the TCPS2 requires that "the institution remains responsible for the ethical acceptability and ethical conduct of research undertaken within its jurisdiction or under its auspices…".

In part 3 of this background paper, some of the provincial and institutional actvities to address multi-center research in Canada are described.

1.2.7. Investigator-Initiated Research

Investigator initiated research is research that is not initiated or conducted by a commercial sponsor. Many major pharmaceutical companies provide funding or clinical trials supplies for such research.[39] [40] In Canada, it is the investigator/institution who is responsible for filing for Health Canada authorization of the clinical trial and so the investigator/institution are considered to be the sponsor of the clinical trial.[41] [42]

Under ICH GCP, the sponsor is responsible for the monitoring of the clinical trial and, for individual investigators and their institution conducting investigator-initiated research, this has implications for their research infrastructure. Monitoring of clinical trials is essentially a quality control procedure to ensure that the integrity of research data as well as the protection of human research subjects. In part 3 of this background paper, some of the institutional models to address monitoring of investigator initiated research as well as some provincial initiatives to improve the quality of research are described.

1.2.8. Need for Economic Development

The globalization for industry funded research and the movement of clinical trials to emerging markets has been noticed by governments and researchers alike.[43] [44] [45] [46] As described above, pharmaceutical industry research spending in Canada has been declining over the past few years.

CenterWatch, a global source for clinical trials information, recently published an analysis of the investigators who completed FDA form 1572 (Statement of Investigator) and whose data were retained in the FDA's Bioresearch Monitoring Information System.[47] While almost 25% of investigators filed two to four FDA forms in 2006, these active investigators comprised only 16% in 2010. Similarly, for the 59 highest volume sites in US and one site in Canada, the level of study activity fell by an average of 21% each year during the past 5 years. This decline in studies at active research sites is attributed by CenterWatch to the increased number of clinical trials conducted in emerging regions such as Latin America, India,

China and Central/Eastern Europe where treatment naïve patients are more readily enrolled and research costs are lower. This trend is accompanied by an increase in the number of novice investigators over the same time period.

At the Clinical Trial Summit, held in Ottawa on September 15, 2011, Health Canada data on the decline in the number of clinical trials in Canada were presented by Rx&D, CIHR and ACAHO (see Figure 2). These three organizations believed, that while patients are available in Canada to be enrolled in clinical trials, the cost/performance, operational environment and recruitment reliability are seen as areas in which Canada has "lost our edge". Countries with a competitive edge are considered to be Spain, UK, Australia and Argentina, not the emerging markets. A call was made to improve the research infrastructure to maintain Canada's attractiveness for fast, efficient and reliable research.

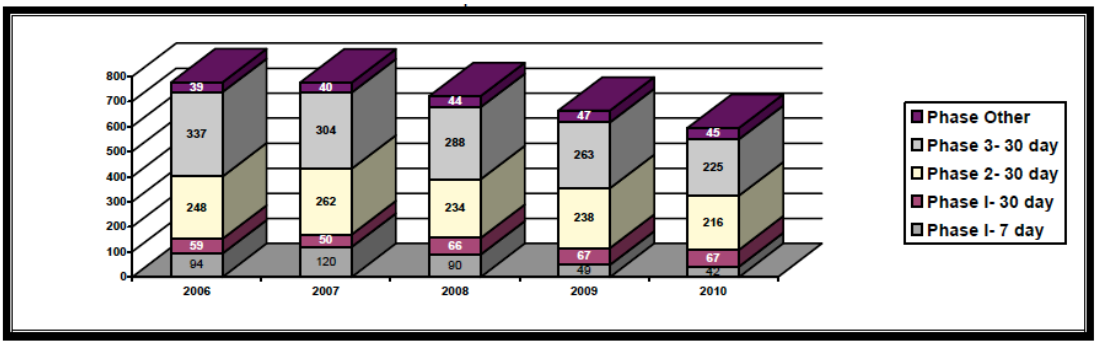

Figure 2 : Declining number of clinical trials in Canada[48]

In a recent speech to the European Federation of Pharmaceutical Industries and Associations, John Dalli, the EU Commissioner responsible for Health and Consumer Policy discussed the need to revise the EU Clinical Trials Directive: [49]

> "*There has been a decline in clinical trials in the EU in recent years of about 15%. At the same time, costs for bureaucracy and resource requirements to handle paperwork have doubled, and delays have increased by 90%. …*
>
> *Clinical trials are crucial for the development of new medicines, and equally to improve and refine treatments with existing medicines.*
>
> *Clinical trials are also a key contributor to growth and jobs in the area of public health. Clinical trials mean research and investment, including inward investment from outside the Union. Today, clinical trials account for investments of over €20 billion per year in the EU.*
>
> *It is therefore crucial to provide the right regulatory framework."*

1.3. Methodology

Information about the international models of oversight of ethics committees was found primarily using the internet, using systematic searches for key words such as "accreditation", "registration" and "research ethics committee".

Semi-structured interviews of 0.5-1.5 hours each were conducted with regards to the provincial and territorial activities. Questions included, but were not limited to:

- Please describe any initiatives in your province / territory that are intended to improve the efficiencies of clinical trial conduct, promote high quality clinical research and improve the protection of research participants
    - Who initiated the activities?
    - What organizations were involved?
    - Have any reciprocity agreements been implemented?
    - What kind of oversight of REBs is done or planned?
- Are there any legal or regulatory actions relevant to REBs
    - Are REBs required to report their activities? If so, to whom?
- Are there any education initiatives that are province / territory wide?
- Are there any specific requirements for multi-center trials? For investigator-initiated trials?
- What is the volume of Health Canada regulated clinical trials reviewed?

Attempts were made to reach individuals in health ministries and health research organizations in each province or territory; however, no responses were received from Nunavut or the Northwest Territories.

Prior to and subsequent to the interviews, information about specific provincial organizations was found using the internet.

2. International Models of Oversight of Ethics Committees

2.1. Overview of Different Types of Models

There are three kinds of models in place in other countries for the oversight of research ethics committees. First, there is a basic registration system in which ethics committees are required to submit an initial application and annual updates on their composition and review activities. Registration systems are present in Brazil, Belgium and the US FDA.

In some countries, additional mechanisms are also put in place over and above the registration system. Examples include the review of policies and procedures in New Zealand, statements of agreement and commitment in Nigeria, and planned site visits in South Africa. In the US, the federal-wide assurance system for federally funded research by the OHRP falls into this category.

Finally, there are accreditation systems that involve more extensive oversight of policies and procedures of the research ethics committees as well as regular site visits. Accreditation systems are present in the Australia, Netherlands, United Kingdom. In addition, AAHRPP accredits programs in the United States and elsewhere.

Since the United States has three different systems in place that each have implications for some research in Canada, this country is dealt with first and separately from the rest. The subsequent sections describe the systems that have been implemented in the other countries (see also Appendix 1). Each country has it's own conventions for naming of the research ethics committee or for its system of oversight (i.e., "accreditation" or "registration"); whenever possible, the local terminology is used below.

2.2. United States

2.2.1. Regulatory Frameworks

There are two regulatory authorities in the United States -- the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS) -- that have both promulgated regulations related to Institutional Review Boards.[50] [51] Their respective authority with respect to clinical trials involving humans is described below.

OHRP regulates research conducted or supported by DHHS and the first human subject protection regulations were issued in 1974. In 1991, the OHRP regulations or the "Common Rule" were adopted by seventeen US federal departments and agencies, including DHHS. The Common Rule includes five subparts that cover the basic protections for all research subjects as well as additional protections for specific vulnerable groups of subjects.

These regulations require that each institution that is engaged in research covered by the Common Rule must provide written federal-wide assurance (FWA) that it complies with requirements set out in those regulations.[52] The FWA requires the institution to assure that all of its activities related to human subjects research, regardless of the source of support, will be guided by ethical principles and the organization is required to pick from a list of applicable standards which include but are not limited to the Declaration of Helsinki, the Belmont Report, the Common rule, FDA regulations, ICH GCP and TCPS.

Before an IRB can be designated under an institution's FWA approved by OHRP, the IRB must be registered with DHHS.[53] Registration involves providing the following data on:

- Name, address and contact information for the IRB and senior officials of the organization and IRB Chairpersons

- IRB roster including name, sex, earned degrees, primary scientific or non-scientific specialty, affiliation with the institution for all IRB members and their alternates
- Approximate number of full time equivalent positions devoted to IRB administrative activities
- Approximate number of active protocols, active protocol conducted or supported by DHHS

In addition, OHRP has the authority to evaluate written substantive indications of non-compliance with the DHHS regulations and to take a range of regulatory actions to protect human research subjects, including restricting or attaching conditions to its approval of the institution's FWA.[54] Compliance oversight determination letters are redacted but are publicly available on the OHRP website.

FDA regulates clinical investigations involving drugs, biologics, and medical devices. Since 2009, FDA has required that IRBs in the United States be registered using a modified version of the OHRP internet system; IRBs outside of the US are not required but may choose to register themselves with FDA.[55] In addition to the data required by OHRP, data must be provided on the approximate number of active protocols involving FDA-regulated products as well as the types of FDA-regulated products (i.e., drugs, devices, biologics, food additives, color additives, or other).

FDA has an inspection program that evaluates clinical investigators, sponsors, and IRBs. [56] [57] [58] FDA has the authority to take regulatory actions, including disqualification of an IRB or an institution.[59] FDA issues warning letters to clinical investigators, sponsors, and IRBs that state FDA's enforcement position and intention to pursue legal remedies if compliance is not achieved. Warning letters are redacted but are publicly available on the FDA website. In egregious non-compliance cases, FDA can restrict or disqualify clinical investigators and maintains a publicly available list of these investigators. Since 1996, FDA has issued 108 warning letters to IRBs.[60]

2.2.2. Organizations Conducting Research in Canada Subject to US Regulations

There are two ways that US regulations on human subject protection may impact research that is conducted in Canada. One involves research that is funded from US federal sources (e.g., National Institute of Health, National Cancer Institute, etc.) whereas the other involves research that is filed to the FDA under a US Investigational New Drug (IND) or Investigational Device Exemption (IDE) Submission.

As of January 2012, 594 Canadian organizations hold an active FWA with OHRP and have therefore committed their organization or a component of their organization to comply with the US Common Rule for research that is conducted at the Canadian

organization and that is supported by DHHS.[A] A complete list of these Canadian organizations and their IRBs is available via the OHRP website.

When a clinical investigator signs the FDA form 1572, *Statement of Investigator,* this includes a commitment to FDA that the research will be conducted according the FDA regulations and includes a commitment that the clinical investigator's IRB will perform its review according to FDA regulations. While signature of this form is not mandatory for non-US investigators, in practice, many sponsors continue to require investigators to sign the FDA form 1572. As of January 2012, over 8,300 FDA 1572 forms from Canadian researchers were filed to INDs with the FDA.[61] The decrease in the number of Canadian researchers who completed FDA 1572 forms in 2009 (see Figure 3) likely reflects the decreased number of studies in Canada, as described above, and the further decrease in 2010 may be attributed to the issuance of the FDA guidance that completion of this form is not required for non-US sites.[62]

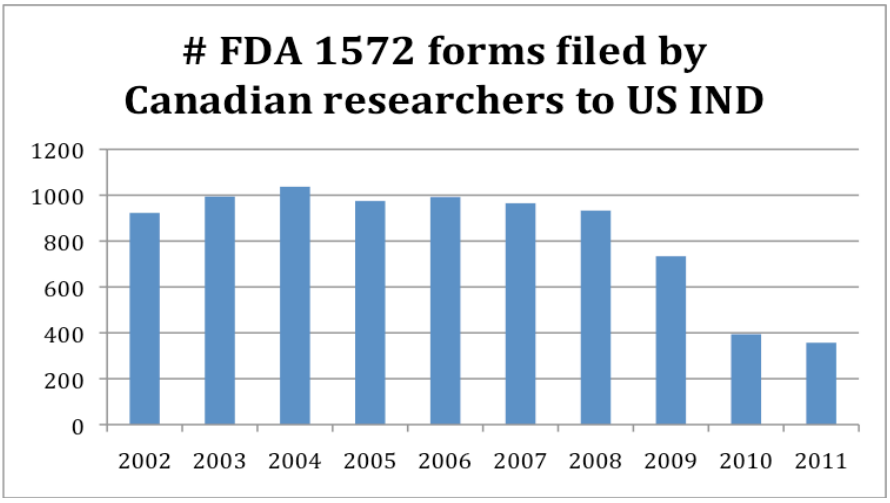

Figure 3: Number of FDA 1572 forms filed by Canadian researchers to the US FDA

2.2.3. Accreditation of Human Research Protection Programs

In May 1999, the Office for Protection from Research Risks (OPRR; the precursor to OHRP) suspended the multiple project assurance at Duke University Medical Center that resulted in the halting of research at that center. This was followed by suspensions of research programs at other research centers by OPRR. In September 1999, the research community was shocked by the death of 18-year-old Jesse Gelsinger, a subject in a phase I gene transfer study at the University of Pennsylvania. These events moved forward the plans in the US to develop standards for the accreditation of IRBs and human research protection programs (HRPPs). The original concept of accreditation came from Public Responsibility in Medicine and Research (PRIM&R) during the late 1990's. The Institute of Medicine conducted a landmark study that addressed accreditation standards for HRPPs as well as various models of accreditation.[63]

Two competing accrediting non-governmental organizations were formed. The National Committee for Quality Assurance (NCQA), a private not-for-profit organization, created an accreditation program for veterans affairs programs in 1999. Subsequently, the NCQA partnered with the Joint Commission to create the Partnership for Human Research Protection in 2003 but this discontinued operations in 2005.

The Association of American Medical Colleges got together with the other founding members to create the Association for the Accreditation of Human Research Protection Programs (AAHRPP) in 2001. The other founding members were the Association of American Medical Colleges, Association of American Universities, Association Public and Land-grant Universities, Consortium of Social Science Associations, Federation of American Societies for Experimental Biology, National Health Council and PRIM&R.

Despite an economic downturn in 2003 and the introduction of the Health Insurance Portability and Accountability Act in 2003, some organizations overcame these negative influences and sought out accreditation because they saw value in having a more efficient and effective HRPP, increased competitiveness and reduced risk exposure.[64]

The AAHRPP accreditation process is based on accreditation standards, which were finalized in 2002 and updated in 2009 with implementation in 2010. The current AAHRPP standards are organized into three domains (Organization, IRB, and Researcher) that comprise an organization's HRPP and include 60 individual elements across these domains. Organizations that wish to seek accreditation by AAHRPP must complete an element-by-element self-assessment against the accreditation standards and provide to AAHRPP supporting evidence that each element is met. The average time to perform the self-assessment and prepare the initial application is 16.5 months (range 12-18 months).[65] AAHRPP staff review each submission and comments are provided back to the applicant.

Once AAHRPP considers an organization to be ready from a documentation perspective, then an on-site evaluation is scheduled. AAHRPP site visitors are volunteers and peers, typically from accredited organizations. They evaluate, through interview and the review of documents on-site, whether the organization's practices are consistent with the accreditation standards. After the site visit, the organization is provided an opportunity to respond to the draft site visit report. AAHRPP's Council on Accreditation reviews the application, draft site visit report, and the organizations' response in order to determine the organization's accreditation status.

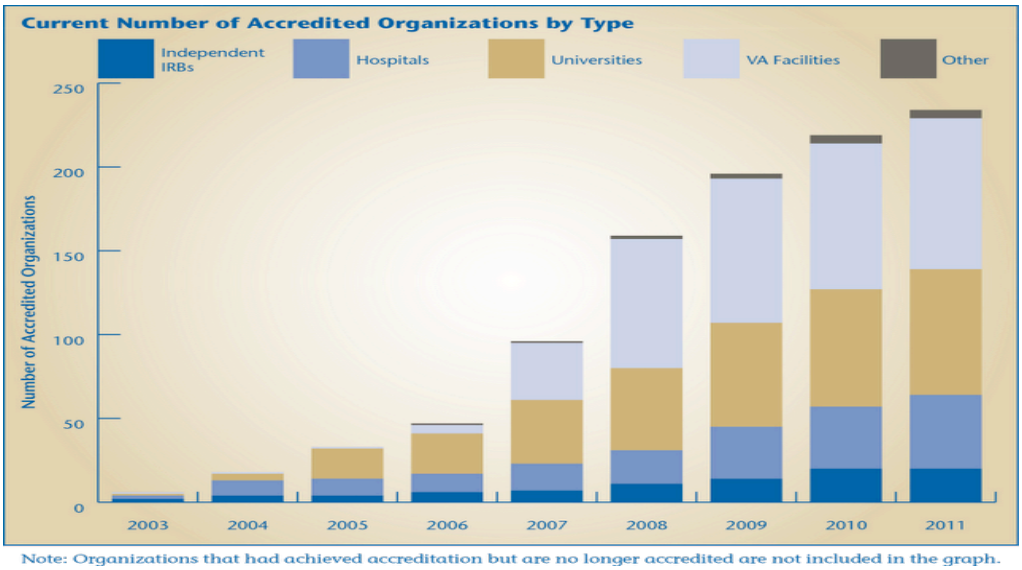

Figure 4: AAHRPP Accredited Organizations, as of September 2011[66]

As of March 2012, 243 organizations have been accredited by AAHRPP including some organizations in Canada, India, China, Korea and Singapore (see also Figure 4). The three accredited Canadian organizations are:

- ethica Clinical Research – a contract research organization which conducts or manages clinical research and also operates Veritas IRB as a non-profit division of ethica.
- IRB Services – a privately owned organization that provides ethics review services in Canada and the United States.
- Diex Research – a clinical research site in Quebec which conducts phase I to IV clinical trials.

It is interesting to note that of the 62 warning letters that FDA has issued to IRBs from 2003 (when the first organizations were accredited by AAHRPP) to 2011, only one was from an organization that was accredited at the time of inspection.[67] An AAHRPP study of FDA inspections outcomes or OHRP determination letters found a statistically significant decrease in the number of regulatory problems found at investigators located at accredited organizations (or organizations seeking accreditation) when compared to non-accredited organizations.[68] For example, the percentage of investigators whose FDA inspection found that no action was indicated was 73% for investigators who were in accredited organizations whereas was 53% for investigators at non-accredited organizations.

2.2.4. Evolving Regulatory Environment in the United States

Over the past two decades, there has been concern about improving the system for protecting human subjects in the United States both from academia[69] [70] [71] as well as from governmental bodies.[72] [73] In this section, many separate initiatives are described.

The Secretary's Advisory Committee on Human Research Protections (SACHRP) provides expert advice and recommendations to the Secretary of DHHS on issues and topics pertaining to the protection of research subjects.[74] It is governed by the Federal Advisory Committee Act and holds three meetings per year. The agenda, minutes and presentation materials are all available publicly on the OHRP website. While SACHRP has made numerous recommendations to the HHS Secretary, very few of these recommendations have resulted in revisions to the regulatory requirements.

The Clinical Trials Transformation Initiative (CTTI), a public-private partnership, was announced at the end of 2007 and formerly established in 2008 by the FDA and Duke University.[75] The intent was to identify practices that through broad adoption will increase the quality and efficiency of clinical trials. CTTI is now comprised of more than 60 organizations from government, industry, patient advocacy groups, professional societies, investigator groups, academic institutions and others. There are seven CTTI projects, of which two on monitoring and SAE reporting have presented recommendations so far. The projects include:

- Effective and efficient monitoring as a component of quality
- Workshops on Quality-by-Design in clinical trials
- Improving unexpected SAE reporting to IND investigators
- IND Safety assessment and communication
- Improving the public interface for use of aggregate date in clinicaltrials.gov
- Site metrics for study start-up
- Use of Central IRBs for multicenter clinical trials

The Presidential Commission for the Study of Bioethical Issues was created in 2009 with the mission to advise the President on emergent bioethical issues.[76] In the fall of 2010, the Commission was asked by the President to perform a thorough review of the rules to protect research participants, in light of the disclosure that the US Public Health Service had conducted research on sexually transmitted diseases in Guatemala involving intentional infection of vulnerable human populations from 1946 to 1948. In response to this request, the Commission published the proceeding of an International Research Panel[77], a full report of the Commissions' ethical analysis of the case[78] as well as a report of the Commission's assessment of research standards.[79] The Commission has made 14 recommendations, including reform of the Common Rule to address investigator responsibilities and to ensure capacity to protect human subjects at research sites and to reduce unnecessary, duplicative review of multi-center research. The Commission noted that several had already been made by presidentially appointed bioethics commissions or advisory bodies in the past.

In July 2011, DHHS announced that they "were contemplating various ways of enhancing the regulations overseeing research on human subjects". The changes under consideration were published in an Advance Notice of Proposed Rulemaking (ANPRM) *Human Subjects Research Protections: Enhancing Protections for Research*

Subjects and Reducing Burden, Delay, and Ambiguity for Investigators.[80] The proposed revisions fall into two main categories; those that improve the effectiveness of oversight and those that enhance the protections for research participants.[81]

The Alliance for Clinical Research Excellence & Safety (ACRES) was co-founded by Dr. Greg Koski (who had been the first director of OHRP in 2000). ACRES envisions an alternate strategic approach in which the research site is held responsible for the quality of research, including protection of research participants. In this proposed model, there would be a global network of accredited research sites and research ethics committees, certified professional research teams, standardized policies and operational procedures and shared information platforms.[82] This approach was endorsed by the International Federation of Associations of Pharmaceutical Physicians in 2010.[83]

In January 2012, the Health Improvement Institute announced that it has launched a project to harmonize health research guidelines.[84] At an invitational meeting of experts in 2011, the participants agreed on the need to establish a harmonization mechanism involving relevant stakeholders and associations. Working groups were created to evaluate existing guidelines, develop "guidelines for guidelines" and to promoted the update and implementation of appropriate standards.

FDA has announced a 2-day public hearing, to be held on April 23-24, 2012, to "obtain input from interested persons on FDA's scope and direction in modernizing the regulations, policies, and practives that apply to the conduct of clinical trials of FDA-regulated products. The purpose of this hearing is to solicit public input on FDA's efforts to modernize the regulatory framework that governs clinical trials and approached to good clinical practice (GCP), including encouraging the use of innovative models that may enhance the effectiveness and efficiency of the clinical trial enterprise".[85]

2.3. Registration Systems

2.3.1. Brazil

2.3.1.1. Regulatory Framework

The National Health Council (CNS), an agency under the Brazil Ministry of Health, approved a resolution in 1996 that put in place requirements for research involving human subjects, including the duties and role of the Research Ethics Committee (CEP) (similar to REBs in Canada). [86] At the same time, the National Committee for Ethics in Research (CONEP) was established as an independent collegiate body, accountable to the CNS with powers to provide consultancy and to deliberate, regulate and inform with respect to all research involving humans.

The CONEP's duties include the registration of institutional and other CEPs as well as the review and oversight of research studies in special areas (e.g., human genetics, human reproduction, research involving pharmaceutical products). The CONEP provides regular guidance on aspects of human research that have been problematic and issued a detailed Operational Manual for Research Ethics Committees in 2008 which includes a flowchart to help CEPs determine when CONEP review is required.[87]

For research projects involving new drugs, vaccines, diagnostic tests, health equipment and devices, after CEP approval has been granted, the research must also be reviewed by the CONEP that issues a technical opinion. Since 2008, this ethics approval process can take place in parallel with the review by the Brazilian regulatory authority, National Health Surveillance Agency (ANVISA), resulting in significant reductions in the time to initiate new research in Brazil.[88]

The 1996 resolution, that first established CEPs, underwent public consultation in 2011 and a revised version is expected in 2012.[89]

2.3.1.2. Registration and accreditation

In 1997, the CONEP became responsible for establishing a system to evaluate and follow up on the activities of CEPs as well as for the reporting of any violations of ethical standards during the conduct of research to the Ministry of Health.[90]

In 2007, the process for registration and accreditation of CEPs was clarified[91] to require CEPs to submit reports to the CONEP every 6 months with a list of research projects and to immediately report to the CONEP any research that is interrupted.[92] The CONEP has the authority to evaluate a CEP for compliance with local requirements at any time and may cancel the registration of the CEP if it determines that the CEP does not meet the required conditions of operation. No site visits or audits of CEPs are conducted by the CONEP.[93] As of December 2010, there were 608 registered CEPs.

2.3.2. Belgium

2.3.2.1. Regulatory Framework

The Hospital Law in Belgium requires that each hospital have an ethics committee. The composition, functioning and mission of local hospital ethics committees was first defined in a Royal Decree in 1994.[94] The Law Concerning Experiments on the Human Person was implemented in 2004, incorporating the EU Clinical Trials Directive 2001/20, and has been revised several times since then.[95] Provisions are made in the law for single-centre experiments as well as multi-centre experiments that require the opinion of a single ethics committee. This law defines the composition of an ethics committee and requires each committee to demonstrate that it reviews at least 5 new multi-centre studies for the provision of a single opinion and at least 20 new research protocols (for a single opinion or otherwise)

per year. Ethics Committees may be established in hospitals or linked to a faculty of medicine or to the Scientific Association of General Practitioners.

Clinical trials involving investigational medicinal products are regulated by the Federal Agency for Medicines and Health Products (AFMPS). Clinical trials must be approved by a recognized ethics committee and the AFMPS must not have indicated any major deficiencies before the research may proceed.

The Belgian Advisory Committee on Bioethics (Comité Consultatif de Bioéthique de Belgique) was established in 1993 by the federal government to provide advice on problems raised by research and to inform the public and authorities about these problems.[96] This committee regularly provides opinions on a variety of topics, such as commercialization of human body parts, biobanks, cloning.[97] Since 1998, the Belgian Advisory Committee on Bioethics has required a report from each ethics committee on their structure and activities.

2.3.2.2. Accreditation of Ethics Committees

Two types of accreditation of hospital-based ethics committees are recognized by AFMPS:

- Full accreditation for those ethics committees that are authorized to provide a single opinion for multi-centre studies and an opinion for single-centre studies. For the period from April 2009 to April 2012, 38 ethics committees have received full accreditation. [98]
- Partial accreditation for those ethics committee that are not authorized to issue a single opinion but may participate in the review process, e.g., review the competence of the investigator, the research site and the informed consent document. Approximately 170 other hospital committees have partial accreditation.[99]

The ethics committees must submit their opinion for each new study to AFMPS as well as an annual report of its activities, including any membership changes and possible conflicts of interest. [100]

At the present time, no site visits are conducted, however, the competent authority is seeking to develop new legislation concerning accreditation and standardization of the ethics review process.[101]

2.4. Registration Systems with Additional Components

2.4.1. New Zealand

2.4.1.1. Regulatory Framework

The New Zealand Health Research Council (HRC) was established in 1990 with a HRC Ethics Committee whose responsibilities included provision of advice on the membership of ethics committees established by other bodies and the

procedures/standards to be used by those committees.[102] The HRC Ethics Committee approves two types of human ethics committees: Health and Disability Ethics Committees (HDECs) established under the New Zealand Public Health and Disability Act 2000 and Institutional Ethics Committees (IECs).[103]

2.4.1.2. House of Representatives Inquiry

The Health Committee of the House of Representatives instigated an inquiry into improving New Zealand's environment to support innovation through clinical trials and, last year, submitted it's report to the House of Representatives.[104] The key recommendations included simplifying and streamlining the ethical review process and urged government to act urgently (within 12 months) to implement the recommendations.

2.4.1.3. Accreditation

Accreditation is required for any ethics committee that reviews HRC funded research as well as all research involving the use of health information or accident compensation cover for clinical trials. The HRC Ethics Committee accredits HDECs and IECs based on:

- Membership
- Policies and Procedures
- Responsiveness of Maori
- Ethical standards which the IEC applies
- Reporting lines

There are six regional HDECs, one multi-regional HDEC, nine academic IECs and one private ethics committee that have been accredited.[105] Accreditation is awarded for a maximum of three calendar years. Annual reports[106] to the HRC Ethics Committee are required and must include the following information:

- Details of the organization with primary responsibility for the EC
- Terms of reference as well as policies and procedures
- Membership, including attendance at EC meetings
- Training
- Response to cultural issues
- Applications for review including number of reviews and outcome
- Complaints
- Delegation of review activities
- List of research studies reviewed including title, investigator, sponsor, consultations, approval dates and status

Accredited ethics committees are required to comply with the Operational Standards for Ethics Committees issued by the Minister of Health.[107] Accreditation may be suspended if the HRC Ethics Committee determines that appropriate standards have not been met.

2.4.2. Nigeria

2.4.2.1. Regulatory Framework

Clinical trials are regulated in Nigeria by the National Agency for Food, Drugs Administration and Control (NAFDAC) under the Federal Ministry of Health. NAFDAC has issued draft clinical trial regulations[108] as well as draft National Guidelines for Good Clinical Practice[109].

In 2007, the Federal Ministry of Health issued the National Code of Health Research Ethics (NCHRE) and this requires institutions conducting health research to have a registered health research ethics committees (HRECs).[110] The National Health Research Ethics Committee (NHREC) in Nigeria has the mandate, from the Ministry of Health, to determine guidelines for the functioning of health as well as to register and audit HRECs.

2.4.2.2. Registration of HRECs

As specified in the National Code, HRECs should be registered with the NHREC. Applications for registration include information about the institution and its HREC including:

- HREC membership
- Training of HREC members on NHREC approved training programs
- Statement of agreement to comply with the National Code
- Statement of commitment to provide resources to support the HREC
- Statement of commitment to provide coverage for liability to HREC members

As of July 2011, nineteen HRECs have been registered, including the NHREC.[111] The registration process takes a maximum of three months.[112] The registration is valid for two years and to be re-registered the institution must submit:

- Current HREC membership list
- Certificates of completion of NHREC approved training programs
- Statement of agreement to comply with the National Code
- Report of fulfillment of the previously stated commitment to provide resources to support the HREC
- Complete record of the activities of the committee, including, attendance at meetings, complaints, litigations, number and titles of research protocols reviewed and the outcome of the review.

2.4.3. South Africa

2.4.3.1. Regulatory Framework

The National Health Research Ethics Council (NHREC), established in 2003, has overall responsibility for determining guidelines for the function of Health Research Ethics Committees (RECs) in South Africa as well as for the registration and audit of RECs.[113] The composition, role and responsibilities of RECs is described in guidance.[114] [115] Research involving human participants must be reviewed by a

research ethics committee and, for clinical trials involving marketed and investigational health products, by the Medicines Control Council.

The NHREC also manages complaints submitted by researchers, RECs, other bodies or the public. During 2010/2011, six complaints were received from participants and researchers.[116]

2.4.3.2. Registration and Accreditation

A call for RECs to register with the Council was made in 2008[117] and, as of January 2011, the NHREC has registered about 33 health research ethics committees. RECs are required to report annually to the NHREC including information about membership, meetings held, numbers of protocols reviewed/approved/rejected, monitoring of research, and complaints.

In addition to assessing the data received from RECs to identify gaps, the NHREC conducts assessment visits to all registered RECs to prepare them for the audit process.[118] Although a plan for the registration, accreditation and audit processes is provided in guidance issued in 2004, working procedures for the auditing of RECs were only developed by the NRHEC in 2010/2011. Further information is not available about assessment visit activities.

2.5. Accreditation Systems

2.5.1. Australia

2.5.1.1. Regulatory Framework

In 1992, legislation established the Australian Health Ethics Committee (AHEC) as a principal committee of the National Health and Medical Research Council (NHMRC) with responsibility to advise Council on ethical issues relating to health and to develop human research guidelines.[119] The National Statement on Ethical Conduct in Research Involving Humans was issued in 1999 with a Human Research Ethics Handbook that contains guidance for application of the National Statement.[120] In addition, specific ethical guidelines have been developed by AHEC, including topics such as assisted reproduction, commercialization of products derived from human tissue, as well as Aboriginal and Torres Strait Islander health research.[121] In 2007, NHRMRC issued an updated National Statement and, in partnership with the Australian Research council and Universities Australia, issued the Australian Code for the Responsible Conduct of Research.

The NHMRC has made available a National Ethics Application Form that is a web-based tool for researchers of all disciplines to submit research to Human Research Ethics Committees (HRECs) for review.[122]

The Therapeutic Goods Administration (TGA) is the regulatory authority, under the Australian Department of Health and Ageing, that regulates medicines,

complementary medicines, medical devices, vaccines, blood products and biologics.[123] The TGA evaluates and authorizes clinical trials and special access arrangements for all types of therapeutic products.[124] There are two schemes under which clinical trials with investigational products or registered products used beyond the conditions of marketing approval may be conducted[125]:

1. Clinical Trial Exemption (CTX) Scheme requires a sponsor to submit an application to the TGA for evaluation of the product. If there are no objections by the TGA about the proposed use of the product, the sponsor may conduct several clinical trials under the CTX application. HREC approval and approval from the institution/organization of the clinical trials is also required.
2. Clinical Trial Notification (CTN) Scheme requires that all materials related to a proposed trial be reviewed by a HREC. The TGA is notified by the sponsor or by the investigator on behalf of the sponsor once the trial is approved. The TGA does not review any data before the trial begins.

In both the CTX and CTN schemes, the institution at which the trial is conduct gives the final approval and is considered to be the "Approving Authority". While the sponsor may choose which scheme is most appropriate, an HREC may also recommend that the CTX scheme be used if it does not have appropriate scientific and technical expertise to assess the safety of the product. Both ICH GCPs and the National Statement apply to the conduct of clinical trials. By approving a clinical trial, the HREC assumes responsibility for monitoring the conduct of the trial.[126]

2.5.1.2. Registration of HRECs

Only HRECs that are registered with the NHMREC may approve clinical trials under the Therapeutic Goods Act. Applications for registration of a HREC are assessed for compliance with the National Statement and include information about:

- The organization with primary responsibility for the HREC
- Establishment of the HREC
- HREC composition
- Indemnification
- HREC policies and procedures

Each registered HREC must submit an annual report the NHMREC with information about membership, meetings held, research reviewed, monitoring of research, complaints.[127] NHMRC assesses the information in the annual reports and compiles aggregated reports to the AHEC. The most recent annual report for 2009[128] indicates that:

- There are 221 registered HRECs. Most of the HRECs are associated with public or private hospitals and universities (70%) or government department/agency (13%), however, there are 5 HRECs that are part of "for profit" organizations.
- There were 2902 HREC members.

- 1658 meetings were held by HRECs with an average of 13.4 proposals considered per meeting
- 22,306 research proposals were reviewed by HRECs of which 99.04% were approved, 7.5% involved children and young people, 4.3% involved people with cognitive impairment, intellectual disability or a mental illness and 13.4% involved clinical trials.
- HRECs conducted monitoring of research by requiring an annual report from researchers and immediate reporting of adverse events, proposed changes to the research, unforeseen events, or early discontinuation of the research.
- 44 HRECs received complaints regarding the conduct of research (100 complaints), about the HREC review (11 complaints) or from Aboriginal or Torres Strait Islander researchers (1 compliant).

2.5.1.3. Clinical Trial Action Group

In 2009, the Minister of Innovation, Industry, Science and Research and the Minister of Health and Ageing formed the Clinical Trial Action Group (CTAG) to identify and progress reforms to ensure that Australia remains competitive in the clinical trials sector. In March 2011, CTAG released its report *Clinically Competitive: Boosting the Business of Clinical Trials in Australia* and its recommendations were endorsed by the Minister, including one specifically directed to NHMRC to implement a system of single ethical review for multi-centre human health and medical research.[129] Progress on the implementation of the 11 recommendations is publicly available on the Human Research Ethics Portal.[130]

2.5.1.4. National Certification Scheme

In 2003, the Australian Law Reform Commission and AHEC released a report, *Essentially Yours: The Protection of Human Genetic Information In Australia,* which recommended that the "first priority" of the NHMRC should be to develop and implement a quality improvement program for HRECs and a "second priority" should be for NHMRC to undertake a review of the need for an accreditation system.[131]

In 2006, the Australian Health Minister's Advisory Council asked the NHMRC to develop and implement a system for the single ethical review of research that would be recognized by all institutions involved in the research.[132] NHMRC established the Harmonization of Multi-centre Ethical Review (HoMER) project that has ultimately led to the National Certification Scheme. While the 2007 National Standard included a chapter on minimizing duplication of ethical review, very little detail on how this could take place was provided. A pilot project, completed in March 2011, demonstrated how a single ethical review by a HREC might be accepted by other participating institutions.[133] A Human Research Ethics Portal was launched in July 2011[134] followed by the issuance of guidance on research governance[135] and monitoring[136].

The NHMRC National Certification Scheme is a voluntary program through which the NHMRC reviews the ethical review processes of institutions to ensure that they can facilitate a single ethical review as per the National Statement.[137] Nominations are accepted twice per year and require submission of the HREC terms of reference, conflict of interest declarations, policies on disclosure and management of conflicts of interest, standard operating procedures, institutional policy on withdrawal of ethical approval as well as policies and procedures on monitoring the conduct of clinical trials or clinical intervention research. This is followed by an assessment visit.

As of January 2011, 43 HREC have been certified under this scheme. Each organization is publicly identified with the types of research that it has been certified to review (e.g., clinical trials by phase, mental health research, qualitative research, population/public health research).

2.5.2. Netherlands

2.5.2.1. Regulatory Framework

Research involving human subjects is regulated in the Netherlands under the Medical Research Involving Human Subjects Act (WMO)[138] that identifies Medical Research Ethics Committees (MRECs) as responsible for the review of medical research and the Central Committee on Research Involving Human Subjects (CCMO) as an oversight body. Hospital Ethics Committees (HECs) review clinical ethics and are separate from the MRECs. A revised version of the WMO, to implement the EU Directive on Good Clinical Practice[139], came into effect in 2006.

The CCMO reviews specific types of medical research, namely gene therapy, xeno-tranplantation, involving embryos or gametocytes, non-therapeutic studies and certain non-therapeutic observational research. The CCMO also issues directives regarding research, including the organization and working method of MRECs [140], membership requirements[141] and multicentre research.[142] A Manual for the Review of Medical Research Involving Human Subjects was issued by the CCMO in 2002 and updated in 2006. In recent years, templates have been developed and made available by the CCMO, e.g., model DSMB charter, clinical trial agreement, model insurance text, informed consent document and research protocol.[143]

In the Netherlands, the CCMO acts as the competent authority for research that is reviewed by an MREC since the competent authority only carries out a marginal review. [144] For the specific types of research that are reviewed by the CCMO, the Minister of Health, Welfare and Sport acts as the competent authority.[145]

The CCMO must approve the appointment of new MRECs members. In 2010, 107 requests for approval of new members were handled of which 7 individuals were not accepted due to lack of experience. In addition, standard operating procedures of the MRECs must be approved by the CCMO.

In 2011, all MRECs will be required to use *ToetsingOnline* for recording the review process. This portal will allow applicants to see the status of their application in the review process and will allow for the collection of metrics on the timeliness of the review by the CCMO.

The CCMO is responsible for *for cause* oversight of the MRECs, in response to incidents, reports or signals. In 2009, the CCMO began supervisory interventions with 2 MRECs and this resulted in the withdrawal of accreditation at one of the MRECs in 2011.

2.5.2.2. Accreditation of MRECs

In 2010, there were 27 accredited MRECs in the Netherlands. Of the accredited MRECs, 8 are associated with university medical centers, 14 are associated with other institutions and hospitals and 6 are non-institutional MRECs.

Since 2008, MRECs are required to review at least 10 protocols per year or they will lose their accreditation.

The CCMO maintains metrics on the operations of MRECs including a register of decisions. MRECs must submit an annual report to the CCMO.

The Netherlands Association of MRECs (NVMREC) encompasses the 27 accredited MRECs as well as approximately 35 non-accredited committees.[146] In the past, the quality of accredited MRECs was evaluated by audits conducted by NVMREC as part of its quality improvement program. Currently, NVMREC has a voluntary "intervistation" or peer visit system that was scheduled to begin in 2011.

2.5.3. United Kingdom

2.5.3.1. Regulatory Framework

In the UK, there are regulations related to research ethics committees (RECs) that are recognized to perform the review of clinical trials involving investigational medicinal products as well as requirements for RECs that are authorized as part of the National Health Service (NHS) for the review other types of research, as described below.

In 2000, the Central Office of Research Ethics Committees (COREC) was established by the Minister of Health to oversee the system of RECs in the NHS.[147] In 2001, the Department of Health published the Governance Arrangements for NHS Research Ethics Committees (GAfREC) which provided general standards and principles for Local RECs (LRECs) and Multi-Centre RECs (MRECs) .[148] Standard operating procedures (SOPs) for the provision of a single UK-wide ethical opinion were implemented in 2004.[149] A program of accreditation of RECs was implemented by COREC in 2005.[150]

Clinical trials with investigational medicinal products or medical devices are regulated by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK. In 2004, the UK Ethics Committee Authority (UKECA) was created and became responsible for establishing, recognizing and monitoring RECs that review research involving investigational medicinal products.[151] The UKECA has the authority to impose conditions on a REC regarding the class of clinical trials that it may review and to revoke its recognition of a REC.

There are two types of recognition by the UKECA:

1. Type 1 is for those RECs that may review phase I clinical trials in healthy volunteers. As of January 2012, there are 24 RECS with Type 1 recognition, including 3 non-NHS or independent RECs.
2. Type 3 is for those RECs that may review clinical trials in patients. As of January 2012, there are 59 RECs with Type 3 recognition.[152]

It is possible for an REC to have both types of recognition. Only RECs recognized by the UKECA may review clinical trials involving investigational medicinal products. RECs that are not recognized by the UKECA may review other types of research.

In 2007, the Appointing Authority for Phase 1 Ethics Committees (AAPEC) was established for the recognition of independent (non-NHS) RECs by UKECA that review clinical trials with investigational medicinal products involving health volunteers. In 2010, AAPEC no longer recognized 2 independent RECs after undertaking a capacity review and consultation. There are currently 5 independent RECs, appointed by the AAPEC and recognized by the UKECA.[153]

Also in 2007, the National Research Ethics Service (NRES) was established which incorporated COREC as well as the NHS in England. The independent RECs appointed by AAPEC are considered to be under the NRES. Authorized RECs in the NRES system are those RECs that are not recognized by the UKECA; they may review all research except for clinical trials involving investigational medicinal products. There are 37 authorized RECs in the UK. The NRES Quality Assurance (QA) department received ISO 9001 certification in 2009 that covered the accreditation programme for all RECs (both recognized and authorized RECs) as well as other NRES activities.

In 2011, the UK Department of Health revised the GAfREC[154] as well as the standard operating procedures[155] for RECs. Currently, each nation of the UK (i.e., England, Wales, Scotland and Northern Ireland) has a Department of Health Research Ethics Services (RES) that is responsible for ensuring that RECs are funded, resources and staffed appropriately. The RES for England also serves as the National Research Ethics Service (NRES) and its responsibilities include managing a national training programme for REC members and staff, maintaining standard operating procedures for RECs and developing a quality assurance programme, including accreditation of

RECs. In addition, the NRES performs some functions on behalf of the UK Ethics Committee Authority to provide advice and handle appeals.

Common application forms and standard operating procedures have been established and maintained by the NRES[156]. It is important to note that these NRES procedures do not apply to RECs that are not part of the UK Health Department RES. For example, a Framework for Research Ethics was put in place by the Economic and Social Research Council for research funded by the Council and is recommended for use by other funders.[157]

The Health Research Authority (HRA) was established in December 2011 as a Special Health Authority by the NHS to protect and promote the interests of patients and the public in health research. [158] The NRES was transferred to the HRA and there are plans to make improvements to the UK-wide e-submission system through IRAS (Integrated Research Application System) as well plans to use IRAS for the assurance and registration of researchers. It is anticipated that legislation will be introduced in 2012 so that HRA will become a non-department public body.

As part of the government's *Red Tape Challenge,* which "aims to cut unnecessary and over burdensome regulations", the MHRA is asking the public for views on the regulations governing their work. Medicines and clinical trials are two of the eight MHRA themes to be included in the debate. As of March 21, 2012, almost 28,000 comments about a wide variety of topics have been submitted to the Cabinet Office.[159]

2.5.3.2. Accreditation of RECs by NRES

NRES has a formal process for the accreditation of RECs that are part of the NHS (i.e., recognized and authorized RECs) to determine compliance with SOPs and GAfREC.[160]

This is a three-stage process involving the completion of a Self-Assessment Tool by the REC followed by an on-site review and finally observation of an REC meeting. The on-site review consists of semi-structured discussions, review of study files, membership and available resources. According to the NRES SOP on accreditation, this process takes approximately 3months from informing the REC of the proposed audit date to the decision letter being issued. The auditor can recommend full accreditation or provisional accreditation, with an action plan to be completed by the REC within 6 months or 3 months for issues that are perceived by the NRES to be high risk. Re-accreditation audits take place within one month of the third year anniversary of the accreditation decision date. The NRES has the authority to suspend, partially or in full, the accreditation of a REC or to withdraw the accreditation status of a REC.

During the period from April 2011 to September 2011, the NRES accreditation activities included[161]:

- One REC held a non-accreditation status due to not completing its action plan within the specified timelines
- Twenty-five RECs were audited and granted full or provisional (re)-accreditation
- Thirteen RECs were granted an extension of 3 or 6 months to complete their action plan
- Fifteen RECs achieved full accreditation after completion of their action plan

Trends are reported periodically regarding issues identified through the audits with respect to membership (e.g., indemnity, training, attendance, constitution, recruitment) and administration (e.g., compliance with SOPs, research ethics database, minutes/letters, timelines, coordinator training).

3. Provincial Activities

3.1. British Columbia

3.1.1. Legal Requirements Impacting REBs

In BC, the *Personal Information Protection Act* requires the consent of an individual prior to the collection, use and disclosure of personal information.[162] Provisions are made so that an organization may disclose without consent of the individual, personal information for a research purposes if certain conditions are met.

For public bodies in BC, the *Freedom of Information and Protection of Privacy Act* identifies the circumstances when a public body may disclose personal information in its custody or under its control for a research purpose.[163]

3.1.2. Michael Smith Foundation for Health Research

The Michael Smith Foundation for Health Research (MSFHR) is funded by the government of British Columbia and is the province's health research support agency.[164] Its mandate is to strengthen BC's health research enterprise. In 2007, it brought together interested stakeholders for a workshop as a key component of the BC Ethics Harmonization Initiative.[165] Following the workshop, the task force (composed of representatives from government, universities, health authorities, BC Cancer Agency, and others) that assisted in planning the initiative made the following recommendations:

- Creating common forms (e.g., application forms, informed consent)
- Developing a shared/common IT platform and tools accessible to researchers and institutions at which human subject research is undertaken in BC
- Exploring how ethics review for multi-centre trials can be more efficient, consistent and timely, possibly with some degree of inter-institutional reciprocity
- Developing common educational and training resources to be shared by research ethics boards.

In January 2010, proposals were requested for the development of a collaborative provincial process for ethics review of health research involving human subjects. The successful proposal was from a consortium of the University of British Columbia (UBC), Simon Fraser University and University of Victoria, who combined represent approximately 80% of academic health research in BC.[C] These universities conducted a pilot project looking at three models for collaborative ethics review.

A finalized model for the ethics review of health research has been developed and now formal legal agreements will be developed. The REBs of Vancouver Coastal Health Authority, Provincial Health Services Authority and Providence Health Care are already affiliated with UBC and currently utilize UBC processes under a Board of Record agreement. It is intended to bring the REBs of the other health authorities into this process.

3.1.3. BC Clinical Research Infrastructure Network

The BC Clinical Research Infrastructure Network (BCCRIN) was formed in April 2010 by the UBC Faculty of Medicine, BC Health Authorities, MSFHR, Life Sciences BC and Genome BC.[166] Membership has since been broadened to include 25 member organizations including the health authorities and universities.

The intent is to build a more streamlined process to attract clinical research to BC by harmonization and building capabilities to support clinical research. BCCRIN with UBC, Children's and Women's Health Centre, Providence Health Care, Vancouver Coastal Health, BC Cancer Agency and Fraser Health Authority are working towards harmonizing the negotiation of clinical trial agreement for industry-sponsored clinical trials.[167] The model clinical trial agreement developed by CIHR, Rx&D and ACAHO is currently being piloted. An MOU has been signed between the same six organizations to work towards harmonization and reciprocity of ethics review.

BCCRIN has a number of other taskforces:

- Professional Development Taskforce is looking at training or mentoring opportunities of research team members.
- Quality Systems Taskforce is looking at site certification or registration to ensure that there are quality systems at each of the research sites
- Research Methodology Taskforce is looking at creating a support hub for investigator-initiated trials to support researchers who need assistance with sample size calculations and statistical analysis plans

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[C] A review of selected ongoing industry-funded studies that are registered in clinical trials.gov with sites in BC, from January 1, 2011 to date, suggests that approximately 40% of the studies are conducted at private sites alone, approximately 40% at public sites alone and approximately 20% at a mixture of public and private sites.

In developing its business plan last year, BCCRIN identified six priorities:

1. Recruitment and retention of research participants
2. Streamlining study start up activities
3. Building research methodology capacity
4. Communication of assets and capabilities in BC
5. Innovative trial design and execution
6. External marketing to promote BC

3.2. Alberta

3.2.1. Legal Requirements Impacting REBs

In Alberta, the *Health Information Act* requires an ethics committee to review and approved research involving health information prior to the release of the information by the custodian. It requires the researcher to enter into an agreement with the custodian. The *Health Information Act Guidelines and Practices* requires that the REB performing such reviews be designated by the Minister.

3.2.2. Alberta Innovates – Health Solutions

Alberta Innovates – Health Solutions (AIHS) is an integral part of Alberta Innovates, which is a strategically aligned and integrated provincial research and innovation system. Under the Alberta Research and Innovation Act and Regulation, AIHS supports, for the economic and social well-being of Albertans, health research and innovation activities directed at the development and growth of health sectors, discovery of new knowledge and the application of that knowledge. As described in *Alberta's Health Research and Innovation Strategy*, one of the innovation platforms is "to enhance Alberta's clinical trials program and address barriers by improving the process for the recruitment of patients and by developing a streamlined research ethics review process".[168]

Since 2010, AIHS has facilitated and provided support services for the Health Research Ethics Harmonization project (HREH) that involves the six health REBs that are designated by the Minister and their host institutions. Reciprocity is one of two key goals of the HREH and was achieved in February 2011 making Alberta the first jurisdiction in Canada to have a *Health Research Ethics Reciprocity Agreement* put in place across the health REBs of the University of Alberta, University of Calgary, University of Lethbridge, the College of Physicians & Surgeons of Alberta, Alberta Health services and AIHS.[169] The agreement describes a two-step process with one REB providing full board review and the REBs of other participating sites performing expedited review of multi-center research. The other REBs may choose to perform full board review, when appropriate. The reciprocity process is currently being piloted and the Harmonization Implementation Committee will finalize the process in 2012. Part of that process includes development of common ethics review application forms, consent form templates and reporting, which are currently under development. A second key HREH goal is to produce provincial

level metrics through migration to a common electronic platform by all health REBs within the next year to support ongoing ethics review systems, communication, and improvement.

A related second provincial initiative for which AIHS provides support and project management is the Alberta Clinical Research Consortium. This initiative is platform-based work to align and harmonize administrative processes across institutions that support clinical research activity in Alberta. The strategic plan of the Alberta Clinical Research Consortium is currently being finalized. Three major thrusts are:

- Process efficiencies – The ACRC will develop clearer guidance and aligned, improved processes for clinical research across the province, including patient recruitment.
- Common legal review – Currently all clinical trial agreements involving research, using public resources in Alberta, are reviewed by two lawyers at University of Calgary and University of Alberta. Technological changes have been made to manage the workflow for clinical trial agreements and improve efficiencies.[170]
- Training standards – The intent is to develop provincial standards and opportunities for clinical research training, identify gaps in training and increase awareness of training opportunities throughout the province.

AIHS also supports two unique initiatives[171]:

- The Community Research Ethics Board of Alberta (CREBA) provides ethics review of health research being conducted in any community or organization that does not have access to one of the other five designated REBs in Alberta. Together, CREBA and the designated REB supported by the College of Physicians & Surgeons of Alberta provide ethics review services to researchers based in the community, including physicians and other professionals in private practice as will as community agencies involved in health-related research.
- ARECCI (A Project Ethics Community Consensus Initiative) was created in 2003 and has developed and refined two web-based decision support tools and a number of educational modules (in person and online) to support ethical considerations being taken into consideration for quality improvement and program evaluation projects. The two tools are the *ARECCI Ethics Screening Tool* and the *ARECCI Guidelines for Quality Improvement and Evaluation Projects*.

3.2.3. Northern Alberta Clinical Trial and Research Centre

The Northern Alberta Clinical Trial and Research Centre is a joint venture between Alberta Health Services and the University of Alberta. It was established in 1999 and partners with 13 hospitals and 6 primary care centres, encompassing over 250 qualified investigators. In 2004, the Centre was "the #1 least expensive location to perform clinical trials in North America".[172]

3.3. Saskatchewan

3.3.1. Legal Requirements Impacting REBs

In Saskatchewan, the *Health Information Protection Act* states that a trustee or designated archive may use or disclose personal health information of research purposes with or without the express consent of the subject provided that the research has been approved by a research ethics committee that has been approved by the Minister.[173] Currently, 4 provincial REBs and one independent REB have been designated by the Minister. Provisions are made for research projects where it is not reasonably practicable for consent of the subject to be obtained.

3.3.2. Saskatchewan Health Research Foundation

The Saskatchewan Health Research Foundation funds and facilitates the work of health researchers, strengthens health research and innovation and maximizes the growth of the R&D sector of the health industry.[174] The 2010-2011 program included thirteen new investigator establishment and equipment grants, totaling $1.15 million. Major ongoing initiatives are underway for patient oriented research, Rick Hansen spinal cord injury research and the funding of clinical trials for MS liberation treatment.

3.3.3. Saskatoon Centre for Patient-Oriented Research

The University of Saskatchewan, as part of a joint initiative with the Saskatoon Regional Health Authority and the Saskatchewan Cancer Agency, launched the Saskatoon Centre for Patient-Oriented Research in the May 2011. This three-year pilot project will give health researchers space for patient centered research at the Saskatoon City Hospital, including 8 dedicated beds. "Until now, Saskatchewan was the only province in Western Canada without a hospital-based patient-oriented research institute or dedicated clinical trials facility."[175]

3.3.4. Saskatchewan Association of Health Sciences Network

The Saskatchewan Association of Health Sciences Network is comprised of members from the University of Saskatchewan, Saskatoon District Health, Regina Health District, Saskatchewan Health, Saskatchewan Learning and the Health Districts. It is leading the ethics harmonization initiative amongst the 4 provincial REBs that have been designated by the Minister of Health. Common application form and consent form templates have been developed. There is interest in developing partial reciprocity agreements between the 4 REBs in Manitoba for multi-center research. It is envisioned that such a system would permit participating REBs to perform expedited review of multi-center research after one REB has provided full board review and approval. Legal issues related to liability and insurance need to be taken into consideration.

3.4. Manitoba

3.4.1. Legal Requirements Impacting REBs

In Manitoba, the *Personal Health Information Act* states that a trustee may disclose personal health information to a person conducting health research provided that the research has been approved by the Health Information Privacy Committee (for information maintained by the government or a government agency) or an institutional research review committee.[176] The person proposing the research project must enter into an agreement with the trustee. If a research project requires direct contact with subjects, then consent of the subjects must be obtained.

3.4.2. University of Manitoba

The University of Manitoba is the largest, most comprehensive and only research-intensive post-secondary educational institution in the province.[177] Two of the five University of Manitoba REBs review health research (Biomedical REB of the Faculty of Medicine and the Health Research Ethics Board overseen by the Office of the Vice-President, Research & International). In the two-year period of 2010 and 2011, the Biomedical REB reviewed 321 research projects which included 209 clinical trials involving drugs, 6 clinical trials involving medical devices and 2 clinical trials involving natural health products.[178]

A Research Quality Management program, which was initiated in the fall of 2008, provides educational support to members of the research community, through collaborative workshop initiatives, or through consultation from the REB or researchers themselves. For investigator-initiated clinical research that would be reviewed by the Biomedical REB and potentially submitted to Health Canada as a Clinical Trial Application, a process is under development for the appropriate and timely follow-up of research activities.

The university is exploring on-line GCP training that would further complement existing resources and has asked Health Canada for collaborative opportunities to provide the research community with educational support specific to the conduct of clinical trials. [179]

3.4.3. The Life Science Association of Manitoba

The Life Science Association of Manitoba provides leadership and support for the prosperity and sustainable development of the Manitoba life science industry.[180] Manitoba is home to many biotechnology and medical device companies. The Life Science Association of Manitoba has developed training programs with industry and Red River College for new and expanding businesses.

3.5. Ontario

3.5.1. Legal Requirements Impacting REBs

In Ontario, the *Personal Health Information Privacy Act* requires that disclosure of personal health information to a researcher for the purpose of a research project may be done provided that the researcher has obtained prior approval of a research ethics review body and has entered into an agreement with the custodian to protect the confidentiality and security of the information.[181]

3.5.2. Ontario Cancer Research Ethics Board

The Ontario Cancer Research Ethics Board was introduced in December 2003 by the Ontario Cancer Research Network (OCRN, now the Ontario Institute for Cancer Research or OICR) in collaboration with Cancer Care Ontario and local REBs in Ontario. The intent was to reduce the workload and duplication associated with reviews of the same study by multiple REBs and to simplify and accelerate the initiation of multi-centre oncology clinical trials in Ontario.[182] In addition, OCREB serves as the REB for OICR's Ontario Tumour Bank. In 2009, the OCREB Advisory Committee was replaced with the OCREB Governance Committee that provides advice and recommendations to the OICR Board to ensure the ongoing independence of OCREB decision-making.

The number of centers using OCREB as the Board of Record for cancer clinical trials has increased over time, as centers did due diligence activities and developed trust in the OCREB process. Currently, 24 centers, out of the 27 centers in Ontario that conduct cancer clinical trials, use OCREB. OCREB reviews each clinical trial using full board review while the centre applications are reviewed by expedited review. OCREB staff perform an assessment of the clinical trials and may request changes prior to the REB review of the research. In 2011, OCREB implemented an online submission system (OCREB Online, aka O2).

OCREB has developed a consent form template that has been accepted by all participating centers and adds institutional requirements based on a center profile that has been approved by the REB. A common consent form template is being developed with the National Cancer Institute of Canada Clinical Trials Group and the BC Cancer Agency REB.

OCREB has reviewed about 61-94 clinical trials per year over the past 5 years and currently oversees approximately 300 active studies involving 785 centre applications. OCREB maintain metrics of the review process for clinical trials as well as the review process for centers. OCREB timelines from submission to approval have consistently been approximately 60 days for the review of new clinical trials. In the fall of 2011, these timelines were reduced to about 40 days by the implementation to the online system that has significantly reduced the administrative workload. Similarly, the expedited review times for review and

approval of centers was reduced from 6-10 business days in 2011 to approximately 3 business days in January 2012.

Educational activities include monthly teleconferences with centers as well as hosting of periodic education days. OCREB has an outreach program with REB coordinators who visit centers to provide education on REB expectations and to facilitate the use of the online system.

Quality activities include plans to establish an internal audit program to evaluate the REB as well as an external audit program to review the consent documents as implemented at centers. Feedback on the OCREB process has been evaluated using customer satisfactions surveys.[183]

3.5.3. Toronto Academic Health Science Network

The Toronto Academic Health Science Network (TAHSN) is a consortium of the University of Toronto and its fourteen affiliated academic hospitals. Its mission is to "serve as a leader in Canadian health care by developing collaborative initiatives that optimize, advance, and sustain a shared academic mission of high quality patient care delivery, education, knowledge transfer, and research innovation".[184] One of the seven TAHSN sub-committees is the TAHSN Research Ethics Committee or TREC.[185]

TREC was established in 2006 with a two year limited mandate and became a Standing Committee in 2009 to inform and advise the TAHSN Research Committee on research ethics. In 2005, it was estimated that approximately 4300 studies were reviewed by REBs across TAHSN – this includes all types of research and the proportion that are clinical trials is not available. In that same year, TAHSN insitutions held the largest number and amount of research funding of the 17 Canadian medical schools.[186]

TREC currently has four working groups: the REB Chairs Working Group, Clinical Research Agreements Working Group, Research Administrators Working Group and *Ad Hoc* Privacy Officers Working Group. Involvement and participation of all TAHSN members to reach consensus on TREC documents and reports has improved the uptake of the harmonized materials. Reports and other documents generated by or related to TREC include:

- *TAHSN Harmonized Human subjects Research Ethics Application*
- *TAHSN Harmonized Checklist and Order of Elements for Informed Consent Materials*
- *TAHSN Harmonized Template Data and Biological Samples Transfer Agreement*
- *TAHSN Task Force on Human Subjects Research Report*
- *Principles for Development of Policy and Guidelines on Security of Personal Health Information used for Research Purposes*
- *TREC Acronym Guide*

Current TREC initiatives include three educational events for 2011/2012 academic year, TREC Task Force on Insurance, TREC Task Force on Standard Operating Procedures as well as the implementation of the Research Privacy eLearning Module across University of Toronto and TAHSN hospitals. Systems are being evaluated so that a common platform for ethics submissions may be implemented in the future.

3.5.4. Council of Academic Hospitals of Ontario

The Council of Academic Hospitals of Ontario is the association of 25 academic hospitals and their research institutions. Last year, CAHO hospitals launched over 670 clinical trials. In 2010, CAHO finalized the *Statement of Principles to be Considered When Negotiating a Clinical Studies Agreement* that was intended to be a set of guiding principles when negotiating with industry.[187]

3.5.5. Public Health Ontario

Public Health Ontario has developed a model of ethics services for public health studies in Ontario that includes a planned mechanism for centralized review of multi-site studies with input from local participating sites.[188] There are 36 public health units across the province, some of which are affiliated with universities. Operational aspects are under development and it is hoped that the proposed REB will be established in late 2012 or early 2013. At the present time, no Health Canada regulated clinical trials are underway.

3.5.6. Clinical Trials Ontario

In April 2010, the Ontario government announced its new Life Sciences Commercialization Strategy with a commitment to establish a new province-wide coordinating infrastructure to streamline administrative processes and ethics reviews for multi-centre clinical trials in order to increase the speed of patient recruitment.[189] The intent of this initiative is to build on Ontario's existing strengths as an attractive location for clinical research and provide Ontario with a more competitive edge to maximize its share of global clinical trials activity. Clinical Trials Ontario (CTO) was incorporated as a not-for-profit organization in December 2011. In January 2012, its skill-based Board of Directors was put in place. The interim Executive Director is currently developing the CTO strategic plan, which will include a sustainability plan for ongoing fiscal stability after the initial government funding is expired.

CTO will have three main areas of focus:

- Streamline the ethics review and other administrative processes for multi-centre trials, including applications and contract negotiations, to expedite patient recruitment and trial start-up times without compromising patient safety
- Standardize REB processes based on internationally accepted common standards
- Promote Ontario's clinical trials sector and the social value of trials

CTO activities are intended to not only attract clinical research to Ontario but will also increase public awareness and confidence in clinical trials.

3.5.7. Educational Opportunities in Ontario

There are a number of educational opportunities related to clinical research in Ontario, including but not limited to:

- Humber College Clinical Research program[190]
- The Michener Institute has a Clinical Research Associate Graduate Certificate program[191]
- McMaster University has a Certified Clinical Research Associate program[192]
- Society of Clinical Research Associates has chapters in Toronto, Ottawa and Kingston[193]
- Clinical Research Association of Canada is developing an online certification program[194]

3.6. Quebec

3.6.1. Legal and Regulatory Requirements Impacting REBs

In 1994, public scrutiny of clinical research in Quebec was increased after the disclosure of falsification of data by Dr. Roger Poisson who was an investigator in a major North American breast cancer study. The Minister established a committee to look into control mechanisms in clinical research. In response to the *Deschamps Report*[195], the Minister put in place the *Plan d'action ministériel en éthique de la recherche et en intégrité scientifique* (PAM).[196] Following the adoption of the PAM, changes were made to the *Quebec Civil Code* to improve the protection of minors and incompetent adults.

The *Quebec Civil Code*, articles 20-25 deal with research involving humans. Article 21 requires that a "minor or incompetent adult may not be submitted to an experiment if the experiment involves serious risk to his health or where he understands the nature and consequences of the experiment, if he objects. … Such an experiment must be part of a research project approved and monitored by an ethics committee…formed by the Minister of Health and Social Services or designated by the Minister…". A legal notice describes the minimum conditions that must be in place for a REB to be formed by or designated by the Minister.[197]

In Quebec, there are two privacy laws for public and private institutions:

- *An Act Respecting Access to Documents Health by Public Bodies and the Protection of Personal Information*
- *An Act Respecting the Protections of Personal Information in the Private Sector*

3.6.2. The Ethics Unit of the Ministry of Health and Social Services

The Ethics Unit of the Ministry of Health and Social Services (MSSS) was created in 2004 to design and implement policies, guidelines and strategies related to ethics. There are approximately 7 staff in the Ethics Unit. Its mandate includes: [198]

- The implementation and monitoring of the ethical framework of research activities related to health and social services
- Reviewing and updating the *Plan d'action ministériel en éthique de la recherche et en intégrité scientifique*
- Monitoring the implementation of Article 21 of the *Quebec Civil Code*
- Supporting ethics committees in the research network
- Developing guidelines on ethics in health and social services

The Ethics Unit maintains a document center on its website which includes guides, policies, ministerial directives and interpretation texts published by the Unit as well as normative provincial, federal and international references.

In 2005, the Ethics Unit launched an online tutorial in research ethics in both French and English. [199] The first module covers basic scientific and ethical knowledge that underlie research. The second module is more specific training director at REB support staff and REB members. The third module is designed for everyone and covers specific topics in greater detail. This tutorial is currently being reviewed and updated.

3.6.3. Designated REBs

In Quebec, there are 58 REBs that have been designated by the Minister to review research including research involving minors or incompetent adults and 33 non-designated REBs that may review research involving competent adults only. In addition, there are 69 clinical ethics committees that have an advisory role regarding ethics in the context of care. [200]

In order to become a designated REB in Quebec, the Chairman of the Board of Directors of the institution must submit to the Minister a formal request for designation.[201] The application must be accompanied by:

- The formal mandate of the REB
- Information about the composition and, for each REB member, proof of their appointment, what role they represent on the REB, and expertise and knowledge of research ethics (e.g., as documented curriculum vitae)
- Written procedures of the REB and an attestation that they have been approved by the Board of Directors of the institution
- Procedures for the ethical evaluation of research
- Mechanisms for ongoing ethical oversight of research
- Processes for management of conflict of interest of REB members
- For non-designated REBs, a copy of its latest annual report

In addition, the application must describe the institutional structure governing research and demonstrate that it addresses the requirements of the PAM, including:

- The regulatory framework addressing each of the 18 requirements of the PAM with an attestation by the Chairman of the Board of Directors that this framework has been adopted
- A declaration certifying that a registry of ongoing institutional research projects has been established
- The measures that have been put in place to maintain a registry of research subject, while respecting confidentiality

Applications for designation are reviewed by the Ethics Unit to ensure that it meets the minimum requirements and is consistent with the *Quebec Civil Code* and the PAM. Modifications or clarifications may be requested by the Ethics Unit. When an application is deemed acceptable, the Minister issues a letter designating the REB under article 21. Designation is valid for three years.

Designated REBs must complete an online annual report to the Minister. In order to facilitate completion of the report, the institution with the designated REB can access this report and enter information on an ongoing basis. The annual report is extremely detailed and some of the information to be included is described in Appendix 2. The annual report must be signed by the Chairperson of the Board of Directors of the institution. The annual report is reviewed by the Ethics Unit and clarification of any deviations or discrepancies from the minimum requirements may be requested.

The Minister has the authority to revoke the designation status of an REB, however, this has not occurred to date.

3.6.4. Fonds de recherche du Québec - Santé

Research that is funded by the Fond de recherche du Québec - Santé (FRQS, formerly Fonds de recherche Santé Quebec or FRSQ) must comply with the *FRSQ Standards on Human Health Research Ethics and Scientific Integrity.*[202]

The FRQS has taken a leadership role in Quebec for clinical research at publicly funded institutions. In 2007, a comprehensive set of standard operating procedures (SOPs) were created specifically for academic research projects as well as pharmaceutical clinical trials as a result of a collaborative effort with FRSQ, Government of Quebec, four Quebec universities as well as 19 FRSQ-funded research centers. With each of the 26 SOPs, a standardized tutorial is provided to assist in the implementation of the procedure. The SOPs are made available in French and English and are intended to be customized by the end users themselves at clinical research sites, research institutions or groups.

In 2009, the FRSQ adopted an action plan to implement the Quebec's Biopharmeutical Strategy.[203] The plan identifies actions to maintain FRSQ structure and coordination of health research in Quebec include:

- Maintain support for centers, groups and research networks to ensure optimum structure of the health research system in Quebec.
- Maintain the availability of SOPs for clinical research and to keep them up-to-date.
- Make training programs available on GCPs.
- Develop a new initiative to support clinical research in consultation with ministerial partners.
- Develop tools to facilitate ethical practices in research (such as training, forms, multi-center evaluation).
- Continue to work with other organizations interested in development standards and practices surrounding research health (ethics, clinical research, other).

Five teams were established and are working on multicenter trials, negotiation of clinical trial agreements, ethics training for researchers, steamlining study start up, and key performance indicators. Outputs from the teams are expected to undergo review by a Steering Committee in April 2012.

3.6.5. Central REB Reporting to the Minister

The Central REB supports researchers in Quebec who do not have access to a designated REB. The Central REB is responsible to the Minister and is hosted in the premises of the FRQS. Initially, the mandate of the Central REB was to review research subject to article 21 of the *Quebec Civil Code.* Since 2008, the mandate of the Central REB was extended by the Minister to include all types of research. The Central REB also acts as an appeal body for any institution that does not have an appeal committee or for the Main REB under the multicenter mechanism (see below).[204]

Detailed guidance documents have been developed to help researchers prepare informed consent documents for research involving adults, minors, or incompetent adults. Recent efforts to improve the timeliness of the Central REB process have resulted in significant improvements; REB review letters are typically issued within 24-48 hours of the REB meeting.

3.6.6. Quebec Multicenter Mechanism

In April 2008, after a series of consultations, the MSSS established the multicentre mechanism for research conducted at more than one Quebec institution in the MSSS system.[205] This mechanism was intended to improve the protection of research subjects, ensure better use of human and financial resources and streamline the process for multicenter research. The Coordinating Principal Researcher is responsible for being the point of contact with the Main REB.

Other participating researchers (local researchers) report to the Coordinating Principal Researcher as well as to their own institution. Upon receipt of the preliminary decision by the Main REB, local REBs conduct a preliminary review of the project focusing on the skills and qualifications of the local researcher, value of the project to the local community, suitability of documents for the institution's subjects and ongoing oversight. After review by the local REB, the institutional authority at the local institution notifies the Main REB of the institution's decision regarding the research.

In response to feedback from researchers and institutions, the MSSS subsequently advised that Principal Researchers who intend to conduct multicenter research at four or fewer Quebec institutions have the option to use the mechanism or apply for ethics review at each participating institution. It is important to note that this mechanism only applies to institutions that are part of the MSSS network (e.g., universities and hospitals) and does not apply to research conducted by researchers in the private sector.

The MSSS has developed documents to support the mechanism, including Frequently Asked Questions, guides, forms, template letters, and explanatory models.[206] Twelve forms developed for the mechanism include an application form, report forms for amendments, modifications, deviations, new information, adverse events, accidents, monitoring or audit by a third party, temporary suspension and resumption, and annual re-approval. These forms are used by researchers for the transmittal of information to the Main REB.

Two years after the implementation of the multicenter mechanism, the MSSS sought feedback on the mechanism from REBs and other institutional stakeholders as well as from researchers and research sponsors.[207] When asked about current perceptions of the mechanism, the majority of REBs and researchers responded that it had not met its goals since it had not improved the protection of research participants, had not reduced human and financial resources, nor simplified the process. Respondents varied in their opinion on whether the guides and forms facilitated the process, likely due to the larger institutions already having their own standard forms and template letters in place.

As part of the review conducted in 2010, one pharmaceutical company analyzed the timelines for REB review of six multicenter clinical trials conducted in Quebec after 2008. The average time to REB approval was approximately 27 weeks for research reviewed by the multicenter mechanism while the average time was about 10 -11 weeks for clinical trials at a single center.

Possible suggestions to improve the mechanism included applying the mechanism to certain types of research only, simplification of the process and technical changes to support the mechanism.

3.6.7. Ministère de Développement économique, Innovation et Exportation

Quebec's Biopharmaceutical Strategy is intended to provide development support for biotech and biopharmaceutical companies.[208] The Quebec government will be providing financing, from 2008-2013, of $122 million to implement its strategy. The strategy has five goals:

1. Step up development and spinoffs from research
2. Support the development of biotechnology firms
3. Support the development of biopharmaceutical firms
4. Maintain a labor force able to meet the industry's needs
5. Promote Quebec's image as a biopharmaceutical hub worldwide

One interesting project under this program involves several private and public clinical research organizations in the Eastern Townships region – namely, Q & T Research, Diex Research, Research Center on Aging, Centre de santé et de services sociaux – Institut universitaire de gériatrie de Sherbrooke and the Centre de recherche clinique Etienne-Le Bel at the Centre hospitalier universitaire de Sherbrooke – with deliverables being rolled out in 2012. The overall objective of their project is to create synergy between these organizations to improve competitiveness by increasing the visibility of clinical research in the region and to provide the population with simple and accessible information tools so that they can learn more about clinical research.[209]

3.7. New Brunswick

3.7.1. Legal Requirements Impacting REBs

New Brunswick has specific privacy legislation for organizations operating in the public sector but has no specific privacy legislation for organizations operating in the private sector.[210] The federal *Personal Information Protection and Electronic Documents Act* applies to the private sector.

The *Personal Health Information Privacy and Access Act* requires consent of the individual for the collection, use and disclosure of personal health information by a custodian.[211] A custodian may disclose personal health information to a researcher if the project has prior approval by a research review body that operates in conformity with the TCPS.[212]

3.7.2. Regional Health Networks

There are two regional health authorities in New Brunswick. Horizon Health Network services the provinces of New Brunswick, Prince Edward Island and Northern Nova Scotia and encompasses over 100 facilities, clinics and offices.[213] Vitalite Health Network has 41 facilities including eleven hospitals.[214] Each regional health authority has an REB that reviews research involving humans.

The Horizon Health Network reviewed 150 research projects last year of which approximately 55 were clinical trials. The report of the last site visit by Accreditation Canada indicates that the Horizon Health Network's "solid ethics framework and a research ethics board" were recognized as one of it strengths. Accreditation Canada indicated that "the Horizon Health Network is the only health authority in Canada to successfully implement a centralized research ethics review process replacing the four separate and differently operating systems that existed prior to amalgamation" and that the "organization is the only institution in Canada to employ a full-time REB Chair".[215] Typical review times are 40 days for a full board review and 10 days for research reviewed by expedited review.

Discussions are currently underway to develop reciprocity agreements between the Horizon Health Network and the medical school of Dalhousie University in St. John. Currently, research at the St. John campus undergoes dual review.

Train-the-trainer sessions have been conducted at Horizon Health Network so that it could implement the "Diving into Clinical Trial? Sink or Swim!" program which was developed by the Capital District Health Authority in Nova Scotia.

3.8. Nova Scotia

3.8.1. Legal Requirements Impacting REBs

There are two provincial requirements that impact REBs in Nova Scotia:

- Personal Health Information International Disclosure Protection Act prohibits disclosure of personal information outside the country
- Personal Health Information Act requires REB approval for the disclosure of personal health information.

3.8.2. Capital District Health Authority

In Nova Scotia, the Capital District Health Authority is the largest academic healthcare facility in Atlantic Canada and is closely affiliated with Dalhousie University and IWK Health Sciences Center. This facility has been exploring ways to harmonize the ethics review process for many years. Last year, the Capital Health REB reviewed 340 submissions of which 87 were clinical trials subject to Health Canada regulations.[216]

Many of Capital Health's researchers are also affiliated with the other institutions of Dalhousie University and the IWK Children's Health Centre and an inter-institutional agreement was put in place. In 2010, a common research data management system was implemented at Dalhousie University, Capital Health and the IWK Health Center to facilitate information sharing across these institutions. With its implementation, the research ethics and contract/grant administration processes were streamlined.[217]

In January 2012, the CEOs of the district health authorities approved moving forward with the plans of the research ethics harmonization group.[218] The plan includes utilizing one of the Capital Health REB Working Groups for facilitating the ethical review of multi-site research within the province. This REB will continue to be managed from the Capital Health REB office but will include members from across each health district in Nova Scotia using TeleHealth videoconferencing. Whenever possible, the REB members from the sites where the research is planned will be assigned as the primary and secondary reviewers of the research. Each existing REB in the health districts would maintain its autonomy, i.e., it has the right to refuse a study at their site. Standard Operating Procedures, indemnification agreements and reciprocity agreements are under development with a goal of implementing the multi-center review process by the fall of 2012.

Research education and auditing has been in place at Capital District Health Authority since 1998 and the program has evolved over time and currently supports about 300 investigators and their research staff. Staff from research institutions in Nova Scotia and from other provinces are welcome to participate in the educational program. A wide array of educational activities, specifically designed to build capacity for high quality research, are made available to new researchers and their staff including, but not limited to:[219]

1. Orientation to institutional requirements, including policies and procedures
2. "Diving into Clinical Trials? Sink or Swim!" – a two day workshop for new research staff
3. Mentorship program for new research coordinators
4. "Nuts and Bolts of Research for Residents"

In addition, a robust program of continuing education is addressed by a variety of lectures, panel discussions, workshops and computer skills training. Telehealth videoconferencing is utilized to extend these programs to 3-5 research sites in Atlantic Canada annually. In addition, train-the-trainer sessions have been conducted so that other organizations can implement the "Diving into Clinical Trial? Sink or Swim!" program. Certificates of attendance are issued for all sessions. In addition, the Society of Clinical Research Associates (SoCRA) certification exam is offered annually.

The close working relationship between the Program Manager-Education and the Program Manager-Research Quality ensures that relevant audit or inspection findings are incorporated into the education sessions as a preventative action. A comprehensive quality management program was implemented at Capital Health in 2003 to:

- Ensure that research is conducting according to the highest scientific and ethical standards and is compliant with local, national and international requirements.
- Promote a culture of research excellence through continuous quality improvement.[220]

Quality planning activities include the development or facilitation of research policies and procedures for the institution as well as providing assistance to research teams on SOPs, templates and other quality tools. For example, research staff are required to complete a "Research Policy Review Checklist" annually to ensure that they are familiar with all institutional policies and this is retained in the employee's training binder.

The Program Manager-Research Quality is also responsible for the conduct of internal quality audits, preparation of research teams for sponsor audits (upon request) and facilitation of regulatory authority inspections. Since 2003, over 70 internal audits have been conducted. The outcome of these quality activities is fed back to educational opportunities to build knowledge as well as policy or process changes, as appropriate.

3.9. Prince Edward Island

The Prince Edward Island REB reviews human subject research involving Health PEI. In 2011, there were approximately 70 research projects that included oncology clinical trials as well as quality improvement and program evaluation projects. The University of PEI does not conduct clinical trials.

3.10. Newfoundland and Labrador

3.10.1. Legal Requirements Impacting REBs

In Newfoundland and Labrador, the Health Research Ethics Authority Act came into force on July 1st, 2011. It was developed over the course of many years in response to the activities of outside researchers who visited the province to conduct research and collect biological samples without the knowledge of local researchers, REBs or health officials[221]. The Act requires that all health research done in the province be reviewed and approved by a local research ethics review board. Research that received REB approval prior to July 1st, 2011 continues to be overseen by the REB that performed the initial review.

3.10.2. Health Research Ethics Authority

The Health Research Ethics Authority (HREA) oversees ethics review of health research by the Health Research Ethics Board (HREB) or an approved health research ethics review body. The HREB was appointed by the Authority to review health research projects involving humans, all clinical trials and genetics research and monitor the research activities of person engaged in health research in the province. Currently there are about 400 active studies overseen by the HREB. [222]

Other health research may be reviewed by other approved ethics review bodies. The Interdisciplinary Committee on Ethics in Human Research (ICEHR) is an ethics review committee of Memorial University that focuses on social sciences and humanities and studies utilizing qualitative methods. The Western Health REB discontinued providing ethics review for research on October 19, 2011.[223]

This past year has been a transition year for the HREA in that all HREB members received orientation training, templates are being updated to reflect HREA, and activities have been ongoing to ensure that all regional health authorities are aware of HREA. Efforts have been made to ensure timeliness of reviews and average time from submission to approval is approximately 14 days.

The HREA has reporting obligations to the Minister; strategic directions and an activity plan are under development and the first annual report will be issued in June.

3.11. Yukon

Although health research is ongoing in the Yukon, no known Health Canada regulated clinical trials are underway.[224]

3.12. Pan-Canadian Activities

3.12.1. Network of Networks

The Network of Networks (or N2) is a not-for-profit organization, created in 2007, that "brings together multiple existing disease networks, universities, institutions, sponsors and other stakeholders willing to join forces to enhance Canada's research capability and capacity". Member organizations have access to:

- A comprehensive set of Standard Operating Procedures for research sites and associated tools such as presentations and quizzes to help in the implementation of the SOPs. These procedures are regularly reviewed and updated to ensure continued compliance with regulatory requirements.
- CITI-Canada, an online research education program with courses on GCP, Responsible Conduct of Research, Basic Biomedical Ethics, Biomedical Safety and Privacy.

N2 has limited staff who support the maintenance of the SOP and training program; staff are physically located at OICR. A close relationship with the Health Product and Food Branch Inspectorate was established. It is through the work of volunteers and committees that the content of these materials are reviewed and updated using feedback from regulatory authority inspections and sponsor audits. Working groups are developing standardized metrics of research operations as well as national recruitment awareness campaigns.

3.12.2. CIHR Strategy for Patient-Oriented Research

In 2011, after extensive consultation, the CIHR announced *Canada's Strategy for Patient-Oriented Research* (SPOR). A National Steering Committee was established to oversee the development and implementation of an action plan that is intended to transform the health care landscape in Canada through research and innovation.[225] There is considerable interest at the provincial level in this funding opportunity. The goals of the SPOR program include:

- To grow Canada's capacity to attract, train and mentor health care professionals and health researchers in patient-oriented research and create sustainable, patient-oriented career paths across the breadth of health disciplines.
- To establish an integrated, leading-edge, pan-Canadian clinical research infrastructure along the full continuum of patient-oriented research. To strengthen organizational, regulatory and financial support for clinical studies in Canada and enhance patient and clinician engagement in these studies.
- To improve processes for the early identification of best practices, expedite their development and harmonization into guidelines for patient care, and support their adoption by clinicians, caregivers and patients.
- To create a collaborative, pan-Canadian process for identifying, establishing and addressing patient-oriented research priorities.

4. Concluding Remarks

In concluding this paper, I would like to share my thoughts on some of the common themes that emerged during the interviews with Canadian colleagues, first, with regards to accreditation and, secondly, with regards to provincial initiatives.

It is readily apparent that accreditation is not well understood across Canada, even though there have been several reports on how such a system might be established. There is no agreement amongst the people that I interviewed on what needs to be accredited: is it the REB or the PEERH? The Regulatory Impact Analysis Statement, which accompanied Health Canada's clinical trial regulations in 2001, identifies the lack of an accreditation system in Canada *for REBs*.

Although the work of the NCEHR task forces and the Experts Committee clearly support accreditation of an organization's entire PEERH, there are some individuals

who prefer to minimize change and, hence, oppose such an approach. On the other hand, individuals who have been involved as site visitors for NCEHR or AAHRPP fully appreciate that the ability of an REB to successfully fulfill its role depends crucially on how it is supported by the highest levels of the organization. Indeed, this is consistent with the TCPS and the legal framework for REBs in the health system in Quebec. The role of organizational support in protecting human research subjects, going beyond a "culture of compliance" and the need to move towards a "culture of conscience" are very well described in the literature.[226 227 228 229] Measures of ethical quality[230] and protection of research participants are sorely needed; the absence of scandal in Canada does not mean that we shouldn't be continually working to improve the system.

Health Canada's efforts with the CGSB to create a national standard for REBs that review clinical trials appears to have confounded the situation since, as written, this standard would apply solely to the REB activities within an organization and will not address all aspects of a PEERH. While there are or will be standards addressing components of a PEERH (i.e., sponsor, investigator and REB), there are no formally defined Canadian standards that would apply to the overall PEERH of an organization and this would need to be addressed before a PEERH accreditation system can be implemented.

A second common concern was raised about whether a Canadian system of accreditation should apply only to clinical trials or whether it should apply to all research. This is a concern because many REBs in Canada review many types of research and there is a fear that, in adopting the national standard, more rigorous biomedical review processes would be inappropriately applied to other types of research. Again, the past work was clear that there needs to be adequate processes in place to protect all human subjects and that the divide between biomedical research and social sciences is not always so clear. This is consistent with the AAHRPP process that accredits the entire program at an organization.

On the other hand, in countries where registration or accreditation systems have been implemented by the health authority, the focus has been on ethics committees that review health research or regulated clinical trials. This has resulted in two types of ethics committees in some countries. In the many countries, there has been a consolidation of ethics committees that review clinical trials, partly from requirements regarding a minimum volume of clinical trials that an accredited or designated ethics committee must review. The outcome appears to be that there are fewer ethics committees which each oversee a significant volume of research studies and, hence, maintain their expertise regarding clinical trial methodology and research ethics.

This is consistent with what is happening in the US where IRBs with a low-volume find it to be more economically efficient if they outsource their ethical review process.[231] American academic institutions are outsourcing industry-funded

research to independent IRBs at an increasing rate.[232] [233] [234] [235] This not only eliminates the redundancy involved in multiple reviews but allows each institution to focus on investigator initiated research as well as other responsibilities related to human subject protection, such as research quality and monitoring.[236]

One of the anticipated benefits of an accreditation system in Canada would be to build trust in those organizations that had achieved accreditation. Individuals, who have been involved in developing reciprocity agreements, remarked that it was or will be possible to operationalise the agreement only after a confidence-building phase. Many individuals expressed a very low level of risk tolerance because we were discussing *human* subject research. I was stuck by the apparent disconnect when told that some of these same organizations did not perform any due diligence activities to assure themselves that their partners in the reciprocity agreement did indeed meet the regulatory, legal, and ethical standards related to ethics review.

The distribution of R&D activity and clinical trials varies across the provinces, as shown in Figure 5 (based on the data provided in the Introduction section). This is reflected in the size and scope of the activities taking place in each province. Although data was obtained from only one clinical trial sponsor, it is likely that the majority of clinical trial sites in Canada are private sites, similar to the US where approximately 75% of clinical trials are conducted in non-academic settings.[237] Analysis of studies in clinicaltrials.gov with sites in Canada suggests that the proportion is about 65% and, when oncology research is excluded, closer to 75%. It is then striking that the majority of provincial initiatives are focused on streamlining and harmonizing activities related to clinical trials conducted by academia and health authorities. The lack of an association that speaks for private researchers and which can represent their needs makes it easy for private researchers to be overlooked. Given that sponsors have data clearly demonstrating that private sites are more efficient, cost effective and produce high quality data, there are lessons to be learned from these sites.

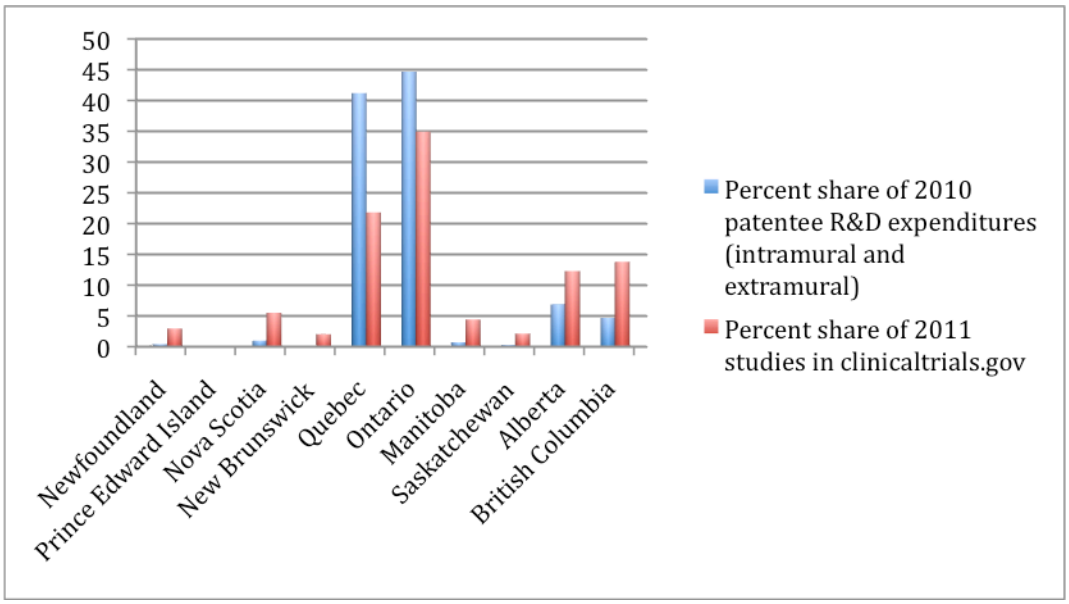

Figure 5: Provincial share of 2010 patentee R&D expenditure and 2011 studies in clinicaltrials.gov

A common theme emerged during the interviews regarding the need for strong national leadership in two areas in order to avoid redundant efforts within each province:

1. Outreach activities to inform and educate Canadians about clinical trials. An example, that was cited by several individuals, of a successful program in the US is the Center for Information and Study on Clinical Research Participation which is a non-profit organization which provides information to medical heroes, "the millions of people to give the gift of participation each year".[238]
2. Recognition of adequate training programs for investigators and their staff that meet organizational, Health Canada and industry needs. Some highly productive research sites indicated that their staff are required to take repetitive and redundant GCP courses each year since each research sponsor has its own requirements.

Finally, the globalization of clinical trials has resulted in changes for Canada and elsewhere. Not only is Canada's "piece of the pie" getting smaller but the "pie" itself is getting smaller.[239] The governments of the United States, European Union, United Kingdom, Australia and New Zealand have already taken notice and will be implementing recommendations to streamline regulation and improve the efficiencies of clinical trials. All Canadians who I contacted during my research for this background paper expressed concern that Canada remains an attractive location for the conduct of clinical trials.

Appendix 1: Table of Oversight Systems by Country (except United States)

Activities	Australia	Belgium	Brazil	Netherlands	New Zealand	Nigeria	South Africa	United Kingdom
Type of system	Human Research Ethics Committees are registered with the National Health and Medical Research Council. Voluntary certification by NHMRC.	Ethics committees are accredited by the Federal Agency for Medicines and Health Products	Research Ethics Committees are registered with the National Committee for Ethics in Research (which is accountable to the National Health Council)	Medical Research Committees are registered with Central Committee on Research Involving Human Subjects	Health and Disability Ethics Committees and Institutional Ethics Committees are accredited by Health Research Council Ethics Committee	Health Research Ethics Committees are registered with National Health Research Ethics Committee	Research Ethics Committees are registered with National Health Research Ethics Council	Research Ethics Committees reviewing clinical trials must be recognized by the UK Ethics Committee Authority. Research Ethics Committees that review health research must be authorized by National Research Ethics Service
Review of Policies/Procedures	Yes	No	No	Yes	Yes	No	No	N/A since SOPs are common in NRES
Reporting	Annual	Annual	Every 6 months	Annual	Annual	Annual	Annual	Metrics reports available through IRAS
Additional requirements	None identified	None identified	None identified	CCMO approves MREC members and MREC SOPs	None identified	Registration include statements of agreement and commitment	None identified	None identified
Site Visits	Voluntary National Certification Scheme	No	Possible but none to date	For cause visits by CCMO	No	No	Site visits are planned in 2011	Mandatory accreditation/site visit for RECs that are part of NRES
Number of Ethics Committees	221 registered HRECs	38 ECs with full accreditation, approx. 170 other hospital committees with partial accreditation	608 registered CEPs	27 accredited MRECs and approx. 35 non-accredited MRECs	6 regional HDECs, 1 multi-regional HDEC, 9 academic IECs and 1 private IEC	19 registered HRECs	33 registered health research ethics committees	24 RECs with Type 1 recognition, 59 RECs with Type 3 recognition, 37 authorized RECs

Appendix 2: Annual Reporting to the Quebec Minister of Health and Social Services by Designated REBs

The following list is an unofficial English translation of some of the information to be provided in the institution's annual submission. It is intended to demonstrate the level of detail and complexity of the information collected by each institution with a designated REB for submission to the Minister of Health and Social Services.

The annual submission includes, but is not limited to:

- Identification of the institution and REB
- Summary of REB activities
    - Copies of any updated procedures
    - Number and average length of REB meetings
    - Number of multicenter projects reviewed
    - Number of projects reviewed involving competent adults, by funding source and by REB decision
    - Number of ongoing projects that REB oversees or are subject to annual re-approval
    - Number of projects that involved amendments
    - Number of times the REB asked external experts to review a project
    - Number of times an REB member identified a real, apparent, or potential conflict of interest
    - Situations when the REB experienced interference or pressure affecting its ability to fulfill its mandate and how this was resolved
    - Whether the operating budget allocated to the REB was sufficient to enable it to fulfill its mandate
- Composition of the REB, including name, competencies/profession, role on the REB, affiliation with the institution, and start/end dates on the REB for each full and alternate member
- Any changes since the last annual report regarding the mandate of the REB, ethical evaluation of research or continuous oversight by the REB
- Evaluation of new research projects
    - Details about the documents required by the REB for the ethics review of research
    - Whether researchers may be present their project, be available during REB meetings
    - Criteria for acceptability of research
    - Appeal process
- Ongoing oversight
    - Whether the REB or a third party has access to project documents for management, monitoring and verification of the progress

    - Whether the REB ensures that research records will be retained appropriately
    - Details of how the REB is notified of changes to a research project, including problems, premature termination, annual reporting, and final reporting
    - How the REB evaluates documents related to ongoing oversight (i.e., full board or expedited review)
    - Processes used for active ongoing monitoring of research and the percentage of new research projects that are actively monitored
    - List of all new research projects reviewed including the institution's reference number, title, quorum, type of project (humanities/social sciences, epidemiological, genetic/genomic), and other characteristics (e.g, multicenter, database or biobank)
    - For each new project that is subject to article 21 of the *Quebec Civil Code* the following information must be provided: the title of the project, name of the principal investigator and co-investigators, start/end dates of the project, funding source, sample size, number of subjects to be enrolled at the institution, summary of the objectives of the research, summary of ethics concerns, date of the REB meeting, quorum, names of persons who evaluated the project, vote (approve, disapprove, abstentions), REB decision, date of the letter indicating that it can start, ongoing monitoring
- Measures taken by the institution
    - Whether the Board of Directors of the institution have taken note of the annual report
    - Regulatory framework of research activities
        - Maintenance of a registry of projects approved by the REB
        - Whether the regulatory framework includes handling cases of scientific misconduct, breach of ethics, management of conflicts of interest, management of double-dipping, incorporation of researchers, management of databases, management of research records
        - Whether the institution informs new researchers of their duties
        - Whether the institution evaluates the qualifications of a researcher before allowing the person to conduct research or assist in these activities
        - Evaluation of research projects by a financial administrative body
        - Control mechanisms for experimental drugs
    - Mechanisms for maintaining a registry of research subjects
        - Whether the institution assures itself that subjects have provided consent prior to the start of research
        - If the institution has a central registry, the number of research subjects that are participating or have participated in an REB approved project during the year
    - Reporting of the REB

        - Whether the REB reports to the board of the institution
        - The appointment or dismissal of REB members
        - Whether the Minister was notified of all changes to REB composition on an ongoing basis
        - Whether the institution ensures that REB members have the training necessary to accomplish their task, including ongoing education
    - Details about complaints and allegations of misconduct
    - Operating budget of the REB, including fees, wages, communications, office expenses, photocopying, meals, professional fees, research fees, costs related to ongoing ethics education, miscellaneous and contingencies

Appendix 3: Acronyms

This list includes acronyms primarily used in Canada and the United States. It is not intended to be an exhaustive list of the international or Canadian acronyms – all acronyms are defined in each section when the term is first used.

AAHRPP	Association for the Accreditation of Human Research Protection Programs, Inc. (US)
ACAHO	Association of Canadian Academic Healthcare Organizations
ACRES	Alliance for Clinical Research Excellence & Safety (US)
AIHS	Alberta Innovates – Health Solutions
ANPRM	Advance Notice of Proposed Rulemaking
ARECCI	A project Ethics Community Consensus Initiative
CCAC	Canadian Council for Animal Care
CCHSA	Canadian Council on Health Services Accreditation (now Accreditation Canada)
CGSB	Canadian General Standards Board
CIHR	Canadian Institutes of Health Research
CREBA	Community Research Ethics Board of Alberta
CRO	Contract research organization
CTO	Clinical Trials Ontario
CTTI	Clinical Trials Transformation Initiative
DHHS	Department of Health and Human Services (US)
EU	European Union
FDA	Food and Drug Administration (US)
FWA	Federal-wide assurance
GCP	Good Clinical Practice
HREA	Health Research Ethics Authority
HRPP	Human Research Protection Program
ICH	International Conference on Harmonization
IND	Investigator New Drug submission
IRB	Institutional Review Board
ISO	International Organization for Standardization
MOU	Memorandum of Understanding
MSSS	Ministère de la Santé et des Services Sociaux du Québec
N2	Network of Networks
NCQA	National Committee for Quality Assurance (US)
NCEHR	National Council on Ethics in Human Research
NSERC	National Science and Engineering Research Council
OCREB	Ontario Cancer Research Ethics Board
OICR	Ontario Institute for Cancer Research
OHRP	Office for Human Research Protections (US)
OPRR	Office for Protection from Research Risks (now OHRP)

PEERH	Program for Ensuring Ethical Research with Humans
PMPRB	Patented Medicines Prices Review Board
PRIM&R	Public Responsibility in Medicine and Research
R&D	Research and Development
REB	Research Ethics Board
Rx&D	Canada's Research-Based Pharmaceutical Companies
SACHR	Secretary's Advisory Committee on Human Research Protections (US)
SMO	Site Management Organization
TAHSN	Toronto Academic Health Science Network
TCPS	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans
TREC	TAHSN Research Ethics Committee
WHO	World Health Organization

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