

Accelerating access for patients to best medicine: The system and the challenge

A feasibility study prepared by

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Executive Summary

We are pleased to submit our report on the clinical trials process in Canada, “Accelerating access for patients to best medicine: The system and the challenge”. This is a preliminary study of the stakeholders and components of the clinical trials system in Canada. Our intention was to describe the major parts of the system, and to arrive at an initial understanding, in order for us to focus attention on those parts of the system that could benefit from adoption of best practices, as part of a major research project.

Based on some forty interviews with patients and opinion leaders, and a web review of the literature, we are confident that the clinical trials system in Canada represents a valuable asset to the innovation and delivery of health care. Clinical trials help generate new knowledge regarding novel medicines, while at the same time contributing significantly to health care delivery, and to the health care research and innovation capacity.

Traditionally, research regarding clinical trials has been sector-based. Projects would study clinical trials from the viewpoint of cost-effectiveness, the medicine chain, health policy development, or the regulatory dimension. The methodology itself might be the focus, or the organizational requirements.

In our study, we started from a system’s analysis viewpoint, an integrated perspective. Our exploratory research endeavors to capture all the components that intersect with clinical trials in the drug development process: players/stakeholders, chains of activities, factors of influence, constraints.

Not surprisingly, we identified patients as being at the core of the process. Chapter 4 is based on their views and observations. Without patients, there would be no clinical trials – at least for the time being, with current science. As patients have a holistic sense of what they live and experience, it is not surprising that they offered opinions on a wide range of issues, covering almost all aspects of the clinical trials process. What they have to say is of no less value than the interviews of a pharma executive, a regulator, or of an academic conducting a trial.

The clinical trials system turned out to be more complex than we initially thought, and information on the system was far less easy to locate than expected. Instead of four nodes or groups of stakeholders, we identified at least thirteen that we were able to describe in Chapters 2 and 5. Our use of quotes throughout the study reinforces the different perspectives that need to be better understood and brought together, if this clinical trial system is to grow and generate the significant benefits to Canadians. But this is a globally competitive game. The UK and other countries are already beginning to address how to capture these benefits more aggressively (see Chapter 6).

In terms of solid, verifiable data on the various components of the system, there is very little available. We estimate the total dollars spent on CTs and related activities across all

industries and academia is between \$800 million and \$1 billion a year, representing tens of thousands of jobs. The lion's share is funded by large pharmaceutical companies. But we cannot tell how many trials are being carried out in Canada at any point in time, which trials are recruiting patients, for what therapies, and where they are located. Patients want to have access to that information, in the form of a comprehensive inventory of clinical trials. The issue is what form that should take, and who should run it.

We know that while Health Canada and its regulatory body have shown some improvement in the last few years, their mean time of approval of new medicines is beginning to creep up again to 1995 levels. This suggests to us strongly that it might be time to explore what might be the optimal model for TPD and the regulatory arm of Health Canada, to ensure it has the level of funding, resources and flexibility to meet the challenges of tomorrow's technology.

Hospitals and universities appear to have a short-term revenue maximization perspective on industry-sponsored clinical trials, and run the risk of shutting themselves out of this growing activity. The slowness, unevenness, and poor funding of research ethics boards is a contributing factor. Already, we see a growing number of private organizations, from private research clinics and private research ethics board, to site management organizations and clinical research organizations who are more than willing to take over the role traditionally held by academic health centers – but at significant profit.

Biotech companies, another set of complex players at different stages of growth and evolution, appear to be the new source of innovation in the pharmaceutical area. But they need help in bringing new products to market, and in jumping through the increasingly challenging barriers of clinical development and regulatory approval.

And CIHR, Canada's star in the funding of health care research, is spending less than 5% of its budget on clinical trials. Even if it had additional funding, there is a perception that it would not have the needed expertise to review and manage these research projects. Yet it is through clinical trials that health care discoveries and new medicines eventually reach the patient.

So in brief, the clinical trials system in Canada is a tightly interwoven innovation system, crossing many lines and boundaries, a system about which we know very little. Because it is multi-disciplinary and multi-jurisdictional, no single federal department can hope to understand it in its integrated state. This has to be done through an independent task force.

We identified a number of research questions at the end of the report (Chapter 8), but if there is one challenge with which we would like to conclude, it is that the clinical trial system is a rich and very beneficial innovation system for Canada, which few if any have studied in an integrated systems way. And unless we do it very soon, and implement urgently some best practices to remain competitive, other countries such as the UK, or the low cost emerging economies in Eastern Europe and Latin America, or the new biocapital

of Singapore will take over this \$1 billion industry. And Canadian patients will be the first to suffer.

We take this opportunity to thank our funders, Health Canada and Industry Canada for giving us a chance to explore this exciting and emerging area, and for their support of this feasibility study.

The Hon. Monique Begin, PC, FRSC, OC
The Hon. Judy Erola, PC
Prof. George A. Wells
Dr. J. André Potworowski

1. Introduction

Objective and scope

This is an integrated systems approach that examines all the elements and players in the dynamic process of clinical trials, as they contribute to (or hinder) the access by patients of new therapeutics.

Our objectives were --

- to identify the roles and contribution of the different stakeholders in the clinical research, testing and regulations of new medicines;
- to examine the interactions between the different stakeholders;
- to identify best practices which would increase innovation and the efficiency of the interactions among the various stakeholders of the clinical research system; and
- to promote these best practices to the target stakeholders, through research transfer methods including web courses and computer-based training and awareness.

The project will be done in two phases. The first phase, ***which is the subject of this report***, is focused on identifying the key stakeholders in the clinical research system, and examining the interaction of the stakeholders. This will lead to identifying where our efforts should be concentrated in the second phase, to obtain a much deeper understanding of the nature of the operations and hence identifying best practices that would lead to increase efficiencies and the most appropriate methods for promoting these best practices.

We want to provide an overview of the key factors that affect the efficiency and benefits of clinical research as it relates to drug testing and approval.

Our starting point has been fixed at the Pre CTA point (pre clinical trial application), once we have a given molecule with promising biological and pharmacological activity, about to enter clinical trials.

Our endpoint is the marketing approval accorded by regulatory bodies and post-marketing surveillance. This overview covers all the aspects, but flags only those that seem to indicate some kind of friction or bottleneck in the process, and which could have the potential for streamlining or improvement, i.e. the target of an eventual best practice.

Team and methodology

The Research Team included:

Monique Bégin & Judy Erola, co-chairs
George A. Wells, Scientific Director
J. André Potworowski, Project Director
M. Scott Watson, Research Associate

The Advisory Board included

Denis Desautels, Centre on Governance, University of Ottawa
Joe Losos, Institute on Population Health, University of Ottawa
Suzanne Cadden, Lorus Therapeutics
Nestor Nituch, Bristol Meyers Squibb

Our methodology was relatively simple. We started from a concept, based on a question as to why it takes so long to get a new drug to market. This concept was refined by the research team, and discussed with our Advisory Board. The Advisory Board helped in further solidifying our initial concept, and identified a list of some 90 potential leaders and players in the field of clinical research and its stakeholders in Canada that could be interviewed. We also conducted a web-search and analysis of the most recent and relevant documents and literature on the subject.

We held approximately forty-five interviews with the following groups:

- patients, patient organizations, and health charities (17),
- executives of global pharma companies (6),
- executive of biotech companies (5)
- clinical investigators and researchers (7),
- federal and provincial public servants (6),
- CRO executives, research clinic directors, and site managers (4)

This report represents a synthesis of the interviews, literature search, and expert views provided by the research team and advisory board. Our conclusions are in a form of a research questions, in keeping with our objective of making this a feasibility study.

Funders and Sponsoring institutions

This first part of this project was funded by Industry Canada and Health Canada

This study was carried out under the auspices of the Centre on Governance and the Institute on Population Health, both at the University of Ottawa, for which we are grateful for their continued intellectual and administrative support.

2. The Drug Development Process in Canada

This chapter describes how drugs are developed and approved in Canada, the various players and stakeholders in the clinical trials system, and some of the benefits of clinical trials accruing to Canadians.

There is no single source of data on how much money is spent on clinical trials and drug approval in Canada. But we estimate that clinical trials, as applied to the testing, evaluation and obtaining approval for new medicines, represents an activity in Canada worth between \$800 million and \$1 billion a year.¹

Bringing a new drug to market is a long and arduous task. It takes about 10 to 15 years in Canada to obtain approval for marketing a new drug.^{2,3,4} The drug development process can generally be divided into four stages. (See Table 1)

Stage I: Pre-clinical

The pre-clinical phase can take up to six or seven years⁵ to complete. Initially, once it discovers a promising molecule, a company needs to protect its intellectual property. This is done in Canada by submitting a Patent Application to the Canadian Intellectual Property Office (CIPO). Examiners ensure the patent fulfils criteria of novelty, non-obviousness and usefulness.⁶ If the examiner is satisfied, a Notice of Allowance is issued.

The pre-clinical phase consists of applied research to determine whether that molecule is safe (toxicity) and has biological activity, and how it should best be formulated for the next phase of clinical trials. The pre-clinical phase toxicity studies depend on the duration of

¹ The Patented Medicine Price Review Board (PMPRB) tracks R&D spending by pharmaceutical companies with active Canadian patents pertaining to a medicine sold in Canada. In 2001 (PMPRB Annual Report, 2001, <http://www.pmprb-cepmb.gc.ca>), PMPRB reports that the total current R&D expenditures (excludes capital equipment and allowable depreciation) was \$1.01 billion. Of this, 8% or \$80 million was for pre-clinical trials, 44% or \$446 million was for clinical trials, and 24% or \$243 million for other R&D, including drug regulation submissions, bioavailability studies and Phase IV clinical trials. But PMPRB's data does not include money spent by companies at the development stage, with no current sales, or by other players. It is estimated that these other players, including the biotechnology industry, the generic drug industry, and government granting agencies may spend an additional \$100-200 million on clinical trials. One can infer, therefore, that clinical research, as applied to the testing, evaluation and obtaining approval for new medicines, represents an activity in Canada worth between \$800 million and \$1 billion a year.

² Biotechnology Patents and Product Approval Processes: Challenges and Opportunities. Submitted to Ontario Ministry of Energy, Science and Technology. The Blair Consulting Group and RIAS Inc. October 2001.

³ Canada's Research-Based Pharmaceutical Companies (Rx&D), www.canadapharma.org/Patient_Pathways/Drug_Process/drugdisc_e.html

⁴ <http://www.fdareview.org/graphics/graph1.jpg>

⁵ www.fdareview.org, *ibid.*

⁶ Beyond Borders, The Canadian Biotechnology Report 2002. Ernst & Young LLP. 2002.

the actual clinical⁷ trial. A key outcome is the estimation of an initial safe starting dose for the human trials.

In this stage, for every 5,000 molecules discovered and designed only 5 enter clinical trials.⁸

In Canada, a pharmaceutical or biotechnology company will then submit an Investigational New Drug (IND) application, now called a Clinical Trial Application or CTA to the Therapeutic Products Directorate of Health Canada (TPD). A company must submit a CTA for every clinical trial. Health Canada must review the application before a company can start clinical trials.

Stage II: Clinical Trials

The second stage involves clinical trials *per se*, that determine a drug's dose, effectiveness and safety. Trials are undertaken in three phases that in total take about 6 to 7 years to complete. During that period, there will be a number of iterations with Health Canada. Phases can be described as:

- Phase I: Safety studies on healthy volunteers (approximately 20-100 people⁹) or actual patients in certain disease areas, e.g. oncology.
- Phase II: Small safety and efficacy studies, including determination of the appropriate dose for phase III with approximately 100 to 300 patients suffering from the illness the drug is intended to treat.
- Phase III: Large safety and efficacy studies with approximately 1,000 to 3,000 patients suffering from the illness the drug is intended to treat.

Stage III: Review and approval process

Once all clinical trials have been completed and met success the third stage begins. The pharmaceutical company submits a New Drug Submission (NDS) application to the TPD. The TPD reviews the application and decides if the drug can be sold in Canada. If, at the end of the review process, and TPD concludes the benefits outweigh the risks, the drug is issued a Notice of Compliance (NOC), as well as a Drug Identification Number that permits the sponsor to market the drug in Canada. This stage takes on the average 23.6 months.¹⁰ In the US, it can range from as low as 2 months (e.g. in the case of approval of drugs for treatment of life-threatening diseases such as HIV/AIDS or cancer) to a high of seven years.¹¹

Stage IV: Drug Approval and Post-Marketing Surveillance

⁷ This is governed by a guideline of the International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use (ICH), http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/ich/multi/timnoncl_e.pdf, adopted by Health Canada

⁸ www.fdareview.org, *ibid.*

⁹ Sample size for phases I, II, and III based on Rx&D data, www.canadapharma.org/Patient_Pathways/Drug_Process/drugdisc_e.html

¹⁰ Rx&D, *ibid.*

¹¹ www.fdareview.org, *ibid.*

The fourth stage begins after a drug is approved in Canada. At this stage, sponsors must negotiate with Patented Medicines Prices Review Board (a quasi-judicial body that regulates maximum prices charged by manufactures of patented drugs in Canada, and reports through the Minister of Health Canada) to determine pricing of the medicine. Also, sponsors must negotiate with Provincial formularies to ensure products are listed for coverage for in-hospital treatment, seniors and people on social assistance.

Pharmaceutical companies continue to research and develop a drug in Phase IV clinical research. This type of research, where the study group is the general population, focuses on the following issues and continues indefinitely:

- Tracking the safety of a drug once it is being sold and used by many people.
- Doing more clinical studies to determine alternative uses for the drug - i.e. other conditions.¹²

Table 1: Typical Drug Development Process

Stage	Step	Comments
Pre-clinical	File Patent Application	To benefit from 20 years of intellectual property protection, companies must apply to Canadian Intellectual Property Office (CIPO) for a drug patent. Review Process for biotech drugs takes 27 – 28 months before a patent is granted. ¹³
	Pre-clinical Testing	Discovered molecules in applied research go through characterization research to determine pharmaceutical potential an toxicity. Can take up to six or seven years.
	Submit Investigational New Drug submission (IND)	Average time for IND approval was 37 days in 2001, a result of TPD's new regulations introduced in September 2001. ¹⁴
Clinical Trials	Phase I Clinical Trials	Phase I trials assess safety on volunteers numbering from 20 to 100. Generally takes 1 year. ¹⁵
	Phase II Clinical Trials	Phase II trials assess safety and efficacy on people with illness numbering from 100 to 300. Generally takes 2 years. ¹⁶
	Phase III Clinical Trials	Phase III trials are very large trials that assess safety, efficacy and toxicity on people with illness numbering from 1000 to 3000. Generally takes 3 years. ¹⁷
Review and approval process	New Drug Submission	
	Health Canada's TPD Review	TPD's Review process, average time in 2001: 23.9 months. ¹⁸
	Obtain Notice of Compliance	

¹² Rx&D, *ibid*.

¹³ Beyond Borders. The Canadian Biotechnology Report 2002. Ernst & Young LLP. 2002.

¹⁴ NOC Survey –2001. An ongoing analysis of the time required for review and approval of drug submissions in Canada. Rx&D. May 2002.

¹⁵ Lipsky, MS, Sharp, LK, From Idea to Market: The Drug Approval Process. J Am Board Fam Pract (2001) 14(5):362-367

¹⁶ Lipsky et al., *ibid*.

¹⁷ Lipsky et al., *ibid*.

¹⁸ NOC Survey - 2001, *ibid*.

Drug Approval and Post-Marketing Surveillance	Set Price of Drug, Reviewed by PMPRB	
	Apply for listing on Provincial Formularies	
	Get Listed on Provincial Formularies	
	Market Drug	
	Phase IV Research	Companies and TPD collect safety information on a drug once it hits the general population. Phase IV studies are conducted to further evaluate the long-term safety and effectiveness of a treatment. They usually take place after the treatment has been approved for standard use. Several hundred to several thousand people may take part in a phase IV study. These studies are less common than phase I, II, or III trials.

A complex system: major players and institutions

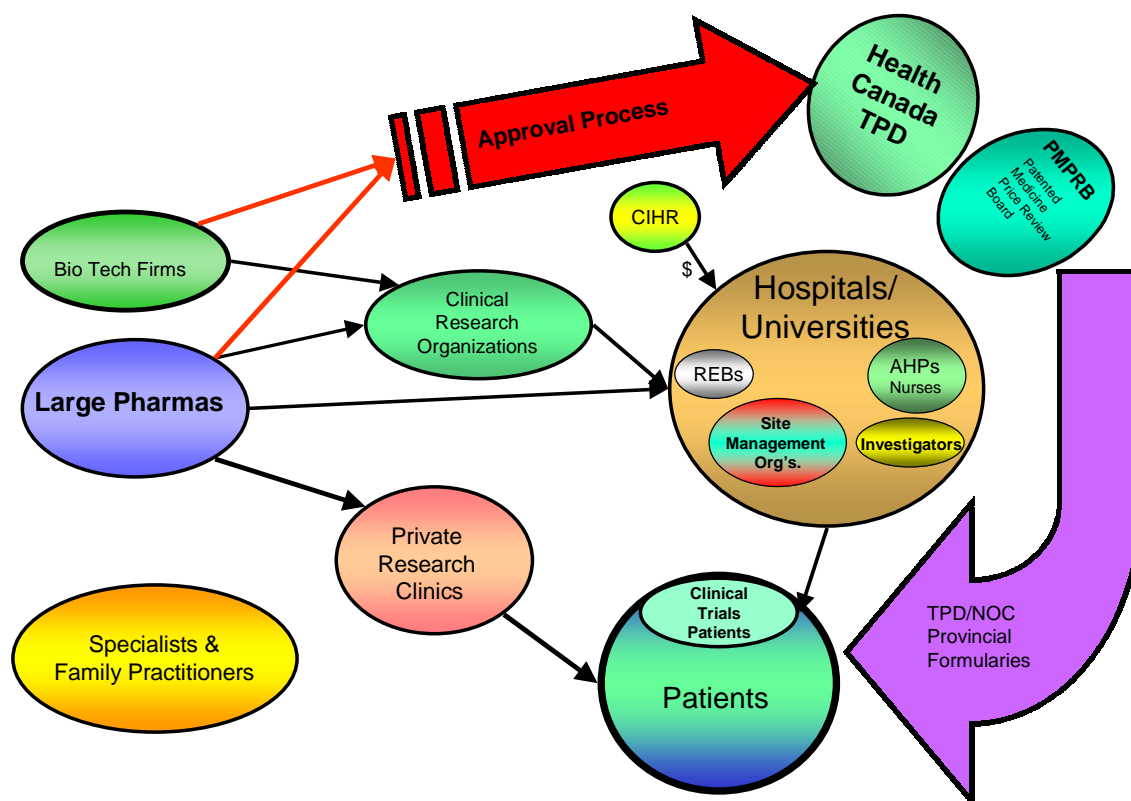
When the initial research proposal was submitted, we considered a model for the drug testing and evaluation system with only four nodes or groups of stakeholders: patients, investigators, industry and regulators. We now have discovered at least 13 different stakeholder groups or players in this very complex system. In looking at the various stakeholders below it is apparent that each has its own different motivation or incentive to be part of a clinical trial¹⁹:

Table 2: Key stakeholders/players and their motivation

Patients	Health of self
Regulators, Health Canada/TPD	Protection of public and patients
Research Ethics Boards	Patient safety and research integrity
Provincial Formularies	Cost control
Research Community	
Allied health professionals: nurses, coordinators, and associates	Personal job and career
Investigators	Research Publications
CIHR	Advancement of knowledge, research
Hospitals and universities	Overheads, research reputation
The Industry – Large global pharma firms	Market and financial growth
The Industry – The new biotech industry	Innovative development
Clinical Research Organizations (CROs)	Service contracts
Private Research Clinics	Service contracts
Site management organizations	Service Contracts

¹⁹ Advisory Board meeting of April 30 2002

Figure 1: The Clinical Trials System in Canada: Key Players and Institutions



Benefits of clinical trials

There are a number of direct and indirect benefits of clinical trials, i.e. the testing and development of a new drug, over and above that of obtaining approval of a new drug.

Clinical trials sponsored by a company are usually done in a medical setting, private or public, and because of company and regulatory requirements, there is a need for data monitoring, and an auditable trace. Accordingly, for an investigator who is participating in company-sponsored clinical trials, this participation will usually improve the overall efficiency and rigour of the research processes and procedures where the research is carried out.

As treatment for diseases become more complex, adoption of new treatment will have broader implications than prescribing new medicines. *“If you’re not involved in clinical trials – how will you learn the system to allow this kind of treatment? Clinical trials allow the healthcare infrastructure to become familiar with the state of the art and the next generation treatment, or therapies.”*²⁰ Clinical Trials provide a major educational benefit

²⁰ Industry interview, CRO

for doctors and nurses, and can help them evolve to a new generation of medicine, and therapeutics. This benefit accrues not only for company-sponsored trials, but also for investigator-initiated trials, or academic trials.

“CTs help build the medical infrastructure. When you are involved in pharmacotherapy, you understand disease in terms of objective measurements, closely defining the markers of disease progression. This spills over to the entire research team: pharmacists, research nurses, academics, clinical trial designers. The whole team becomes much more knowledgeable about a given disease. In principle, a clinical trial is intended to study the drug, but in reality it’s about studying and understanding the disease.

All the stuff an investigator asks a patient to do in a visit during a clinical trial – simple questionnaires, looking at coughing, wheezing, shortness of breath, in the case of asthma, monitoring these things on a regular, even a daily basis, and noting the environmental factors that affect disease states -- all of these provide a much more systematic understanding of the disease, way beyond the types of questions asked in the course of a normal average clinical visits. And there is an inevitable spillover to the care a patient receives.

In a broader sense, clinical trials provide benefits far greater than for a single institution. They contribute to the development of competitive therapeutic centers, attract and help form leaders in specific disciplines, and improve policies with regards to medical treatment, health care management, and broad health care resources utilization.

Clinical trials can also help groups that are looking much more closely at economic/ social impact of health care programs. Everyone is looking for outcomes of therapies and treatments – and we need more information before we know if a therapy is good, bad indifferent. Again, the way to obtaining this information is through clinical trials.”²¹

As will be seen in the following chapter, clinical trials provide direct benefits to patients, particularly in terms of access to medical specialists and healthcare workers.

²¹ Interview with large pharma executive 4

3. Are Clinical trials in Canada an innovation system?

A key hypothesis is that we can study the processes and stakeholders around the testing and evaluating of new medicines in terms of an innovation system. This chapter explores this hypothesis, and examines a number of studies that have looked at some aspects of this system.

An innovation system²² describes the regional or national organizations that have to collaborate to bring an innovation to market, i.e. research organizations, universities, government laboratories, large corporations, SMEs, banks and financial institutions, etc. It looks at the knowledge flows, the regulatory controls and whatever policy measures governments can put in place to increase innovation.

A technology cluster is defined by Michael Porter as “a **geographically proximate group of interconnected companies and associated institutions in a particular field, linked by commonalities and complementarities**”.²³ It has a clear geographical focus concentrated around a city or region, e.g. Silicon Valley and San Jose, Research Triangle, etc. It is too early to tell whether drug development in Canada has such geographically concentrated clusters.

In the original proposal for this study, we initially considered four nodes or groups of stakeholders: the patient community, the industry (large pharma companies and biotech firms), the research community (university/faculty of medicine/ clinical investigators), and the regulators (FDA/HC/TPD). This study shows that there are at least 13 such groups or nodes, which have to collaborate to ensure that medicines are properly evaluated and tested in order to reach patients. This is very complex system.

By studying these groups as an integrated system, however, we may eventually be in a position to accelerate the rate of innovation and speed up access by patients to new medicines. One challenge, once we better understand the various components and players in the system, is to determine whether there can be any formal networking efforts or initiative to link the various players together, improve communications, build synergy, strengthen infrastructure and help increase capacity.

The benefit of examining the testing and development of new drugs through the filter of an innovation system is that it forces us to examine all the components holistically, as an integrated system, as opposed to the more prevalent view of institutions and groups conflicting with one another, e.g. government regulators vs. private companies. This approach has the potential of moving from a conflicting relation, to a new paradigm where innovators and regulators collaborate to improve access to new drugs for patients.

²² Freeman, Christopher. 1995. The 'national system of innovation' in historical perspective. Cambridge Journal of Economics, 19(1): 5-24

²³ “Location, competition, and economic development: Local clusters in a global economy” Michael E Porter Economic Development Quarterly; Thousand Oaks; Feb 2000

As will be seen below, other countries and organizations have used a systems approach in looking at clinical trials and clinical research, suggesting that this approach has some value.

Other studies of clinical trials system

A number of organizations studied clinical trials in a systematic way, and some of these are presented here.

The industrialization of clinical research

Dick Rettig of the RAND Corporation analyzed the components of the clinical trial system in the US, noting a growing trend to industrialization or privatization of some of the key components.²⁴ He reviews the role of the FDA, the academic research centers, patients and patient enrollment, and the emerging private sector players: the Clinical Research Organizations, the Site Management Organizations and the private, for profit Institutional Review Boards.

Clinical trials are central to translating the promise of biomedical research into improved clinical practice, the “neck of the scientific bottle” through which all advances in biomedicine must flow before they can benefit the public.

Rettig begins by noting recent controversies surrounding clinical trials and clinical research in the US:

- Criticism and deficiencies in Institutional Review Boards (our Research Ethics Boards) and the suspension of federally-sponsored research at several major US research and academic research centers.
- Growing media questions about paying physicians to recruit patients for clinical trials, and other conflicts of interests.
- Questioning whether the FDA’s role is approving drugs too quickly,
- and the suppression of publication of trial results that are unfavorable to a company.

He points to a significant increase in R&D spending both by the pharmaceutical industry, as well as by the US NIH, and the growing pressure to increase the number of clinical trials to bring these new medicines to market.

He notes that the FDA has shortened its review of new drugs greatly in past decade, through the Prescription Drug User Fee in 1992 (PDUFA), and the Food and Drug Administration Modernization Act (FDAMA) of 1997. The median NDA review time has dropped from thirty months to below fifteen months. This reflects a change in philosophy of drug evaluation from one of avoiding premature release of new drugs until safety has been decisively established, to one of facilitating rapid access to the benefits of new therapeutics.

²⁴ “The industrialization of clinical research”, Richard A. Rettig, Health Affairs, March-April 2000

The key trends of industrialization are leading to an emergence of clinical trials as a large, rapidly growing line of 'business'.

It reflects an intensified search by the pharmaceutical industry for efficiency throughout the product development cycle, especially in the organization and conduct of drug clinical trials.

Lastly, it generates competition for market share in clinical research among new organizational players, such as Clinical Research Organizations (CROs), Site Management Organizations (SMOs), independent Research Ethics Board (REBs), and traditional academic health centers, which are increasingly finding themselves displaced from a previously unchallenged central position.

The new trends in clinical research is challenging all of the major players –

- The NIH on its priorities and resource allocation
- Academic medicine regarding infrastructure support and professional reward of faculty;
- The FDA in the evaluation of new therapeutics and postmarket surveillance
- REBs regarding the protection of human subjects
- Health services research in assessing outcomes and effectiveness in early-stage therapeutics development
- And third-party insurers in evaluating coverage of new therapies

Evidence suggests that all parties are under stress and that prudent steps towards greater transparency are warranted.

The need for transparency links all the thorny question in the clinical trials domain, e.g. suppression of research results by drug firms, bias in interpreting inconclusive results, conflict of interest. Many of these issues can be addressed by registering all clinical trials, public and privately funded. There are some initiatives that are being undertaken in the US in this direction.

The growing importance of CTs and the emergence of major private-sector players, in Rettig's view, points to the need for a better organization for "managing" this enterprise from a policy standpoint.

Association of Clinical Research Professionals (ACRP)

The ACRP is a 16,000 member association of clinical research professional from Europe and North America. Their purpose is to provide global leadership for the clinical research profession by promoting and advancing the highest ethical standards and practices.²⁵

²⁵ <http://www.acrpnnet.org>

There are many factors impacting clinical research today and the Future Trends Committee of ACRP identified three topics to focus on for their Clinical Research in Transition, ACRP's White Paper for 2001.²⁶

- The Developing e-Environment section (challenges associated with the move from paper to electronic-based clinical trials).
- Investigator Scrutiny and Certification (the federal government's growing interest in evaluating the quality and conduct of clinical trials).
- Public Perception (the attitudes toward clinical research created by mass media).

Association of American Medical Colleges (AAMC)

The AAMC is an association of medical schools, teaching hospitals, and academic societies, and works with its members to set a national agenda for medical education, biomedical research, and health care.²⁷

The AAMC, the American Medical Association and the Wake Forest University School of Medicine called together "The Clinical Research Summit" in 1998-1999. It brought together ten focus groups: the insurance and managed care industry, the corporate and government purchasers of health care, patients and patient advocates, non-physician clinical researchers, basic scientists and five groups of clinical research physicians at different levels of experience.²⁸

Problem areas identified were:

- There is no agreed-upon definition of clinical research.
- There is an imperfect public understanding of clinical research.
- There is a lack of data to tell whether investment in clinical research is being well spent and whether certain areas need to have more resources.
- There is insufficient funding in certain areas of clinical research. Examples include clinical research like outcomes research and the most basic types of clinical research linking laboratory scientists to the early disease mechanisms in human subjects.
- There is a need for more clinical investigators.
- There is a need for better education of clinical research practitioners.
- There is poor coordination between HMOs and academic medical centers and between schools of nursing and public health on the one hand and schools of medicine on the other. There is a concern about the financial risk for academic medical centers and their ability to sustain their systems for clinical research.
- There is no clear, dynamic agenda for clinical research.

²⁶ ACRP 2001 White Paper. Clinical Research in Transition: Technology, Safety and Perception.

www.acrpnnet.org

²⁷ <http://www.aamc.org/>

²⁸ Based on remarks delivered at the 25th Anniversary AAAS Colloquium on Science and Technology Policy, held April 11-13, 2000, in Washington, D.C.

CFI Clinical Research Workshops

The Canada Foundation for Innovation (CFI) is an independent corporation established by the Canadian Government in 1997.²⁹ CFI's aims are to strengthen the capability of Canadian universities, colleges, research hospitals, and other not-for-profit institutions to carry out world-class research and technology development.³⁰

CFI, in consultation with the three federal granting agencies, the Canadian Institutes for Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC) and Genome Canada, has held a workshop on clinical research in May 2001. The thrust of the workshop was to identify new areas of science that will have a significant on clinical research.

For example, genomics and proteomics will have a significant impact on accelerating the rate discovery of new targets for interventions. Ideally this research will translate into multitudes of new medical products. Assessing these medical interventions will be a major task over the next decade. The volume of research will be overwhelming if the traditional clinical trials approach is used.³¹

The workshops concluded that new clinical trial methodologies will be developed, and that strategies would be developed for rapid and safe transfer of new treatments from the lab to the patient. These strategies will require collaborative efforts between researchers with genetic, clinical, bio-computing, bio-statistical, technology assessment, human factors engineering, artificial intelligence, informatics and communications technology expertise.

Because of the participants present, the workshops focused only on six clinical areas: cancer, cerebro- and cardio-vascular diseases, diabetes/endocrine, infectious diseases/HIV, musculo-skeletal diseases, and neuro-psychiatric and brain disorders.

Summary findings

There is indication that clinical trials can be usefully examined as an integrated innovation system, with the expectation that this approach might provide a helpful way of increasing the overall effectiveness and capacity of that system

²⁹ As a corporation without share capital, incorporated by special act of parliament, Bill C 93, Budget Implementation act of 1997.

³⁰ <http://www.innovation.ca/>

³¹ *Report on the discussions at the workshop on clinical research. Canadian Foundation for Innovation.*

4. Clinical Trials and the Welfare of Patients

This chapter examines clinical trials and its different aspects from the viewpoint of the patient.

Research regarding clinical trials has traditionally been sector-based. Projects have studied clinical trials from the cost-effectiveness angle, the medicine chain viewpoint, the health policy development, or the regulatory dimension. The methodology itself might be the focus, or the organizational requirements.

Beginning from a system's analysis viewpoint, the present exploratory research endeavors to capture all components that intersect with clinical trials in the drug development process: players/stakeholders, chains of activities, factors of influence, constraints.

Not surprisingly, we identified patients as being at the core of the process. This chapter is based on their views and observations. Without patients, there would be no clinical trials – at least for the time being, with current science. As patients have a holistic sense of what they live, it is not surprising that they offered opinions on a wide range of issues, covering almost all aspects of the clinical trials process. What they have to say is of no less value than the interviews of a pharma executive, a regulator, or of an academic conducting a trial.

The intrinsic value of clinical trials to patients

A key theme of this study is that clinical trials provide a fundamental benefit to patients. Pharmaceutical discoveries (breakthrough medicines and improved drug therapies) assist Canadians to live longer, often with a better quality of life. New pharmaceuticals can control and even prevent disease, helping people to avoid more expensive and invasive treatments while saving health care dollars. While good lifestyles and preventive medicine play an important role, according to the Canadian industry, pharmaceuticals helped reduce the hospitalization rate by 32.3% since 1985.³²

Clinical trials could not take place without patients' participation. Despite the remarkable work of our patients' networks and advocacy groups, as well as that of health charities, Canadians do not yet benefit from a wide-base joint effort such as the American Coalition of National Cancer Cooperative Groups. How patients are a critical contributor to it is truly remarkable. Although focused on cancer clinical trials only (cancer is one of the highest causes of deaths in North America), the Coalition offers valid insights and initiatives³³ at what should be done to “*address serious issues (...) such as improving the clinical trials*

³² Canada's Research-Based Pharmaceutical Companies (Rx&D) (2002). *The Value of Medicines*, Ottawa (ON), January 2002.

³³ The Coalition published in their March 2002's newsletter the first results of their recently created inventory of clinical trials, by type of cancer, an over 2000 registrations inventory. This will be discussed later in our report discussion of examples of best practices.

experience for patients and physicians, regulatory requirements, competition for federal funding (...)”, as our Web-based literature review revealed.³⁴ Based in Philadelphia, the Coalition was created in 1997 around the National Cancer Institute (NCI). It is a network of over 17,000 parties interested in cancer clinical trials that include cooperative groups, cancer centres, academic medical centres, community hospitals, physician practices, and patient advocacy groups. Some Canadian sites of cancer clinical trials for adult patients are part of this Coalition and, in the case of pediatric trials, Canadian sites are connected to the Children’s Oncology Group, a branch of the American Coalition.

In Canada, the closest to the American oncology coalition would be the Canadian HIV Trials Network (CTN).³⁵ A non-profit, national organization, the CTN was established in response to the needs and concerns of Canadian clinical investigators, persons living with HIV/AIDS, the pharmaceutical industry, community physicians, specialists, and laboratories. The CTN is funded by Health Canada, and jointly supported by the University of British Columbia and St. Paul’s Hospital, Vancouver. The HIV/CTN scientific process has now been subsumed by the Canadian Institutes for Health Research (CIHR) and may provide a model for the CIHR to follow in clinical trials for other diseases. The HIV/CTN includes HIV patients in every phase of the clinical trials, from ethics review to the design of the trial, to a central registry leading to dissemination of information to the community. In the words of one patient network:

*“This is the hallmark of the HIV/AIDS community and puts us ahead of other patients groups.”*³⁶

Patients do not necessarily play a lead role in other Canadian clinical trial networks the way they do in the HIV/AIDS coalition. The National Cancer Institute of Canada’s Clinical Trial Group (NCIC CTG)³⁷, the Canadian Stroke Network (CSN)³⁸, and the Canadian Arthritis Network Clinical Research Services (CAN CRS)³⁹ as facilitators for clinical trials through diverse initiatives will be discussed later in the report. The Canadian Cystic Fibrosis Foundation supports the Clinical Studies Network (CSN).⁴⁰

The response from patients, patients’ networks and health charities in Canada is remarkably similar to what the American Coalition of National Cancer Cooperative Groups found: that the value of clinical research is twofold.

Firstly, patients who take part in a clinical trial may be helped by the treatment they receive. Even though there is no guarantee that a new medication or procedure will be effective, the Coalition states that many trial participants concluded that the possible benefits outweigh the risks. Indeed many stories exist where cancer patients attribute

³⁴ <http://www.cancertrials-help.org>

³⁵ <http://www.hivnet.ubc.ca/ctn.html>

³⁶ Patient Network -6

³⁷ <http://www.ctg.queensu.ca>

³⁸ www.canadianstrokenetwork.ca

³⁹ http://www.arthritisnetwork.ca/products_and_services/clinical_trials.asp

⁴⁰ Same initials, but different than the Canadian Stroke Network.

their extended life to being involved in a clinical trial.⁴¹ And whatever the results of drug value, while in a clinical trial, patients get the best possible care.

Secondly, clinical trials contribute to the overall knowledge and progress against cancer. It cannot be disputed that many people treated for cancer are now living longer owing to knowledge gained through clinical trials.

The American Coalition states that clinical trials are no longer seen as just a last resort for cancer patients. In fact, today, patients often choose to receive their first treatment in a clinical trial. (And they should; we were told by patients that in oncology cases, for example, the very first treatment the patient gets is the critical one. If that is so, accessing the newest medication can make the difference.)

In 2000, this American Coalition, together with a few other players as well as pollster Harris Interactive Inc., undertook a quantitative survey of public attitudes towards cancer clinical trials. Patients who participated in a clinical trial reported it as a very positive experience.

“More than three in four would recommend participation [in a clinical trial] to someone else with cancer.”⁴²

Having access to the best quality care is the major reason cited by patients for participating, while getting more care and attention comes fourth. This was confirmed by one investigator, who heads a private clinical research clinic, but he also notes that

“Quality of health care is difficult to measure and to compare. Indeed, while clinical trials are very demanding for sites, they are also very demanding for patients as many visits and procedures are planned to build a dossier that will satisfy scientific standards and regulatory requirements. For example, a patient on a 3 years osteoporosis study might benefit from 18 medical visits! Few patients and doctors would spend that kind of time with the usual medical follow-up in a clinic. The third party (RAMQ or OHIP) payer does not have sufficient resources for that purpose (cost benefits ratio). In essence, the purpose of treatments provided during a routine medical visit compared to a protocol visit are ultimately not the same.”⁴³

In between, comes the importance of participation as a benefit to future patients and of receiving newer/better treatment. In general, respondents considered their outcomes as being at least as good as those of patients receiving the standard treatment.

⁴¹ Jennings, Terry (2002). “Trial by Gleevec: It’s Not Easy Being a Research Subject in a Study of a Breakthrough Cancer Drug. But It Sure Beats the Alternative”, *The Washington Post*, July 2, 2002. www.washingtonpost.com

⁴² Comis, Robert L., Carolyn R. Aldigé, Ellen L. Stovall, Linda U. Krebs, Peter J. Risher and Humphrey J. Taylor, (2000). *A Quantitative Survey of Public Attitudes Towards Cancer Clinical Trials*, Coalition of National Cancer Cooperative Groups, Cancer Research Foundation of America, Cancer Leadership Council and Oncology Nursing Society, 10 p. Link from: www.cancertrials-help.org

⁴³ Interview with head of a research clinic

Recruitment of adult oncology patients is the key mission of the American Coalition of National Cancer Cooperative Groups. Their website states that “... fewer than 5% of adult cancer patients in the US are enrolled in clinical trials”.⁴⁴ The Coalition wants to double accrual in cancer clinical trials in the U.S. from 20,000 to 40,000 persons over the next 3-5 years. The corresponding figure for Canada, according to Dr. Bernard J. Cummings (Toronto), President of the International Society for Radiation Oncology, is 3% of adult cancer patients’ participation. However, children suffering from cancer are practically all participating in clinical trials, according to what a particularly well-informed patient advocate⁴⁵ told us. In a country like Canada, the low number of cases can also be a problem at times. Addressing the case of cystic fibrosis (CF), a health charity explained how, for some diseases, “...there is not always a significant critical mass to conduct comprehensive studies.” (There are approximately 3,300 individuals suffering of CF in Canada.)

The patient views: patients, patient networks and health charities

For the purpose of this report, 5 patients on, or having been on, clinical trials, 6 members of patients’ networks and 6 health charities representing various diseases or chronic debilitating conditions⁴⁶ were randomly identified and interviewed through open-ended questionnaires seeking their experiences and opinions about clinical trials. Health charities and patients’ networks represented from hundreds to thousands of patients. Some of the patients had been/are on two or three clinical trials. Although most trials were on drug testing, the group included one clinical trial on nutrition (dietary fat and cancer), and one on bio-feedback pain. Three specific open-ended questionnaires were drawn which were e-mailed or post-mailed to a random list of possible respondents, together with a consent form and a letter of invitation about the research project. Personal communications were established with all respondents and about half were interviewed by telephone, while the other half replied to the questionnaires by e-mail.

All three parties strongly supported clinical trials and the need to increase their number, but they all stressed the importance of improving the process at many different levels. On the whole, we observe a remarkable unanimity of opinions and recommendations.

The need for patient/consumer participation at all levels - ethics panels, protocols, study design, dissemination of research results, government agencies (both federal and provincial) knowledge transfer - is the one issue on which there was total agreement. Respondents were not satisfied with “token” representation but numbers that constitute a critical mass.

*“Health Canada does not have sufficient input from consumer/patients (...) those with direct knowledge and experience”.*⁴⁷

⁴⁴ www.cancertrials-help.org

⁴⁵ Interview with Patient Network 5

⁴⁶ These are: cancer, HIV/AIDS, Parkinson, arthritis, Alzheimer, cystic fibrosis, diabetes, mental health disorders, as well as pediatric conditions.

⁴⁷ Interview with Patient Network-1B

“Ethics Review committees must include patient/consumer input. People on ethics committees cannot relate to people with disease, and rely on assumptions and generally accepted truths.”⁴⁸

“We need more effective transfer of knowledge. The only worse thing about good research not funded is good research not applied”.⁴⁹

“Yes, Health Canada does consult but often hurriedly and after the fact. Consumers/patients are not truly involved in a partnership sense and there is room for improvement”.⁵⁰

Patients’ recruitment and retention are critical for the success of clinical trials and our interviews focused on the issue. (Retention had not been an issue among our respondents, although some had had moments of hesitation during their treatment.) However, in probing how a patient is recruited, two facts became shockingly clear: it is the patient’s *specialist* who recruits a patient into a trial or, regrettably, does not:

“Mon rhumatologue (...) ne me parle jamais de recherche. C’est moi qui glâne l’information sur le Web et lui fais des suggestions ou pose des questions quant aux traitements”.⁵¹

Secondly, the *family physician’s* role and level of awareness of clinical trials are non-existent:

“The family physician (FP) is out of the loop and overwhelmed. The FP is unable to manage the “Silos” in the system. When a patient is enrolled in a clinical trial, the patient records should be communicated to the FP to ensure continuity of care. Concerns regarding confidentiality prevent good communications between the FP and the clinical investigator. This could be overcome using modern technology”.⁵²

“Canadian patients are not knowledgeable and informed, they simply do not know enough about clinical trials, particularly cancer patients. They are unaware of the benefits of clinical trials, that they will receive the best available care. The patient often feels abandoned, never knowing the results of the trial. The patient’s participation should be acknowledged if only with a simple thank-you”.⁵³

“The level of risk the patient will assume depends on the level of incapacity and pain of the individual patient. Canadians should develop a more positive attitude to clinical trials(...) it is the only way to learn and to know.”⁵⁴

⁴⁸ Interview with Patient Network-4

⁴⁹ Interview with Patient Network-5

⁵⁰ Interview with Health Charity -3

⁵¹ Interview with Patient Network-3

⁵² Interview with Patient Network-5

⁵³ Interview with Patient Network-5

⁵⁴ Interview with Patient Network 1B

“Here in Ontario, I have found that family physicians have pathetically short amounts of time to spend with me as their patient. No family physician I ever had, had any information about clinical trials.”⁵⁵

In general, the trials were considered a positive experience for the same reasons given in the American Harris poll cited earlier.

“I thought it would be a lot more frightening that it actually was.”⁵⁶

“My feeling is if I were not on this trial, I would not be so closely observed – there is no fooling around.”⁵⁷

Once informed of a trial possibility, patients had no particular concern except for the fear of being on placebo and therefore wasting time in the management of their disease. However, in some cases, a key factor in deciding to participate or not had to do with the sudden lack of access to the trial drug at the end of the research project, when it has yet to be approved by Health Canada and/or put on provincial formularies. In the latter case, prohibitive cost is often a major barrier for patients. For example, medication for rheumatoid arthritis can be as much as \$20,000 per year.⁵⁸

“Continued access to effective treatment should be a priority, without cost, with sustainability for the duration of the person’s illness and continuity for the rest of their lives. It is highly inhumane in the current practice to have a person regain their quality of life, and watch their symptoms dissipate, only to come to the end of the CT and degenerate to the way they were prior to the CT.”⁵⁹

“Once the trial I was on ended, no one was interested in me.”⁶⁰

The HIV/AIDS CTN ethics review panels have avoided the immediate post trial problem by stipulating on-going access to the drug as a condition of participation.

All respondents were critical of the delays and lack of transparency in the listing of new therapies on the provincial Drug Formularies. Inequities in access exist throughout the country.

“Another major impediment is the lack of co-ordination within provincial drug formularies. Listing of new medications are too often a result of strong lobbying/advocacy and not science-based.”⁶¹

⁵⁵ Interview with Patient 5

⁵⁶ Interview with Patient 1

⁵⁷ Interview with Patient 3

⁵⁸ Patient Network 3

⁵⁹ Interview with Patient Network 2

⁶⁰ Interview with Patient 5

⁶¹ Interview with Health Charity-3

“The process of Formulary inclusion needs improvement and requires a rigorous, scientific methodology.”⁶²

“Provincial drug plans often do not cover new medications creating real problems for patients. Delays and unevenness of access to medication in Canada is a real shame”.⁶³

The responses regarding the Regulatory Process (Health Canada, TPD) were uniformly critical, with the exception of one respondent.⁶⁴ Respondents praised Health Canada’s credibility, but they strongly object to the delays in drug reviews. They question the need to duplicate what other conscientious national regulatory bodies are doing. They want Health Canada to modernize and make the best use of technology. There is strong support for harmonization, alliances and reciprocity in drug reviews.

“Drug reviews are too slow. There is no need to duplicate and repeat reviews done in similar countries,(...) have confidence in US FDA and Europe. (...) TPD is not sufficiently funded. Is in favour of cost recovery (industry pays for drug reviews) even though this is a controversial issue. Alliances/harmonization with international community is necessary as evidence from Europe and US is credible”.⁶⁵

“Should begin by implementing recommendations of the many reviews and reports of the past ten years. Use Cost Recovery funds to fund the review process. Modernize ..use electronic forms etc. Needs leadership with a sense of urgency. Follow the examples of other countries such as Sweden, the UK, US. Make use of alliances and harmonization. Give true fast track priority to review breakthrough therapies. Second guessing by the provinces using therapeutic committees adds even greater delay and governments will often leverage public opinion, i.e. special interest groups opposed to change to support these delays.”⁶⁶

“Ma réponse est un “non” catégorique. Mes recommandations: que le Canada (Santé Canada) négocie une alliance multiple avec l’Union Européenne, la Grande-Bretagne, des pays de l’OCDE comme l’Australie, voire les Etats-Unis, le G-8, pour partager/réduire les coûts des étapes/opérations, d’évaluation et d’étude, et pour raccourcir les délais d’approbation des nouveaux traitements/médicaments, après s’être entendus sur des standards de qualité communs. En parlant de la lenteur de Santé Canada, on dit (vérifier les sondages) que les Canadiens veulent une approbation ‘made in Canada’ pour être assurés de la sécurité/efficacité du médicament. Mais ceci pourrait être surmonté.”⁶⁷

⁶² Interview with Health Charity-5

⁶³ Interview with Patient Network 4

⁶⁴ Interview with Health Charity-5

⁶⁵ Interview with Patient Network 1B

⁶⁶ Interview with Patient Network 5

⁶⁷ Interview with Patient Ntwork-3

“Emergency Drug relief program is very helpful to many patients in difficult stages of diseases but accessibility is very spotty. Depends on your doctor.”⁶⁸

More Specific Issues

Following is a list of other observations collected through the interviews:

- Reimbursement of expenses, fee to participate: immaterial, even if a small stipend for expenses incurred, as is the case in some trials, is made available. Only one patient recalls having been paid a fee to participate in a trial using quite invasive treatment.⁶⁹ What is an issue however, is the absence of transparency, total transparency, on who pays what to whom, as a simple matter of public accountability.

“I believe that there should be total transparency in the conduct of clinical trials, not just of patients, but also researchers/investigators and equally important, the contracts signed by the institution and sponsor. This is becoming increasingly important in the ownership of genetic codes, cell tissue, etc.”⁷⁰

- On giving informed consent: opinions vary on this point. The majority find the consent interview very satisfactory. The form itself, however, is most complex, in ‘legalese’ and hard to understand.

“The clearer the consent form, the better the protocol.”⁷¹

Patients’ networks and health charities are clear on the fact that they should not deal with patients’ consent except to lobby for transparent and plain language forms. Regarding children’s clinical trials, Canada should enforce the United Nations Convention on the Rights of the Child, especially Articles 3, 5, 12, 13 and 25.⁷²

- On knowing about ongoing clinical trials:

“I would very much appreciate having access to a central site for all CTs conducted in Canada.”⁷³

⁶⁸ Interview with Patient Network-1A

⁶⁹ Interview with Patient Network 5

⁷⁰ Interview with Patient Network-4

⁷¹ Interview with Patient Network-4

⁷² There is also an ICH guideline on Clinical Investigations of Medicinal Products in the Pediatric Population (<http://www.ich.org/pdf/ICH/e11step4.pdf>).

⁷³ Interview with Patient-5

There is a strong and general consensus in favour of such initiative. All groups interviewed told us of their best efforts to disseminate what they learn about on-going (or past) clinical trials: newsletters, web sites, media interviews, public speaking, etc. One health charity states, for example, that it *“provides updates to the international CF clinical trials database, which is maintained by the Cystic Fibrosis Foundation of the United States.”*⁷⁴

- On obtaining, or not, the results of one’s trial: patients want to know, whatever the results:

*“At the end of the study, when the data has been compiled, I would like to know what drug I received.”*⁷⁵

(...) *“whatever the results,...again, a central Registry would be helpful.”*⁷⁶

*“I have seen patients pursue horrendous treatment as last hopes, when if it were clearly stated that it would do them no good, they might not put themselves through it.”*⁷⁷

On this point, several interviewees referred us to the Cochrane Collaboration, which they praise.

However, as one patient⁷⁸ remarked: *“It’s a good idea in itself and we need such meta-analysis, but they are very cautious, take a long time and the results come much too long after the trials outcomes. What is missing is an in-between service such as the B.C. Cancer agency monthly updated report on treatments. The British Columbia Cancer Care Program is an example of best practices. Its Data Base is excellent and the Website broadcasts updated treatment guidelines on a regular basis. Treatment is more aggressive and better outcomes reflect this methodology. Strong leadership linking clinical care to good research has made the BC. Cancer Care Agency a source of pride to B.C.”*

*“An Information Bulletin published by CIHR on a bi-yearly basis of all available CT’s, their benefits and side effects.”*⁷⁹

- On research ethics boards: there is considerable concern about clear roles and top standards, as well as the best “neutral” party. As in peer reviews, *“safety, credibility and quality”*⁸⁰ are of the essence. However, respondents have mixed feelings as to who should give leadership (Health Canada or the CIHR) and under

⁷⁴ Interview with health charity 6

⁷⁵ Interview with Patient-4

⁷⁶ Interview with Patient Network-1A

⁷⁷ Interview with Patient-2

⁷⁸ Interview with Patient Network-5

⁷⁹ Interview with Patient-1

⁸⁰ Interview with Health Charity-5

what form (a single central agency or audits conducted as the FDA does). There is support for an Auditing Body similar to the US FDA.

“Panels should be carefully constructed to be sensitive to the developmental differences of population groups, i.e. children. Parents (of children who may be enrolled in clinical trials) are becoming much more aware of the deficiencies in the system and are demanding standards.”⁸¹

“Health Canada should set the standards and monitor as does the FDA.”⁸²

“Only if it is the gold standard... not the lowest common denominator, and must take into consideration the special needs of population groups. HIV people are extremely stigmatized.”⁸³

- On the role of CIHR: when respondents know of the Institutes, *“the jury is still out”⁸⁴* as to their possible central role in ethics and peer reviewing, and in dissemination of research outcomes. On CIHR valuing and supporting clinical trials, answers were as follows:

“Non! Pourquoi? Je l’ignore.”⁸⁵

“... they are not a major player in this field.”⁸⁶

“Bias towards basic vs. clinical. Real skepticism within the clinical research community that clinical trials would receive appropriate peer review, to the point that many feel it is not worth applying.”⁸⁷

“Seems to be biased more to basic than clinical, though recent experience with Institute for Aging has been very positive.”⁸⁸

“ I was recently invited to a Knowledge Translation workshop held by CIHR and I feel that CIHR is moving in the right direction and am heartened by CIHR’S efforts to involve patients”.⁸⁹

- On clinical trials for children: risk is a major factor in recruitment. General agreement that:

⁸¹ Interview with Health Charity-2

⁸² Interview with Health Charity-1

⁸³ Interview with Patient Network-6

⁸⁴ Interview with Health Charity-3

⁸⁵ Interview with Patient Network-3

⁸⁶ Interview with Health Charity-4

⁸⁷ Interview with Health Charity-2

⁸⁸ Interview with Health Charity-1

⁸⁹ Interview with Patient Network-4

“Fear of the unknown is even higher for children because of the long term effects on development and the controversy of dosage. The benefits of accessibility while on a trial are a plus ... however, in post-trial this becomes a problem as most new therapies are not listed on insurance plans or provincial formularies and the cost becomes prohibitive.”⁹⁰

“Yes, with the additional principles respecting the Rights of the Child and real involvement of the child and parents. May be additional cost implications such as child care, transportation etc.”⁹¹

- On who conducts the best clinical trials: a few more think that universities and research institutes do a better job because they are more “neutral” although others observe that pharmaceutical companies are more rigorous and know the regulatory process far better. There is definitely suspicion vis-a-vis the pharmaceutical companies regarding the integrity of their research results, accountability in the whole system of clinical trials, and the need for involving patients at all stages of the research projects.

“I have discovered through my work with the Cochrane collaboration that many drug trials are not of high quality and the evidence is often poor”.⁹²

“All equally capable of conducting good trials, however, pharma companies are reluctant to disclose negative results. Preference runs to other than pharmaceuticals.”⁹³

“I have problems with pharma trials because of the repression of negative information. I am also concerned that Contract Research Organizations who are more and more managing clinical trials are not neutral...they are accountable to the pharma company to whom they are under contract. Are they becoming a monopoly?”⁹⁴

“Attitude is a problem, particularly in pharma sponsored trials who often choose the most stable people and those who are likely to provide the results sought in the trial. Need real people to produce real world results.”⁹⁵

Summary of Findings

Patients support clinical trials and feel they bring an important benefit for Canada in terms of health, individually and collectively. The expansion of knowledge and the improvements in treatment that result from CTs are embraced by Canadians who wish to participate fully. There is realization that more funding will be required, but with the public

⁹⁰ Interview with Health Charity-2

⁹¹ Interview with Health Charity-2

⁹² Interview with Patient Network-1A

⁹³ Interview with Patient Network-1B

⁹⁴ Interview with Patient Network-5

⁹⁵ Interview with Patient Network-6

actively informed and engaged, and with political will, Canada could and should be a much bigger player in the field of clinical trials. Because they are one of the few stakeholder groups that see the clinical trial system holistically, patients have strong views on the regulatory approval system, provincial formularies, involvement in all stages of clinical trials project, post-marketing surveillance, and the real potential for making Canada an international leader in innovative approaches to clinical trials.

5. Components of the system

This chapter describes the other major components or stakeholder groups in the clinical trials system

While patients provide a holistic perspective of the testing and evaluation of drugs process, other major players have a more specific viewpoint to offer. These include the following:

- Regulators: Health Canada and Therapeutic Products Directorate
- Research Ethics Boards
- Provincial Formularies
- Research Community:
 - Allied health professionals: nurses, coordinators and associates
 - Investigators
 - CIHR
 - Hospitals and universities
- Global Pharma Industry
- Biotech industry
- Clinical Research Organizations (CROs)
- Private Research Clinics
- Site management organizations

The Regulators: Health Canada and the Therapeutic Products Directorate

The Therapeutic Drugs Directorate is the body within Health Canada that issues permissions to hold clinical trials and approves drugs for marketing. The Biologics and Genetic Therapies Directorate focuses on large biological molecules, vaccines, and other biotech products, and will not be treated here. Health Canada's TPD provides a fact sheet describing their review process.⁹⁶ Highlights from this fact sheet include the following:

- Drug applications are reviewed by scientist in the TPD, and on occasion, outside experts to assess safety, efficacy and quality of a drug.
- The TPD has set internationally competitive performance targets for conduct of review. Review time is affected by type of product, size and quality of submission, and TPD's workload and human resources. TPD states the drug review process takes an average of 18 months.
- To ensure efficiency, the TPD has implemented or is pursuing:
 - electronic drug submission templates;
 - participating in ICH (International Conference on Harmonization) Guidelines;

⁹⁶ http://www.hc-sc.gc.ca/hpb-dgpps/therapeut/zfiles/english/fact-sht/fact_drug_e.html

- implementing a team approach to product reviews;
 - upgrading IT capabilities; and
 - strengthening scientific resources.
- Once a new drug is approved, regulatory control continues. The distributor of the drug must report any new information concerning serious side effects and any new studies providing new safety information. The TPD monitors adverse events, known as pharmacovigilance, but doesn't say how involved in this process they are.

The typical approval process for New Therapeutic Products includes:⁹⁷

- Pre-Screening. Preliminary assessment of completeness and patent check are undertaken.
- Screening. Full screening against submission requirements takes place, companies are invoiced and submission assigned to review division.
- Evaluation. Two concurrent evaluations; Safety and Efficacy Evaluation (clinical) and Chemistry and Manufacturing Evaluation (quality).
- Label Review.
- Approval.

The Approval and Review Times for drugs

An issue that has been identified over and over again is the time it takes for the Therapeutic Products Directorate at Health Canada to approve new drugs for patients. It should be made clear that in this current study, we did not carry out an independent assessment of review and approval times, nor did we do an organizational review of TPD and collect any primary data on how well TPD is doing in relation to similar organizations in other countries. We can only offer a summary of other studies and analyses.

Over the last twenty years, several reviews surfaced analyzing and criticizing the inefficiencies of the Canadian Drug Approval process.^{98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112}

⁹⁷ Biotechnology Patents and Product Approval Processes: Challenges and Opportunities. Submitted to Ontario Ministry of Energy, Science and Technology. The Blair Consulting Group and RIAS Inc. October 2001.

⁹⁸ Eastman, H.C. *Report of the Commission of Inquiry on the Pharmaceutical Industry*. Supply and Services Canada: Ottawa, ON, 1985.

⁹⁹ Nielsen Task Force. *Health and Sports Program: a study team report to the Task Force on Program Review*. Supply and Services Canada: Ottawa, ON, 1987.

¹⁰⁰ Auditor General of Canada. *Report to the House of Commons, fiscal year ending 31 March 1987*. Supply and Services Canada: Ottawa, ON, 1987.

¹⁰¹ Working Group on Drug Submission Review. *Memorandum to the Minister (the Stein Report)*. Health and Welfare Canada: Ottawa, ON, 1987.

¹⁰² Overstreet, R.E., Berger, J., Turriff, C. *Program evaluation study of the Drug Safety, Quality and Efficacy Program*. Health and Welfare Canada: Ottawa, ON, 1989.

¹⁰³ Gagnon, D. *Working in partnerships...drug review for the future*. Health and Welfare Canada: Ottawa, ON, 1992.

¹⁰⁴ Rawson, N.S.B., Kaitin, K.I., Thomas, K.E., Perry, G. Drug review in Canada: a comparison with Australia, Sweden, the United Kingdom, and the United States. *Drug Inform J* 1998; 32:1133-1141.

Many of these studies use different methodologies for measuring the performance of the drug approval process, with different conclusions. One organization that has achieved credibility with all concerned parties, including industry and government agencies, is CMR International¹¹³, an independent UK-based research organization founded in 1981.

One Canadian landmark study on this question was carried out in 1992 by Dr. Denis Gagnon, Laval University Vice-Rector of Research, for the Minister of National Health and Welfare.¹¹⁴ This report was commissioned by the government in response to the major increase in review and approval times of New Drug Submissions from PMAC members (now Rx&D) from 702 days in 1986 to 1,163 days in 1991. Dr. Gagnon's report provided 152 recommendations. Most notably, Dr. Gagnon recommended the creation of a drug review agency at arms length from the government, reporting directly to Parliament through the Minister of National Health and Welfare now Health Canada. Priority of review would be assigned to review drugs offering the greatest therapeutic benefits.

Gagnon cited that patient groups such as cancer patients were being denied timely access to new medicines that were available to patients in other countries. This was because other countries faced with similar problems, had dramatically altered their drug review process to ensure citizens of their countries had timely access to the new drugs. He mentioned Australia, Great Britain and Sweden, countries with previous backlogs, who by making changes to their regulatory process, had ensured that new drugs were reviewed quickly and efficiently.

At that time, Dr. Gagnon noted, "Patients have rights to new drugs that often provide benefits not afforded by previously available products. The drug review process is bureaucratic and cumbersome. It does delay the provision of new medicines to Canadians and it must be changed." Interestingly, he notes "Millions of Europeans have early access to new drugs, sometimes years before Canadian patients."

¹⁰⁵ Therapeutic Products Program. *Annual drug submission performance report, 2000*. Health Canada: Ottawa, ON, 2001.

¹⁰⁶ Rawson, N.S.B. Time required for approval of new drugs in Canada, Australia, Sweden, the United Kingdom and the United States in 1996 – 1998. *Can Med Assoc J* 2000; 162: 501-504.

¹⁰⁷ Rawson, N.S.B., Deficiencies in approval of, access to, and post-marketing follow-up of new drugs in Canada: A personal viewpoint. *Pharmacoepidemiology and Drug Safety (Spring 2002 – In Press)*.

¹⁰⁸ *Therapeutic Products Program: baseline assessment of drug submission review process*. PricewaterhouseCoopers: Ottawa, ON, 1999

¹⁰⁹ Robert Peterson *Pharmacoepidemiology and Drug Safety (Spring 2002 – In Press)*.

¹¹⁰ Rawson, N.S.B. Human resources for the approval of new drugs in Canada, Australia, Sweden, the United Kingdom and the United States. *Can J Clin Pharmacol (in press)*.

¹¹¹ Rawson, N.S.B. Human resources for the approval of new drugs in Canada, Australia, Sweden, the United Kingdom and the United States. *Ibid*.

¹¹² Brown, K.R., Douglas, R.G., New challenges in quality control and licensure: regulation. *Int J Tech Assess Health Care* 1994; 10:55-64.

¹¹³ www.cmr.org

¹¹⁴ Gagnon, *ibid*.

Dr. Gagnon noted “the consequences of maintaining the status quo are the continuing effects on health for those patients being denied early access to new essential drugs, and the continuing waste of resources from an inefficient system.”

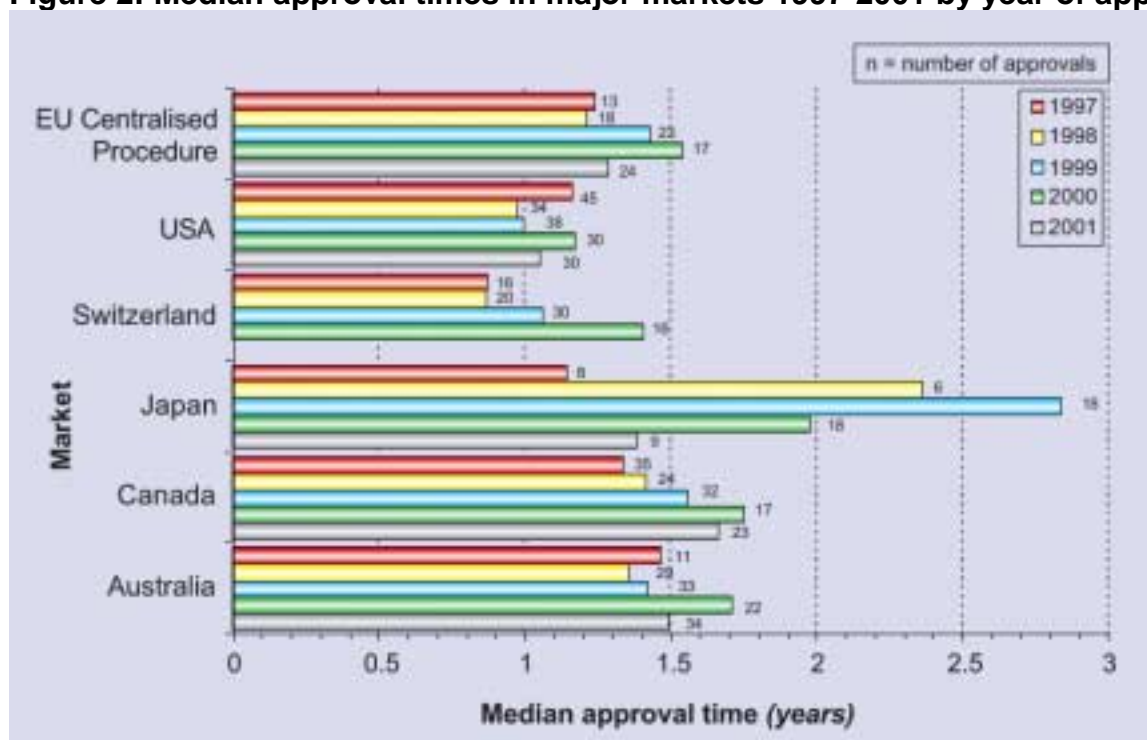
Dr. Gagnon also proposed a National Post-marketing Pharmaceutical Surveillance Program to be implemented.

Recent Studies and Analyses

Health Canada’s TPD has set performance targets of 355 days for the entire process, whereas the actual average approval time remains at 710 days.¹¹⁵

As of 2001, the TPD of Health Canada took on average 23.6 months to approve a new drug. In 2001, 24 new drug submissions and four new biologic submissions were approved and sold in Canada.¹¹⁶

Figure 2: Median approval times in major markets 1997-2001 by year of approval¹¹⁷



CMR International has compared median approval times in major markets between 1995-1999.¹¹⁸ Canada took somewhat more time than the USA and Australia, but much less time than Japan in approving new drugs. The median approval time in Canada dropped

¹¹⁵ Biotechnology Patents and Product Approval Processes: Challenges and Opportunities. Submitted to Ontario Ministry of Energy, Science and Technology. The Blair Consulting Group and RIAS Inc. October 2001.

¹¹⁶ Rx&D NOC Survey 2001, May 2002

¹¹⁷ R&D Briefing No 35, The impact of the changing regulatory environment on review times, CMR International, October 2002, www.cmr.org

¹¹⁸ CMR R&D Briefing No.31, February 2001, www.cmr.org

from approximately 1.7 to 1.3 years between 1996 and 1997, but has been creeping up ever since. Figure 2 shows the latest analysis, comparing mean approval times between 1997 to 2001:

The decrease in approval times seen in the major markets (Australia, Canada, EU, Switzerland and the USA) between 1995 and 1997¹¹⁹ did not continue between 1998 and 2000. Since 1998, median approval times, with the exception of Japan, have slowly increased to reach a peak in 2000. More promising approval times were seen in 2001 for all of the major markets, however the USA, Canada and Australia still had longer approval times in 2001 than were achieved in 1998 (see Figure 2). Overall, median approval times for new active substance (NAS) applications are quickest in the USA, with Switzerland following closely behind.

Companies are not happy:

“Once all the trials are completed, and you are ready to submit the package to Health Canada, the time to give notice of compliance (NOC) is two years, even for accelerated review (uniqueness, significant need for given population) as opposed to run of the mill. A key example is Indinavir, one of the first proven molecules for HIV, an important medical and social breakthrough. The – NOC took 42 days in US, vs. 180 days in Canada.”¹²⁰

There has been a seven year effort to revise some of these approval requirements. Moreover, in September 2001, Health Canada/TPD agreed to shorten the IND approval period for clinical trials from 60 to 30 days. But in one industry representative’s view,

“...they move at a geological pace. For example, there were new clinical trials approval guidelines announced last year, there was a draft document that was issued with these guidelines, almost a year later, that document is still in draft form!”¹²¹

Most industry representatives also say that the 30 days IND approval period is still too long for Phase I studies, which in other countries such as the UK, Belgium or the US is only seven days. However, TPD now has a target of seven days approval for phase I studies.

Academics’ views of TPD

The degree and type of contact with TPD, as well as the resulting relationships, varied widely with the researchers. A sampling of these different views is as follows:

A researcher with extensive experience with TPD noted that their group has developed a good efficient relationship with individuals at TPD and have specific personnel in their group that work with them. They are aware of the regulatory

¹¹⁹ CMR R&D Briefing No.31, ibid

¹²⁰ Interview with arge pharma executive

¹²¹ Interview with large pharma executive 6

*requirements needed in a clinical trial application and, as a result, TPD has generally met target dates. It was noted that their dealings with TPD primarily concern approvals for starting a clinical trial and not drug approval.*¹²²

*A researcher encountering TPD as an outside consultant for industry, found TPD to be quite reasonable, with the appropriate questions asked and the process being fair.*¹²³

*A researcher noted that, in general, there is a personnel issue in Health Canada with the number of good health scientists not matching the number of important health science issues. The budget is not adequate and they have trouble retaining good people. Although the role of Health Canada in research is not clear, regulatory role of TPD is clear and all TPD activities are better if at arm's length from industry.*¹²⁴

*A specific point of frustration was the new requirement of an IND protocol needed for any drug used for an off label indication in a clinical trial. The problem is not one of letting them know but the resulting time delays in their processing and the major learning hurdle since researchers often lack the experience of doing these protocols.*¹²⁵

*TPD should develop more of a facilitating role, than a simple control mode, but they will need the necessary personnel and resources to do the work efficiently.*¹²⁶

Researchers believe that TPD is trying hard to define more of a role for itself (such as in phase IV trials). Suggestions were made that TPD should endeavour to better understand the academic community, make stronger academic partnerships and develop academic research satellites.

Patients' views of TPD

As mentioned earlier, patient responses regarding the Regulatory Process (Health Canada, TPD) were mostly critical, and while they praised Health Canada's credibility, they strongly object to the delays in drug reviews. They question the need to duplicate what other conscientious national regulatory bodies are doing, and would like Health Canada to modernize and make the best use of technology.

Summary of Findings

In reviewing the regulatory approval system in Canada, namely the Therapeutic Products Directorate (TPD) in Health Canada, it has to be stressed that we did not carry out any primary data collection and analysis, nor did we carry out an organizational review of TPD,

¹²² Interview with researcher 1

¹²³ Interview with researcher 2

¹²⁴ Interview with researcher 3

¹²⁵ Interview with researcher 4

¹²⁶ Interview with researcher 4

but relied exclusively on secondary data and findings. There are clear signals from some stakeholders, namely patients and the pharma industry that approval times for medicines are too slow. International comparison data shows that Canada is in the upper mid-range of major industrialized countries, within a range of +/- 3 to 4 months. These are average or median approval times. There appears to be a trend¹²⁷ over the last five years towards an increase in approval time by TPD by almost 30%, relative to 1997 levels. Some are suggesting that the current TPD model may not have the flexibility or resources to meet future challenges.

The Research Ethics Board process

Research Ethics Boards (REBs) can be found at research hospitals and universities, or can be independent, that is operate as a for-profit enterprise, where members of the ethics board are paid experts, and fees are charged to the study sponsors.¹²⁸ The mandate of Research Ethics Boards is to protect the rights and welfare of research subjects participating in studies associated with their institutions. A clinical trial project cannot go forward without first obtaining the approval of an ethics review board, also known as research ethics board (REB), or in the US, Institutional Review Board (IRB). It is the REB's responsibility for reviewing clinical study protocols from a patient's safety perspective and allowing the study to take place in their institution. Before patients can be entered into a trial, they must provide informed consent, and it is the REB's role to approve that as well.

In today's clinical research environment, however, problems may arise, as many clinical trials are multi-centred. In such cases, a given clinical trial protocol can be reviewed by more than one REB, which may give rise to discrepancies in the decision to approve or to not approve the study. Moreover, a Canadian REB cannot benefit from the expertise of another REB that is or has previously reviewed the same protocol. REBs are not allowed to talk to each other, and because of current confidentiality rules, cannot refer to each other's decisions.¹²⁹

Most large drug companies point out to the Research Ethics Board process as a major bottleneck, and an ongoing source of frustration. The REB process across the various institutions is not harmonized or consistent, and has no standards. Many REBs appear overwhelmed by the volume of applications, and suffer from challenges related to capacity, timing and consistency.

Delays with REBs are one of the most cited complaints from pharmaceutical companies:

¹²⁷ See NOC Survey, Rx&D, May 2002

¹²⁸ Ferris, LE. Industry-sponsored pharmaceutical trials and research ethics boards: Are they cloaked in too much secrecy? CMAJ. May 14, 2002:1279-1280

¹²⁹ Ferris et al., *ibid.*

*“The delays often depend on specific therapeutics, and target patient population. There are many REBs, each has somewhat different requirements, different meeting dates, which makes it difficult to streamline and coordinate. We’ve worked with centralized private ethics board, but we can use them only for independent private research clinics.”*¹³⁰

*“Some Research Ethics Boards may have difficulty in finding the right balance between scientific expertise and lay people to protect interest of general public. For example, there was a case a few years ago in which an REB turned down a protocol on the grounds that it was unethical to pay physicians a per patient fee. This was deemed an inducement to enroll patients, and yet physician investigators must be compensated for their time spent on CT work and this is a generally accepted practice.”*¹³¹

In 1997, the United Kingdom tried to implement a process where Multi-centre Research Ethics Committees would review multi-site study protocols prior to local REBs. No doubt, local REBS found their subordinate role difficult and variability in clinical trial protocol approval persisted.^{132, 133} In the UK, there is one Multi-centre Research Ethics Committees in each English region and one each in Scotland and Wales. Their decisions are binding for the whole of the UK. Any application involving five or more local REBs goes first to the multi-centre committee. Most problems (in terms of review time and idiosyncrasies) lie at the interface between the multi-centre and local REBs.¹³⁴ It was suggested that a national advisory body is needed to communicate with local REBs, organize training programs and give clear guidance.¹³⁵

The American FDA’s legislation has a whole section on how REB’s (IRBs) should be constituted, and provide for an auditing mechanism for REBs.

A major cause contributing to their inefficiencies is the *poor training and insufficient funding* allocated to institutional Research Ethics Boards, as recently observed in Quebec by that province’s auditor general and others:

“...la formation sur l’éthique dispensée aux acteurs impliqués dans les travaux de recherche ainsi que le soutien accordé aux comités laissent à désirer. En effet, il n’existe aucun programme structuré de formation s’adressant aux chercheurs, au personnel de recherche et aux membres des comités d’éthique. Finalement, les centres hospitaliers que nous avons vérifiés n’ont pas évalué les besoins en ressources humaines, matérielles et financières pour que les comités d’éthique

¹³⁰ Interview with large pharma executive

¹³¹ Interview with large pharma executive 2

¹³² Tully J, Ninis N, Booy R, Viner R. The new system of review by multicentre research ethics committees: prospective study. *BMJ* 2000;320(7243):1179-82.

¹³³ Lux AL, Edwards SW, Osborne JP. Responses of local research ethics committees to a study with approval from a multicentre research ethics committee. *BMJ* 2000;320:1182-83.

¹³⁴ KGGMM. Multicentre research ethics committees: has the cure been worse than the disease? *BJM* 2000;320:1157-58

¹³⁵ Alberti et al., *ibid.*

puissent remplir pleinement leur rôle. D'ailleurs, les membres de ces comités considèrent que le soutien qui leur est offert est insuffisant.”¹³⁶

“At any one point, there are 800 trials on the go in our Hospital, 400 new reviews a year, of which 220 are major reviews. I see it like working in any under-funded area. Our REB processes are too slow and this is by design because they are staffed by volunteers. When you work with volunteers, you need lead time, don't necessarily have fast turnaround. Of the fees that we charge, the dollars go to the staff and chair.

We were among the first institution to start charging for REB reviews. This created a revolt among investigators, because they were afraid that industry would go elsewhere, but all it elicited was yawn from industry. We would want to increase these to \$3K and offer faster service, but has some institutional barriers to face.”¹³⁷

There are several initiatives underway to remedy some of these problems, including web-based educational programs, attempts at coordinating cancer REBs, in the context of the Ontario Cancer Network, and the newly-created Canadian Association of Research Ethics Board (CAREB).

CAREB was established (in June 2001) by a group of REB administrators and chairs in response to an identified need for an organized, national voice. It will be a grassroots organization, involving and serving the needs of all research ethics boards across Canada, promoting the highest standards of ethics in research with human participants, and making clear the needs of REBs to perform that function, amidst the plethora of government, institution and industry voices with sometimes conflicting messages.¹³⁸

Health Canada is currently undertaking a study on the governance of REBs¹³⁹, and is exploring guidelines for eventually certifying REBs in Canada.

“But the current system is not adaptive. Organizationally, we pay lip service to REB cooperation, but don't do that in reality. There are legal barriers for improving the system, for instance, drug reviewers can't speak to REB, only to study sponsors, and REBs can't speak to one another, because of confidentiality of materials. Investigators sign NDAs, but for REBs confidentiality is implicit in their modus operandi.”¹⁴⁰

¹³⁶ Tome I du Rapport du Vérificateur général à l'Assemblée nationale pour l'année 2000-2001, Faits Saillants, http://www.vgq.gouv.qc.ca/rappann/rapp_2001_1/Faits/Index.html

¹³⁷ Head of a hospital ERB

¹³⁸ <http://www.uwo.ca/research/ethics/careb/Aug2001OnePager-E.htm>

¹³⁹ The project is called “Governance of Research Involving Humans”. Over the last year, Health Canada conducted a series of consultations with funders, sponsors, institutional representatives, REBs research administrators, researchers and subjects/participants, to identify concerns and expectations. These were concluded in the summer of 2002, and are currently being analyzed. Issues discussed included standards, policies, accreditation, certification and verification of REBs.

¹⁴⁰ Head of a hospital ERB

Academics' views on REBs

Researchers' opinions vary on the competency of ethics committees but there was unanimous agreement on the lack of national standards, wide variation in assessment, uneven capacity and slowness of the process. As one researcher noted '*ethics is a hit and miss game across study sites.*'¹⁴¹ In particular, the lack of consistency was noted when large national multicentre studies were being conducted, with different ethics committees regarding different aspects as being critically important and all modify the common consent form. Although local viewpoints are important, as one researcher noted, differences often reflect the competency of the board members rather than local community values. It was noted that ethics committees are getting involved with issues that are not directly ethical issues (such as, hospital resource consumption and allocation).

Considering the issues of ethics outside the Canadian borders, warnings were raised that in some cooperative agreements with the US, their government rules may apply and these rules need to be followed exactly and are strictly enforced.

Several researchers suggested the establishment of an arm's length National organization accrediting ethics committees, but that it was essential that such an organization be free of bias. Suggestions were made that if one ethics board approves a protocol then it should be given an expedited review at the other sites; however, this process can only be considered if standard requirements for ethics are set and are, at a minimum, met at each of the sites. But one researcher warned that central ethic committees have not met with success in some instances.

Patients groups' views on REBs

Patients groups have considerable concern about clear roles and top standards in ethics review, as well as the best "neutral" party. As in peer reviews, "*safety, credibility and quality*" are of the essence.¹⁴² However, respondents have mixed feelings as to who should give leadership (Health Canada or the CIHR) and under what form (a single central agency or audits conducted as the FDA does). There is support for an Auditing Body similar to the US FDA.

*"Panels should be carefully constructed to be sensitive to the developmental differences of population groups, i.e. children. Parents (of children who may be enrolled in clinical trials) are becoming much more aware of the deficiencies in the system and are demanding standards."*¹⁴³

*"Health Canada should set the standards and monitor as does the FDA."*¹⁴⁴

¹⁴¹ Interview with researcher 5

¹⁴² Interview with Health Charity 5

¹⁴³ Interview with Health Charity 2

¹⁴⁴ Interview with Health Charity 1

“Only if it is the gold standard... not the lowest common denominator, and must take into consideration the special needs of population groups. HIV people are extremely stigmatized.”¹⁴⁵

Summary of Findings

Research Ethics Boards seem to be a major factor slowing the clinical trials process. But their fundamental role in protecting the safety of patients in clinical trials and the integrity of research is seen as important. Patients want more involvement in the process, industry and researchers want faster approval times, and more knowledgeable board members. Funding, training, and lack of Canada-wide standards or guidelines are issues.

Provincial Formularies and other regulatory agencies in Canada

The process of drug approval by provincial formularies is not evident or transparent in most provinces.

Pharmaceutical companies find it difficult to spend so much money on drug development, only to be stopped by provincial formularies:

“Yes, a drug might become listed on a formulary, but no one is reimbursing patients. Some formularies will have a larger set of criteria. Quebec for example will list 60-70% of new drugs as open listing, while Ontario lists only 20 % of new molecules, and half of these have a restrictive listing, and often these are the innovative new drugs. The Provinces’ objective is managing costs, not health.”¹⁴⁶

“It is increasingly difficult to secure global investment in clinical trials and drug development in the face of increasing constraints on getting new drugs to market. A key problem is not obtaining formulary listing for our products, and not getting to market. The Canadian climate is seen as increasingly unfriendly to the market. With over 50% of our sales coming from formularies, formulary access remains crucial to our success. There seems to be a trend for provincial formularies becoming payers of last resort. The increasing difficulty to get to market, and get our ROI, hampers our ability to secure global investment.”¹⁴⁷

This view is shared for different reasons by patient groups. All patient respondents, as mentioned in an earlier section, were critical of the delays and lack of transparency in the listing of new therapies on the provincial Drug Formularies. Inequities in access exist throughout the country.

“Another major impediment is the lack of co-ordination within provincial drug formularies. Listing of new medications are too often a result of strong lobbying/advocacy and not science based.”¹⁴⁸

¹⁴⁵ Interview with Patient Network 6

¹⁴⁶ Interview with large pharma executive 1

¹⁴⁷ Interview with large pharma executive 2

¹⁴⁸ Interview with Health Charity-3

“The process of Formulary inclusion needs improvement and requires a rigorous, scientific methodology.”¹⁴⁹

“Provincial drug plans often do not cover new medications creating real problems for patients. Delays and unevenness of access to medication in Canada is a real shame.”¹⁵⁰

As provinces and territories have the responsibility to cover the costs of certain population groups for prescription drugs there exists significant variability in access to new medicines. There is also significant variation in how provinces and territories make the decision to list drugs on their formularies.¹⁵¹ Even if a new drug is approved for formulary listing, there is almost always a significant delay between federal approval and provincial listing. But there is some movement. In September of 2002,

“Health Ministers announced the establishment of a single, common drug review to be housed at the Canadian Coordinating Office for Health Technology Assessment (CCOHTA). CCOHTA will begin reviews early in the new year. This will streamline the drug assessment and drug plan listing processes.”¹⁵²

A common review process, however, is only one step towards a harmonized formulary system across the country.

Summary of Findings

Both the pharmaceutical industry and the patients groups feel the process for inclusion in the different provincial formularies is unclear and lacks transparency. Patients want access to new drugs, firms want access to markets. Recent federal provincial discussions have moved towards a uniform review system, but there is still far from an equitable, harmonized National System.

The Research Community

Allied Health Professionals: Nurses, Coordinators and Associates

One group of professionals, which we broadly refer to as allied health professionals, includes a number of sub-groups. According to SOCRA, Society for Clinical Research Associates,

If you work with clinical trials supporting the research institution or manufacturer of a new drug, product, or treatment regimen, then you are a clinical research professional. Whether called an investigator, monitor, auditor, data manager,

¹⁴⁹ Interview with Health Charity-5

¹⁵⁰ Interview with Patient Network 4

¹⁵¹ Anis AH. Pharmaceutical policies in Canada: another example of federal-provincial discord. *Can Med Assoc J* 2000; 162:523-526

¹⁵² Conference of Federal - Provincial - Territorial Ministers of Health, Banff, Alberta - September 4 - 5, 2002

*clinical coordinator, research nurse, or research professional - you are an integral part of the research team.*¹⁵³

Yet a number of these professionals play a critical and under-appreciated role in clinical trials.

The **research nurse or clinical research coordinator** is essentially responsible for contacting patients, explaining to them the protocol and consent form, and interacting with them throughout the trial, and is usually hired under contract by the clinical trial project.

Monitors are hired either by Clinical Research Organizations, or pharmaceutical companies. They oversee the clinical trial project at a site, review the filled out data forms, expenses, project schedules, etc.

In the course of our interviews and literature review, we have found both groups referred to as CRAs or clinical research assistants, although the usage is more prevalent in industry, where the terms CRA and Monitor are interchangeable. This confusion in nomenclature, however, does not affect the important but different roles each play.

The role of clinical research coordinators, some of whom might not have a nursing degree, is critical to the successful carrying out of clinical trials. They contribute to patient recruitment, transfer of knowledge, and provide direct contact with patients. They have direct influence on how the patient experiences the clinical trial, and have first hand contact of all the personal issues and problems a patient may face in the course of a trial.

A recent study of the role of clinical research coordinators (and the authors refer to them as CRAs) in cancer clinical trials confirms the critical importance of this group of professionals on patient accrual. In their opinion, system factors, including increased demands from regulatory bodies and pharmaceutical companies coupled with tighter timelines, pose increased work pressure on CRAs, and “*affected patient accrual more so than physician or patient factors.*”¹⁵⁴

As to what a pharma company looks for in a research nurse or clinical research coordinators:

*“We look for dedication, experience in nursing, hands on experience in clinical research. We want a nurse who can and knows how to look after patients, explain things to patient, is available, trustworthy, e.g. will not force patient to do something they don’t want, can identify the concern of patient, and is available to answer our question, and spend hours with our monitors, and be comfortable with our pickiness -- and we ARE very picky.”*¹⁵⁵

¹⁵³ www.socra.org

¹⁵⁴ Grunfeld, E, Zitzelsberger, L, Coristine, M, Aspelund, F. Barriers and Facilitators to Enrollment in Cancer Clinical Trials: Qualitative Study of the Perspectives of Clinical Research Associates. In press, Cancer.

¹⁵⁵ Interview with large pharma executive

One Canadian company that offers training for clinical research coordinators is Endpoint Research Ltd., in Toronto. Their “New Directions Coordinator Training Program” trains clinical research coordinators and research nurses on the fundamentals of performing research within the regulated drug development environment. They essentially train them on how to run trials across therapeutic areas – e.g. administrative tasks, ensure documents filled out, medical tasks (e.g. taking blood pressures for those coordinators who are not nurses), etc. This is 3-4 day workshop for experienced as well as novice study coordinators. Over the last five years, they trained more than 400 coordinators.¹⁵⁶

Monitors oversee the setting up and implementation of the clinical trial project:

“They have no patient contact and only review of study participants’ charts. A monitor might typically remain on any given trial for 6 months to 4 years. The Monitor, also called CRA, represents the sponsor at the site of a clinical trial, and reviews or monitors the progress of a clinical trial project, trains others, and helps troubleshoot problems at a site. He or she may even be involved in site selection or site validation. A senior Monitor or CRA may monitor activities of a team of 15 CRAs and 80 sites or more on a given Clinical Trial. Monitors are generally hired by pharmaceutical companies or clinical research organizations. There is high competition for good monitors. In our company alone, we currently have 72 vacancies.”¹⁵⁷

Monitors are considered very well paid.

Summary of Findings

The critical role of front line health professionals who run or oversee clinical trials has not always been fully appreciated. Challenges in terms of training and supply suggest a need for a broader human resources strategy approach for this group of stakeholders.

Investigators

Selecting good investigators is a challenge. A good investigator is not necessarily the top person in his or field, but more someone who understands and has access to a pool of patients. As one pharma executive said,

“From our investigators, we want the individual to be an expert in the particular therapeutic domain, a good coordinator, honest, trustworthy, and have a good patient population – we want a site which sees lots of cases, of the common variety (vs. esoteric varieties of disease) – You can be the best investigators, but if you have no patient, then it’s no good for us (but we can use the person as a speaker or researcher); good speakers don’t necessarily make good investigators.”¹⁵⁸

¹⁵⁶ Source: Endpoint and www.endpoint.ca

¹⁵⁷ Interview with a clinical research organization monitor.

¹⁵⁸ Interview with large pharma executive

The US NIH Director's Panel on Clinical Research made recommendations to stimulate increased physician involvement in clinical research.¹⁵⁹ This was done due to the fact that clinical research grants from the National Institutes of Health (NIH) to physicians had declined from 40% 30 years ago to 25% in 1998.

The panel made the following recommendations to the NIH.

- NIH funding for clinical research should at least be maintained.
- There should be continuing mentoring opportunities in clinical research for medical students.
- Clinical research training should be promoted by offering courses and grant opportunities in clinical research to young investigators emerging from specialty training programs and provide partial salary support for mentors.
- Study sections should be restructured so that review of patient-oriented research applications could include more physicians
- Encourage clinical investigators and basic scientists to work closely together and weld collaborations between academic clinical investigators and colleagues in pharmaceutical and biotechnology companies.
- Develop joint policy between academic health centers and NIH for the support of clinical research and clinical research training.

A number of large pharmas, who run many multi-site studies, mentioned the difficulties of accommodating the input of academic investigators:

“We don’t have the capacity to have all the investigators participate in the writing of a protocol, and accommodate their inputs – especially when our company does work in over 50 countries. There is an internal competition within our global company, and each region accumulates brownie points whenever we get a trial. There is a Principal investigator for each site, rarely for each study. But there is a Lead author(s) for the whole study whose name(s) are on the publication.”¹⁶⁰

At the end of the day, however, it is the investigator who can make the difference in the clinical research system:

“We need more entrepreneurship in clinical research. There are very few people who have dedicated their personal research career to Clinical Research. There is a lack of opinion leaders. What we need is a role model, like McMaster’s Salim Yusuf. A leading clinical researcher needs to have the freedom to do clinical research. This means not just being a good scientists, but also know the business dimension of CTs, as well as the political and social dimensions. To be a complete investigator, you need to be able to work on multi-dimensional problems. We have to initiate all new doctors to the multi-dimensional aspects of CTs. The situation has gravely deteriorated, people don’t even know basic statistics.

¹⁵⁹ Clinical research: perceptions, reality, and proposed solutions. National Institutes of Health Director's Panel on Clinical Research. *JAMA* 1998 Oct 28;280(16):1427-31

¹⁶⁰ Interview with large pharma executive

The peer review process of CIHR is just a big bureaucracy, which stops innovation, and holds it back – it just turns me off.”¹⁶¹

“There is a shortage of individuals and institutions structured to conduct research in high quality/high volume. Canada has much more capacity to do research than a mindset or willingness to do clinical studies — the challenge is to get more people interested in doing clinical research.”¹⁶²

A role for family physicians

There appears to be a need for an increased role for family physicians in CTs, and a need to educate them about CTs. This is currently seen as a major gap.

One way is to see it as a research implementation system, where out of the clinical trial, there comes out a critical knowledge transfer to the regulators, the GPs, and eventually to the patient. Ensuring a smooth linkage will help recruit patients for trials, as well as help market the drug. In effect, it can be seen as an ongoing CME (continuing medical education).

Summary of Findings

Investigators have a key role to play in leading clinical trials at a given site. Findings suggest that there may not be enough of clinical investigators with the right mix of leadership, scientific expertise, and access to patient, with a willingness to work with and collaborate with industry. Moreover, the role of family practitioners seems almost non-existent in the CT system.

The Canadian Institutes of Health Research (CIHR)

In general, there is a perception that CIHR could be far more involved in clinical trials than it currently is:

It would be useful for CIHR ... if they realized that many of the key questions relevant to them would be answered if there were more clinical research, and that it would help them to invest health care dollars better.¹⁶³

CIHR is the largest source of federal funding for health research, with an annual budget of \$390 million in 2001.

Under the joint Rx&D-CIHR partnership program, funding for clinical trials between January 2000 and December 2001 was \$40.6 million, of which approximately \$5 million was the share of CIHR. This covered 11 clinical trials.¹⁶⁴ This is less than 1% when

¹⁶¹ Interview with large pharma executive 3

¹⁶² Interview with large pharma executive 4

¹⁶³ Interview with large pharma executive 4

¹⁶⁴ CIHR/Rx&D Progress Report (2000-2001)

compared to the \$800 million - \$1 billion of direct and related costs spent in total in 2001 on clinical trials that we estimated in Chapter 2.

“Clinical trials are costly and compared to awards, one can fund few CTs whereas the same money could fund many awards. However the impact and benefits derived from CTs and CR are very significant and this is an essential ingredient in the strategic health agenda of the CIHR. The CIHR role is to encourage the generation, pursuit and development of new knowledge that impacts on health. CIHR does not fund regulatory or marketing aspects of CT, CR that private sector undertakes in the course of their business affairs.

*We may support clinical trials related to the novel application for existing therapeutics, or new therapeutics in discovery phase, but we will not support work related to efficacy testing or testing to satisfy strictly regulatory requirements. It is expected that the projects (i.e. CTs) make a contribution to science – we are not a contractor. We are there to encourage, facilitate conduct of excellent science in a collaborative environment.”*¹⁶⁵

In general, scientists and researchers felt that they have a good relationship with ongoing peer review funding agencies, including the CIHR. They were aware that while the funding level needed for a clinical trial was high, the number of grants awarded was much lower than in other areas of research. But the impact of such studies was high in terms of directly saving lives and optimizing health care. As one researcher noted, one *‘cannot put a value on the hormone replacement therapy and coronary heart disease issue that can affect three billion people, and no basic science study can get such a direct impact’*. Another researcher indicated that some basic science groups do not understand the necessity of clinical trials and why they are so expensive.

Lack of proper funding for clinical trials was a universal concern. Several opinions around this point were expressed:

*“Compared to our research colleagues in the US, it is a joke.”*¹⁶⁶

*“At the NIH there is much more funding to do the clinical trial right with proper monitoring and so on.”*¹⁶⁷

*“Researchers often are pulling punches by doing less ambitious studies since that is what can be funded.”*¹⁶⁸

*“CIHR does not have adequate funding levels needed for clinical trials.”*¹⁶⁹

¹⁶⁵ CIHR interview

¹⁶⁶ Interview with researcher

¹⁶⁷ Interview with researcher

¹⁶⁸ Interview with researcher

¹⁶⁹ Interview with researcher

It was noted that some groups have more funding available to them than the entire budget of the CIHR clinical trial's group; another researcher noted that CIHR is not swayed by political arguments so possibly funding is not as great as it could be. In many cases there is no option for researchers except to move closer to the private sector (as one researcher noted, *'do it or become irrelevant'*¹⁷⁰). Although there is goodwill in Canada for collaborating and attempting to enroll patients in a CIHR study for less funding than is needed, it is difficult to compete with industry for the levels of funding offered per patient. It was noted that CIHR was finally paying for indirect costs.

*"There is a serious bottleneck at CIHR in clinical trials. The clinical trials' program is critical but there are not enough personnel to run the program to keep up to the level of recent success; the program has evolved but success has outgrown its resources."*¹⁷¹

One researcher ventured the opinion that if this were a *'genome program'* this would not have happened. This is even more concerning in that even with the recent increases in clinical trials, one experienced researcher noted that CIHR still does not fund enough clinical trials.

An intriguing suggestion was made by one of the researchers. Expressing the belief that there has been *'no mega-trial solely conducted in Canada, solely paid by CIHR'* and that *'a country the size of Canada should be able to mount one major clinical trial a year'*, possibly a blue ribbon panel could determine appropriate studies (along the lines of the Women Health Initiative) at arms lengths from government and industry interests. It was noted that *with 300 million prescriptions per year, a surcharge of 10-cents would generate the 30 million dollars needed to mount and complete such a study.*

Suggestions for better involvement of CIHR in the clinical trials system were made. These included strategically planning together (along the lines of the Canadian Strategy for Cancer Control): strategizing and prioritizing research; getting important players talking with one another; and avoiding duplication.

Summary of Findings

CIHR is the major federal funder of health research in Canada, but spends less than 5% of its budget on clinical trials. There appears to be ample opportunity to increase not only funding but the priority of CTs in the CIHR portfolio, and internal resources and expertise within CIHR dedicated to CTs.

Hospitals and universities

A large number of clinical trials occur in teaching or university affiliated hospitals. Some have organized themselves to optimize the benefits of industry-sponsored clinical trials:

¹⁷⁰ Interview with researcher

¹⁷¹ Interview with researcher

“Some institutions are better than others. Some have complex administrative processes, including a two-tiered system of scientific and ethics review, which adds time to the conduct of CTs. In many institutions, there is a turnover of administrators, legal advisors, etc. creating the usual delays.”

One executive complained about the practice of charging overhead on industry contribution to research projects which are initiated by an academic researcher. For him, this is a very different situation from contract research, when a company approaches a university to carry out trials on a specific product:

“It is galling that overhead is still levied on investigator-initiated CTs which the pharmaceutical company chooses to support. I have no problem with overhead levied on our CTs which we ask the investigator/institution to perform, but any money going to overhead –reduces money going to other activities, e.g. it reduces the money available for research, and also reduces our cost competitiveness for global investment.”¹⁷²

“Institutions can be overzealous in the re-capture of O/H. This can sometime raise the costs for a study from \$10K to \$14K per patient– In a competitive field, that’s a 30-50% disadvantage.”¹⁷³

Summary of Findings

Hospitals and universities are currently the major performer of clinical trials. Some of their current administrative practices, while in the short term appear advantageous to the institution, may in the longer term reduce their attractiveness to funders of clinical trials, especially large pharmaceutical companies.

The Industry – Large global pharmaceutical firms

There are 63 companies in Canada that are members of Rx&D, the industry association for the large non-generic pharmaceutical industry. Rx&D surveyed 34 member companies to determine that 364 new medicines were in development in Canada.¹⁷⁴

These companies employ over 23,000 employees, including 4,353 researchers¹⁷⁵. The Canadian pharmaceutical industry spends \$1.131¹⁷⁶ billion on research and development.

Companies member of the Canadian Drug Manufacturers Association (CDMA), i.e. the generic drug manufacturers in Canada, spent \$240 million on R&D in Canada¹⁷⁷. Most of

¹⁷² Interview with large pharma executive 2

¹⁷³ Interview with large pharma executive 4

¹⁷⁴ The Value of Medicines, January 2002. Prepared by Canada’s Research-Based Pharmaceutical Companies (Rx&D). Ottawa, ON, 2002

¹⁷⁵ *ibid.*

¹⁷⁶ Rx&D news release, August 20, 2002.

¹⁷⁷ Canadian Drug Manufacturers Association, www.cdma-acfpp.org

their clinical trials are bioequivalence studies, to demonstrate that their proposed generic product is the same as the original patented medicine.

The recurring issue is that there is no central, reliable source of information on all Canadian clinical trials, how many are being carried out, where, for what purpose, and especially important for patients, how to enroll into these trials. We estimate that of the total \$800 million to \$1 billion spent in 2001 on clinical trials and related activities, the lion's share is by large pharma companies, members of Rx&D. As will be seen below, when an industry has such a large role to play in research, there is an uneasy relationship that can develop between the research community and the pharma industry, with regards to industry-sponsored research, characterized at times by a lack of mutual trust.

Many of the global companies in Canada compete aggressively with other sister divisions around the world to attract clinical trials to Canada. So it is useful to examine what are the factors that influence global headquarters to choose Canada over other countries, such as Brazil or Poland.

Table 3: Estimated share of Clinical Trials activities for selected Canadian companies

Canadian Company	Share of global CT activities
A	15%
B	5-15%
C	5-6% (static)
D	N/a
E	N/a
F	2-4% (stable)

But by and large, as the table above shows, Canadian companies have not fared too badly, given that Canada represents a market share of approximately 2% of world sales. It is interesting to explore further some of the factors that give Canada a competitive edge.

Several factors come into play when industry chooses where to perform clinical trials. According to conversations with several industry executives, they look for:

- Excellent efficient sites and site managers who are very reliable, accurate, up-to-date, and trustworthy.

“We look for investigators who are heavily published, have done trials and have the required infrastructure. This depends on the area, but for example, they must have access to an MRI if they are doing a study on Multiple Sclerosis. So this generally limits it to teaching hospitals. Another essential

element of infrastructure are research nurses, and of course, the investigator's interest in the study.”¹⁷⁸

- Confidentiality, especially if it is a new drug that has not yet been approved by regulators in the USA.
- Access to patients for Phases 2, 3 and 4 trials. In Canada it is very difficult for new small molecule drugs due to genotyping (patient selection based on genetic profile).

“In Canada, we have a population of 31 million spread over 6000km. If we were required to recruit 1000 patients, we would be hard pressed. We find ourselves competing for patients, e.g. in rheumatoid arthritis, against other companies for a limited number of eligible patients, because not everyone will meet exclusion/inclusion trials. The pool is limited.”¹⁷⁹

- Excellent, efficient credible statistical design and analysis services. This can be hard to find, as academics are not very business like. Recruiting costs can be high, up to \$10,000 per patient and can take two or three years just to get trials up and running.
- Efficient, strong research ethics boards. Most ethics boards in Canada are afraid of really good science. Most REBs are unbusiness-like academics. Meetings are irregular and slowed up by social scientists. One reason Canadian biotech firms go to USA for phase 1 and 2 trials is to go where the ethics committees have stronger science and statistics credentials.
- International patient access for phase 3 or 4 trials.
- Fair overheads.

Top five impediments to faster trials.

Companies interviewed were asked to list the key factors that posed barriers or impediments to smoother, faster trials. Again, this is a qualitative picture, as opposed to a quantitative survey, but this leaves open the possibility of polling more carefully companies for their perception as to where the system slows the process, especially once the new regulatory and approval regimes have been implemented. The top three barriers are access to patients, the REB approval process, and the long time for TPD approval.

¹⁷⁸ Interview with large pharma executive 6

¹⁷⁹ Interview with large pharma executive

Table 4: Top impediments to faster clinical trials as seen by selected Pharma cos.

	A	B	C	D	E	F
Access to/Recruitment of patients	x	x	x		x	x
REB approval process	x	x	x	x		x
TPD long time of approvals (NOCs, INDs)	x	x	x			x
Poor access to Formularies		x	x			
Contract delays with institution		x				x
Dealing with investigators unsolicited inputs		x				
Acceptability of protocol	x					
Comparatively higher cost of CT			x			
Not enough leaders & entrepreneurs in CR				x		

How academic researchers see large pharma

The necessity of working with large pharmas was noted since they had the resources and were the source of interesting products providing researchers access to new drugs. Although at an individual level there were many positive interactions with highly competent and interesting people, the issue was how to work with the industry. A sampling of various views is as follows:

*Personally has never been comfortable taking industry funding since you do not control the question. An experienced, well known investigator can 'play hardball' and get a more acceptable question since they are in a better position; still they are never in absolute control and it is a struggle to craft the question. In particular young investigators need to be careful. For a large and expensive study to be done, partnership with industry seems to be the only viable way of doing it, but results are always questioned.*¹⁸⁰

*Most companies are very ethical since it is in their best interests and they are reasonably good to work with. As an investigator, felt relatively comfortable with no pressure to change 'things'.*¹⁸¹

*Large pharma wants the reputation of the investigator and not necessarily their ideas. They have the resources to set their own research agenda. Although they can provide unrestricted grants, these grants are well planned with the seeking out of opinion leaders.*¹⁸²

*Company culture is very important and the experience of working with large pharma varies widely by company. Some have experience in working with academics in a particular disease area and know the knowledge and experience that these researchers can offer. Although they are in business for profit one can still work effectively with these types. However, with companies getting involved in new disease areas, they do not know or understand the academics in that area and tend to regard them as service orientated with little content knowledge.*¹⁸³

¹⁸⁰ Interview with researcher 3

¹⁸¹ Interview with researcher 2

¹⁸² Interview with researcher 4

¹⁸³ Interview with researcher 1

*Large pharma want their products approved and are looking to the “smallest” possible study to get their product to market and are not solely interested in patient care with the inclusion of the most meaningful clinical endpoints. Regulatory agencies play a major role here ensuring industry looks at appropriate endpoints. Industry looks for “biologic activity” versus outcomes evaluating “more good than harm”; often involves a highly restrictive patient population in which endpoint works. Although, another researcher noted that industry often push too much for regulatory approval and what is in the best interests of the company but this could be a ‘rebound from regulatory requirements’.*¹⁸⁴

*They provide a valuable service in developing new medications for patient care but need to remember there is more to patient care than “drugs” and industry needs to mix good clinical practice with good business practice.*¹⁸⁵

*Positive relationship with an ability to work with industry and independently analyze and publish results since his group is relatively large with core funding. If he could not partner then his group would be a smaller organization.*¹⁸⁶

*Need to work with industry but it is essential that each partnership is examined individually with the key on the partnership level, not on the service level.*¹⁸⁷

Summary of Findings

As the major funder of clinical trials in Canada, industry plays a major role in the system. Many companies in Canada compete with their sister divisions around the world for attracting more clinical trials research money to Canada. This requires better collaboration with researchers, who at times view the industry with suspicion. There are opportunities for developing better partnerships among these different stakeholders, based on a better mutual understanding of each group’s legitimate agendas.

The Industry - The new biotechnology firms

There are over 360 biotechnology firms in Canada, employing some 10,000 scientific researchers and skilled workers. With annual sales totaling more than \$2 billion, Canadian biotechnology companies invest close to \$828 million a year in research and development across the country. More than 75% are small but rapidly growing companies with 50 or fewer employees. One quarter of the companies are publicly traded.¹⁸⁸

¹⁸⁴ Interview with researcher 4

¹⁸⁵ Interview with researcher 4

¹⁸⁶ Interview with researcher 2

¹⁸⁷ Interview with researcher 1

¹⁸⁸ Source: BioteCanada, www.biotech.ca

As of April 1, 2001 Canadian Biotechnology Companies had 645 biopharmaceutical products under development or launched.¹⁸⁹ The products were in the following stages of development; 256 in research, 133 in pre-clinical, 62 in Phase I, 69 in Phase II, 35 in Phase 3, 7 were at approval and 83 had been launched. The top 4 therapeutic areas included Cancer (21%), Central Nervous System (10%), Infectious Disease (8.5%) and Cardiovascular (7.9%).

Canadian biotech firms are vulnerable inasmuch as they have little or no manufacturing capacity in Canada to go to Phase I trials. Their focus is on generating new good ideas, trying to get more results of Canadian research into clinical trials, and keep these in Canada.

A key challenge is to encourage more Phase I trials to be carried out in Canada. Part of the challenge is to find a manufacturer who can produce a formulation that can be ingested by a patient for phase 1 trial. (One company we interviewed had to go to Colorado to find a manufacturer for its oligonucleotide product, and that manufacturer is now seeking to expand into Canada). There is a need in Canada for increased capacity in contract manufacturing, especially early phase contract manufacturing. Carrying out phase I trials could generate significant research revenues and investments.

Another challenge is to obtain quick approval for an IND to carry out a phase I trial, in order to screen out as quickly as possible those molecules that are not working. Biotech companies have been turning to the UK or the US who can facilitate Phase I. Some countries have even built special Phase I clinical trials units.

Health Canada now has a 7 day *target* for approval period for phase I trials, and TPD is generally meeting this target.

The views of Biotech companies

The following is a summary of a separate consultation with biotech firms. A total of six companies were interviewed.¹⁹⁰ Companies were all Canadian-owned, and headquartered in Canada. Three companies were located in Western Canada (Alberta and British Columbia) and three in Ontario. The size of companies ranged from small (< 20 staff) to over 100. Respondents held various functions, such as CEO, or Vice-Presidents/Directors of Clinical and Regulatory Affairs, or Compliance. Respondents were assured company results would be blinded to protect any proprietary information.

¹⁸⁹ *Canadian Biopharmaceutical Companies. Status of Research, Development & Clinical Trials.* Industry Canada, CIHR, GenomeCanada. April 2001.

¹⁹⁰ This is based on a separate study (unpublished) by Suzane Cadden of Lorus Therapeutics and member of BioteCanada's government relations committee. Respondents were asked the five questions as listed below:

How many trials do you have in Phase I, II, and III?, How long did it take to go from pharmacology studies (animals) to your first time in man (FTIM) study?, Where were the FTIM studies conducted?, What factors governed the choice of country for each phase of trial?, Note any specific challenges to initiating clinical trials for your company? (E.g. financing, expertise, manufacturing).

One initial finding is that issues facing biotech firms vary greatly, depending on the type, product family and stage of evolution of a company. Any future study should examine a broader sample size of biopharmaceutical companies to capture these different stages in company lifecycle and products to further identify trends and issues. For example, the existence of partnerships with large pharma for particular technologies which may be easy for some firms, may minimize the perception that financing, or access to expertise is an issue for others. Similarly, the level of financing available to one company (years of cash, burn-rate) may also influence perceptions of certain barriers. The particular therapeutic and technology areas of a company also drives many of these responses. For examples, companies with biotechnology products -- which are harder to manufacture than conventional oral dosage forms -- face a different set of issues and challenges.

Factors Governing Choice of Country for Each Phase of Trial

When choosing a country for placement of clinical studies, four of the six companies noted that Canada was their first choice for FTIM (First Time in Man). The reasons were primarily that they were Canadian-based companies, and it was considered appropriate to conduct the first study in Canada. One cited as an additional consideration the tax credits, and another the close locale of the FTIM site, and their history in the original development of the product. Another cited a history with a government institution in the original development of the product. One noted that the company perceived that early Canadian trials with the product would translate into more favorable regulatory approval conditions (which were not borne out given later discussions with Health Canada).

Three companies noted that they had not conducted their FTIM in Canada. The reasons cited were the need to access US opinion leaders more quickly, and the ease of dealing with the FDA for the FTIM, and subsequent planned trials (in the US, subsequent trials on a drug in the same indication require a less time consuming process than in Canada). Running trials in the US also was perceived to have advantages in terms of attracting large global pharma licensing partners.

Additional Specific Barriers

One company had no specific problems with regard to finances, availability of resources or manufacturing issues, however they did note that occasionally they needed to access specific US expertise (e.g. in toxicology).

Three of five companies felt that dealing with the FDA was easier than dealing with Health Canada. Reasons cited were the accessibility of the FDA, the clear positions taken by the FDA (in contrast, Health Canada was seen to not make decisions or to waiver between positions), and the ease of the IND process (less complicated forms, less time for subsequent protocols). Two of the three noted that the UK was also easier to deal with than Health Canada. Of the remaining two companies, one company had yet to go through the process completely with Health Canada, and another felt the interactions and process had been satisfactory.

Three companies cited the lack of finances and the current market conditions as key factors limiting decisions on clinical studies and programs.

Three companies expressed concerns about the lack of available drug development expertise in Canada. Two companies specifically noted that staff drawn from Canadian large pharma seemed frequently inexperienced in the activities of early stage drug development. It was also noted that such staff have difficulty in the transition to small biotech, where there is considerably less resource to draw upon. In one case, it was noted that attempts to attract US drug development candidates were difficult, Canadian being seen as somewhat of a technology 'backwater'. An additional company noted that they could not access the expertise to meet requirements of a senior drug development position (the incumbent was drawn from the US).

One company noted the Canadian Ethics Review system was a barrier. They cited the US system as a positive example of streamlining and co-operation. They raised the question that when one university ethics committee reviews and approves a protocol, what value is added by having the same process repeated at a second, separate institution.

Academic Researchers' views of the biotech sector

There was general agreement that small biotech was an exciting and rewarding group to work with but the size, restricted focus and attitudes of many of the companies was a deterrent. As the researchers noted, many are a "one trick pony"¹⁹¹ and "working on a shoestring"¹⁹² and because of this lack of diversity and depth "everything is on the line"¹⁹³ and they are consumed by the "worry that things will go wrong"¹⁹⁴. This can result in a difficult working environment with a tendency to micro-manage in areas where they have little experience and to not strictly adhere to protocol. In short, they do not take full advantage of the academic community. As a researcher noted,

*"the experience is not as positive as it could be but it should be a good fit; we have the expertise they need and we are willing to help Canadian biotech as part of being good citizens."*¹⁹⁵

Small biotechs are often top heavy in chemists and engineers, but are trying to make their work apply in the health care sector. They do not have extensive expertise or experience in medicine and the difficulty, as noted by one researcher, is "they don't know what they don't know."¹⁹⁶ They know they do not have the expertise and experience on how to do pre and late clinical testing but they can't let go and micro-manage. They have developed in an atmosphere of protecting patents etc, and this secretive mode has carried over to the clinical testing phase. Yet they have interesting new ideas and people who are exciting to work with.

¹⁹¹ Interview with researcher 4

¹⁹² Interview with researcher 2

¹⁹³ Interview with researcher 1

¹⁹⁴ Interview with researcher 1

¹⁹⁵ Interview with researcher 1

¹⁹⁶ Interview with researcher 1

Summary of Findings:

Canadian Biotechnology firms come in different stages of evolutions, with different types of products, and each category has different needs. These should be studied further to gain a proper understanding of the different categories in that industry, and its needs for specific assistance. In addition to the inevitable need for financing, there is a shortage of resources and skills in the early phases of drug development, both in terms of outsourcing (formulation, manufacturing) and in finding appropriate senior executives with the required experience. This particularly challenging when the new companies, generally founded by chemists or engineers, need to tackle the regulatory complexities of the health sector. Again, interaction with other stakeholders, e.g. university-based researchers in the health sector, could be better focused and improved.

Clinical Research Organizations(CROs)

Clinical Research Organizations carry out all aspects related to clinical trials on contract for pharmaceutical or biotechnology companies. In Canada, the total value of clinical research flowing through CROs is estimated at \$100-150 million a year. There are over 30 CRO companies operating in Canada¹⁹⁷, some of which are branch offices for large multinational companies. Of these, approximately a third have a significant level of activity. The top international CROs are Quintiles, Covance, and PAREXEL. While the top large global pharma companies depend on CROs very little, others, including biotechnology companies without any clinical trial infrastructure, will use them more widely.

Rettig¹⁹⁸ notes that a 1999 survey counted no less than 550 CROs in the US, and attributes their recent growth in numbers to the following factors:

- Pressure to cut costs in drug development cycle has led pharma industry to conclude that some bottlenecks can be managed more effectively by external than internal resources.
- As a large number of new compounds are approaching market approval stage, CROs can offer some pharma companies an attractive way to escape limits of existing organizational capacity.
- Industry consolidation makes it easier to contract out a service than merge two departments.
- Biotech companies have great scientific competence, but lack the internal resources and experience to conduct pre-clinical and clinical research.
- As global markets require companies to seek approval in various national markets simultaneously, international CROs are better able to provide expertise about regulatory requirements of a specific country, and can tailor clinical trials accordingly.

¹⁹⁷ The Canadian Biotechnology, Industry and Suppliers Guide 2002 lists 9 firms categorized as CROs, but there are at least two more companies known to be CROs which are not included.

¹⁹⁸ "The industrialization of clinical research", Richard A. Rettig, Health Affairs, March-April 2000

- CROs can develop niche expertise in certain therapeutic areas, of interest to companies with promising research but limited experience in given therapeutic area.

Services offered by a CRO can include some or all of the following:

- Drug development (pre-clinical services, pharmaceutical sciences, drug packaging, labeling and distribution)
- Quality control
- Clinical trials management services
- Regulatory services, including dealing with compliance with FDA requirements and those relevant to non-US authorities
- Related resources, including studies of outcomes research, pharmacoeconomics, quality-of-life analysis and patient satisfaction studies.

Summary of Findings

The importance of Clinical Research Organizations (CROs) in the Canadian clinical trials system is not well documented, nor is their linkage to the Canadian research community fully established. This is an area that should be studied in more detail, as CROs are an important private sector stakeholder in the clinical trials system.

Private Clinical Research Clinics

Some investigators have set up successful private research clinics, some with overnight stay, dedicated specifically for clinical trials. In addition to tighter budgetary controls and lower overhead, these specialized clinics can use the services of private Research Ethics Board with faster turnaround, and take much less time for contract response and authorization.

In the words of a large pharma executive, this is a growing trend:

*“Where we are doing research in hospitals, we have to use the hospital’s administration and ERBs. But many investigators are moving towards private clinics, we estimate that up to 20-25% doing it. Ten years ago, it was between 0-5%.”*¹⁹⁹

Examples of such research centers include Probit Medical Research²⁰⁰ in Kitchener-Waterloo, which does trials under contract for pharmaceutical companies. Headed by dermatologist Kim Papp, they also offer a site management service. They have expanded their personnel, and obtained the cooperation of the local hospital, which gives them enough patients from that catchment area to support such an operation.

¹⁹⁹ Interview with Large Pharma executive

²⁰⁰ Industry interview, and www.probitmedical.com

Another example is Dr. Piyush Patel, based in Mississauga, CEO of Allied Clinical Research²⁰¹, a Clinical Research Organization. They have a site/ office practice, have been successful at running trials, it is a good business for them, especially in respiratory diseases such as asthma.

In Sherbrooke, Quebec, QT Research²⁰² has been in operation for 7 years. Today they have 22 employees, including 9 research nurses. They try to do fewer studies but with more patients. Currently, they do 10-15 trials /year. Their studies focus on the efficacy of compounds with ambulatory subjects, i.e. subjects that require no beds. If a patient is hospitalized and bedridden, then they decline the study. Having beds would require a totally different set-up, with 24 hour service, caring of patients, nurses, etc. as well as a different set of Operating Procedures.

They definitely do not consider themselves a health care clinic, they charge nothing to the provincial health care, and the vast majority of their work is done with research protocols. *“This is a research center—patients know they are in a research center”*.

The size and streamlined organization of these private research clinics allows them to respond extremely quickly to industry clients. For example, the time needed to agree on a protocol can take as little as a few hours up to a week. Internally, they can agree whether to accept a study or not within a day.

One head of a private research clinic identified the need for greater support of private research clinics dedicated to the conducting of industry-sponsored clinical trials:

“If we had the opportunity to network with other private research centers, these would be some of the themes we would like to explore:

- *How do research centres adapt and react to specific negative factors, e.g. the health system, negative TV shows on CTs, patients and patient recruiting?*
- *How do they adapt to an environment where there are four different ethics boards, where some boards take significantly more time than others, and one has to take the same study to different boards.*

Ultimately we are competitors, but also we are not, because the better we are as Canadian centres, the bigger the pie will be for all of us. But we have no venue to discuss best practices for running our sites.”²⁰³

Private REBs

The increase in number of private research clinics, and the attraction by industry of bypassing slower institutional REBs has given rise to private, for profit REBs. Ethics

²⁰¹ Industry interview, and www.allied-research.com

²⁰² <http://www.qtresearch.com/>

²⁰³ Interview with head of a private research clinic.

approval, usually obtained through a private service like IRB Services²⁰⁴ in Toronto, takes two or three weeks, and is “generally as rigorous if not more than university or hospital-based REBs²⁰⁵”. Part of the reason may be that as private, for-profit organizations, they can pay the Board members at an appropriate level, and consequently are better resourced with better expertise than hospital or university REBs.

Rettig, who estimates that there may be 50 or 60 such private REBs in the US, suggests there is no evidence that private REBs are more or less easily influenced by outside pressure than other institutional REBs²⁰⁶. This, however, has not been studied or documented systematically in Canada.

Summary of Findings

Private research clinics are a growing phenomenon. There is little data as to how many there are, and how fast they are growing. While providing an efficient and cost-effective service to companies and taking good care of patients, little is known as to how well they are linked to the knowledge network of Canadian health research, and maximize benefits to Canadians as a whole. Of equal concern is the role of private REBs. It is not known at this stage whether these organizations can provide a viable alternative to university and hospital-based institutions, with the same benefits to Canadians.

Site Management Organizations

A number of organizations offer their services to hospitals or health centers to manage their clinical trials organizations. One example is CTD Clinical Trials Development Inc. in Toronto, a subsidiary of Endpoint, which provides clinical trials management and marketing services to health institutions. It helps hospitals manage clinical trials: identify, market and build their clinical trials capacity all the way from REB application writing, to helping investigators write contracts, to negotiating contracts and hire personnel, as well as “selling” the institution to potential research sponsors in the pharmaceutical, biotech or medical device industries. CTD exists since September 2001, and their first site is Sunnybrook and Women’s College Health Science Centre in Toronto.²⁰⁷

Another is the Saskatchewan Drug Research Institute in Saskatoon (see Chapter 7, on best practices).

Services offered by Site Management Organizations include marketing investigative sites to sponsors and CROs, negotiating contracts, obtaining IRB (REB) approval and handling regulatory documents, enlisting clinical investigators, training investigators and coordinators, recruiting and enrolling patients, and improving and standardizing sites and practices.²⁰⁸

²⁰⁴ <http://www.digiserve.com/irbs/>

²⁰⁵ Industry interview. In one instance, a private REB rejected a study approved by a university REB.

²⁰⁶ “The industrialization of clinical research”, Richard A. Rettig, Health Affairs, March-April 2000

²⁰⁷ Industry interview

²⁰⁸ “The industrialization of clinical research”, Richard A. Rettig, Health Affairs, March-April 2000

Summary of Findings

In our view, site management organizations can do a lot to improve over time the desirability of a hospital to become a clinical trial centre for industry, and should be studied in more detail as to whether and how this model could be propagated.

The cost of clinical trials

Several of the global pharma executives interviewed agree that Canada is slightly less expensive than the US, but more expensive than the rest of the world in carrying out industry-sponsored clinical trials. This is likely due to several factors, possibly including the cost-advantage of a publicly supported health systems, R&D tax credits, and lower labor costs. However, we did not see any comparative analysis which would quantify any of these factors.

There has been a recent review of how poorly hospitals keep track of their costs, including those of industry-sponsored clinical trials. In terms of looking at the public-private allocation of costs, the Verificateur Général du Québec criticized recently the accounting practices and inability of hospitals to account for and recover money paid by firms for clinical trials. There is a need to have measures in place to capture that properly.²⁰⁹

From a large pharma's perspective, here is one view of cost allocation:

The motivation for doing research is to make money. Investigators get paid by us, but they can't double dip – the fee paid to the doctor is budgeted in terms of tasks carried out: for work carried out, tests, paperwork, per patient fee—covers cost, and success premium. A physician is lucky if he/she make 10% on a study.

The patient fee includes finding, treating and retaining the patient. For example, the patient may have to stay in the study for six months, according to the protocol, and if they lose him at four months, then there is a problem.²¹⁰

Summary of Findings

Cost analysis of clinical trials is an important factor, but we have not seen any systematic comparative cost studies.

Where do Canadian Clinical Trials occur?

It is hard to determine the amount of clinical trial activity in Canada, or how many patients are in trials. To answer this question would require a comprehensive database of all clinical trials in Canada. However, at this point in time, there is no such central registry. Moreover, as far as we can determine, no country has established such a comprehensive registry of clinical trials. There have been a number of attempts to create web sites that offer partial listings, as described below:

²⁰⁹ Tome I du Rapport du Vérificateur général à l'Assemblée nationale pour l'année 2000-2001, Faits Saillants, http://www.vgq.gouv.qc.ca/rappann/rapp_2001_1/Faits/Index.html

²¹⁰ Interview with large pharma executive 6

- A good compilation of clinical trials can be found at the US *www.ClinicalTrials.gov*. The website is maintained by the U.S. National Institutes of Health, through its National Library of Medicine. This website listed at the time of search (summer 2002) a total of 283 Canadian Clinical Trials. 246 trials are cancer related (87%), 15 are infectious disease related (6%), and 10 are cardiovascular related (3%).
- *www.centerwach.com*, a US-based site which listed only 120 Canadian trials.
- *www.cancertrialshelp.org*, another US site, sponsored by the American Coalition of National Cancer Cooperative Groups (see chapter 4).²¹¹
- *www.medistudy.com*, a Canadian web site, operated by Endpoint Inc., which currently lists 25 active trials.
- *www.hivnet.ubc.ca/ctn.html*, sponsored by the Canadian HIV Trials Network (CTN) (see Chapter 4)

There are other disease specific web sites, but as can be seen, the data on Canadian trials is spotty, incomplete and uneven.

A key point is to keep track not only of industry-sponsored clinical trials, but also academic trials initiated by university researchers attached to an academic health center or teaching hospital. Most of the academic health centres have some kind of clinical trial support group. The largest is McMaster. It runs the biggest trials in North America, but the trials are often Phase 4.

One study surveyed the distribution of Canadian clinical research facilities as follows; British Columbia (3), Alberta (2), Saskatchewan (2), Manitoba (3), Ontario (44), Quebec (14), New Brunswick (1), Prince Edward Island (2), Nova Scotia (2) Newfoundland (1), Yukon (1), Northwest Territories (1), Nunavut (1)²¹².

Some large pharmas show no specific preferences for location of CTs and follow the general population distribution, paying specific attention to the investigator.

One pharma executive shared his company's preferences:

*"Hamilton is more interesting than Toronto, otherwise we distribute our CTs in Quebec, Ontario, and Alberta. There is a lack of critical mass in BC. They are also the black sheep, they are not vital to our interests, and their government was never favourable to the pharmaceutical industry. Halifax and Atlantic Canada, they are very feeble on our radar screen."*²¹³

²¹¹ This site is linked to <http://cancernet.nci.nih.gov>, which lists 262 Canadian cancer trials.

²¹² Canadian Clinical Trials Facilities & Capabilities 2001. A collaborative project of the Canadian Institutes of Health Research, Genome Canada and Industry Canada. 2001

²¹³ Interview with large pharma executive 3

Summary of Findings

The lack of a comprehensive data base or inventory of all clinical trials makes it difficult to analyze their location, distribution, or therapeutic areas. Clearly, as was mentioned in Chapter 4, patients would also find such an inventory invaluable, as a way of facilitating access to trials.

6. Competing against the rest of the world in Clinical Trials

This chapter examines the competitive factors that make Canada attractive to global investments in clinical trials.

As emerges from the preceding chapters, clinical trials are a complex activity, involving many players, which also generates a number of clearly identifiable benefits to Canada. So it is important to determine how well Canada stacks up against the rest of the world in this area. This becomes particularly important when trying to attract more investment in this R&D activity from the major industrial players. A number of countries are streamlining their clinical trials system to become more competitive, notably the UK, Sweden, and Australia. Most recently, the island state of Singapore is positioning itself to become a major player in biotechnology and drug development, with a gateway to a 100 million patient population in Asia. So it is useful to discover from industry players how well does Canada compare, and where are our competitive advantages.

“We have been participating for a number of years in multi-centre, multi-national studies on arthrosis – the same studies now include Latin America, Eastern Europe. And Latin America will have 70% of the patients. But in Canada, we are 40% more expensive than South America in term of operating costs. Our advantage in Canada is that we provide extremely solid data, and respond rapidly.”²¹⁴

What makes us attractive internationally, compared to our sister subsidiaries:

- *High quality data: Our Canadian Subsidiary provides the US parent with high quality data. In our multi-national venture studies, there is a very low number of errors in our data. The analysis is usually done in the US. They will review it, and if there are discrepancies, will send it back. We have one of the lowest rate of discrepancies/ mistakes of all our centers in the world. We have people dedicated to ensure quality of data, checking it, and going back to sites if necessary.*
- *Our health care system: There is a similarity of health care between Canada and US. For example, in the treatment of angina and coronary disease, we have less aggressive investigation – but the morbidity and mortality rates are similar.*
- *We are neighbors of the US, culturally close, and it's easy to talk to each other and exchange information.*²¹⁵

²¹⁴ Interview with an investigator

²¹⁵ Interview with a large pharma executive 1

What makes Canada competitive?

“The quality of work done in Canada is very high, sufficiently for presenting to the FDA. The FDA is presently reluctant to recognize work done in some countries.

The Canadian Market is relatively small – it represents only 2% of world sales – Yet Canada is among the top 10 markets (6th or 7th), because of the high rate of drug use. Drug prices in Canada are low compared to most western countries because of drug pricing regulation by the PMPRB. Pricing constraints make Canada less attractive for investment purposes.

The high level of reputation of many clinical researchers: many have an international reputation, are international thought leaders. CTs involve these clinical leaders, specialists, and because they have been involved with products, they can talk to peers, colleagues – not just based on the literature, but on their own experience.

Our resource costs are lower than those in the US (the most expensive jurisdiction). However, we’re more expensive than the rest of the world, excluding Japan.

Publicly funded medicine. This becomes important if a patient suffers an adverse event, whether expected or unexpected, the patient is treated. The sponsoring company indemnifies the institution and investigator, and all the normal costs associated with study – screening patients, documenting, tests required by the protocol, are included in the budget of the study.

Tax advantages, at the federal and provincial levels. If a study represents true scientific research and development, it can be eligible for tax credits by CCRA. It is an advantage, but because of our organizational structure, it is not seen by people who budget a study. The tax rebate goes to the corporation – but it is not seen by the cost center. We cannot charge the global discovery center less. So in the end, any tax credit has a marginal influence on the global centre’s decision as to which country they decide to place the study.”²¹⁶

Pharma executives were asked to point out some of the factors in Canada that make us *less competitive* by slowing the process down. One factor is the growing administrative burden in hospitals and universities:

“A few years ago, there were only 1 out of 10 sites which would require a formal contract, all the others would be satisfied with the protocol as the contract document. Today 9 ½ sites out of 10 require a contract – this is the result of administrators. Some of the delays in the process arise especially when the site

²¹⁶ Interview with large pharma executive 2

requires changes to clauses affecting compensation, liability, or possible patent infringements. These growing administrative/ bureaucratic requirements have added significant time and expense to our CTs.”²¹⁷

“We have 5-6% of the global share of our company’s CTs. We’ve managed to hold on to this, despite growth of areas where CT are much cheaper: Latin America, former Central European States, China – these are much lower cost jurisdictions. It is becoming harder to justify Canada as a prime choice for CTs.”²¹⁸

In our interviews with some government agencies, it was not apparent that focusing efforts on attracting more clinical trial investment into Canada was a noticeable priority. Rather, this concern was seen to be part of a broader effort to attract companies to locate here.²¹⁹

A UK case study on competitive strategy: The Pharmaceutical Industry Competitiveness Task Force: Clinical Research Report

Unlike Canada, the UK apparently has invested some effort in looking at their clinical trial system in an integrated way, with the intention of significantly increasing investment and capacity.

The UK-based Pharmaceutical Industry Competitiveness Task Force reviewed the opportunities and costs associated with the clinical research infrastructure in the NHS as a base for research by pharmaceutical companies.²²⁰ They sought also to promote and support R&D of value to patients and the health service and in doing so, keeping the NHS at the forefront of modern treatments and research.

This Government/Industry working group identified three main parameters; speed (in terms of start up times of clinical research), quality, and cost of research. The group considered how both industry and NHS can have a positive influence on these factors.

To streamline the process, the studies calls for simultaneous review of protocols by the various levels of Research Ethics Committees (RECs), both multi-centred and site specific. It calls for review targets of 60 days. New governance rules were passed in July 2001 to ensure RECs comply. Importantly, Industry and MCA are working together to set up joint training initiatives to improve quality of submissions.

To ensure high quality research, the Department of Health has set standards and responsibilities for all research conducted within the NHS. The NHS is bringing together a

²¹⁷ Interview with a large pharma executive 1

²¹⁸ Interview with large pharma executive 2

²¹⁹ Interview with DFAIT

²²⁰ United Kingdom Department of Health & Association of the British Pharmaceutical Industry. www.doh.gov.uk/pictf/pictfclinicalresearch.pdf

number of clinical research networks and centres. They also aim to ensure high quality training exists to sustain a pool of suitably trained individuals.

The Department of Health also reviewed its guidance on the basis of costs charged by the NHS to industry, with the intention of improving the transparency and consistency in pricing.

Importantly, the task group set up a series of performance indicators to enable monitoring of progress. These indicators include:

- UK Percentage of patients enrolled in international studies, normalised for population.
- Proportion of studies completed within planned timelines.
- Average industry grant cost per patient recruited to clinical trials.
- Percentage of international studies undertaken partially or wholly in the UK.
- Overall time taken from first submission of protocols to final medicines regulatory approval (CTX), REC approval and NHS hospital approval to proceed with clinical trial at first site.
- Proportion of studies approved by Research Ethics Committee (MRECs and LRECs) without deferral.

Summary of findings

A number of factors make Canada attractive to international firms for holding clinical trials: high quality of data, high quality of investigators, a public health care system, tax credits on R&D, proximity to US, and lower costs than US. But making Canada more attractive to global firms has not yet emerged as a government priority. One good example of a country that seems to have addressed this head on in an integrated way, for the good of patients and the economy, is the UK.

7. Examples of some best practices

This chapter examines a few selected examples of “best practices”, which can improve the effectiveness, quality, or speed of clinical trials.

Saskatchewan data base

Saskatchewan Health²²¹, a provincial government department, funds a wide range of health services to the approximate one million residents of the province. It is the custodian of a large amount of health data--most of which are computerized and centralized. These data can be linked using a unique number assigned to each resident to enable cross-sectional or longitudinal exposure-outcome research. Saskatchewan's health data have been used for a number of studies pertaining to drugs, and are maintained by the Epidemiology, Research and Evaluation Unit in the Population Health Branch. They cover data on hospitalization, medical services, including physician visits, and drug utilization. These are most effective and powerful for research purposes when they are linked.

The Halifax Centre for Clinical Research (CCR)

Since 1992, the Centre for Clinical Research (CCR) supported, promoting and encouraged clinical research at the Halifax-based Capital Health District by providing an accountable, fair and understandable administrative structure.²²²

The CCR manages budget development, contract negotiations, project facilitation and human resources initiatives for the research employees. Experienced research accounting services ensure funds are used properly. Expert, in-house administrative support enables investigators to dedicate the maximum time possible to research. It also ensures accurate project tracking and management control.

The CCR routinely administers upwards of 800 clinical research projects simultaneously. This workload is possible because the staff's sole function is to facilitate research. The stable resource of over 300 personnel includes more than 140 experienced research coordinators, all of whom are externally funded from research projects. Many offer years of in-depth knowledge of specific medical fields. Others have a broad range of research expertise.

It all started ten years ago, when Lisa Underwood, a lawyer by training, was given the job of director of research services for the teaching hospital associated with Dalhousie. There was an empty building, the old pathology lab, with lots of empty space. She got an office, no furniture, or telephone, and had only six months' salary.

²²¹ http://www.health.gov.sk.ca/ph_ph_ere_data_intro.html

²²² <http://www.cdha.nshealth.ca/research/index.html>

Some of the factors that led to her new job included the fact that

- Clinical Research became a priority at that time.
- There was no record in the hospital of what was happening in terms of Clinical research.
- There was need to recover the indirect costs (O/H).
- There was a need to develop a new infrastructure.

Her philosophy in approaching this task was to be facilitative, and make the job facing the researchers as easy as possible.

In her first month, she held meetings with divisions and heads of the hospital departments, and simply asked what could they use in terms of service?...and started providing this service.

She developed policies and procedures that were fair, understandable, and intended to help the researchers, especially in such areas as budgets and contracts. She provided the service the researchers wanted. At first, they did not want anything. Eventually, however, the level of trust increased to such a level that they would present her with a protocol on her desk, and simply ask her “is it viable, and can we do it?”

What she felt they needed most:

- Help with budget, costing things out. Initially, they had no idea how to do this systematically, there was no continuity, or standards.
- Some help in the negotiations between the sponsor and the investigator.
- Some assistance in hiring, orienting, training, staffing of research coordinator/ CRA/ research nurse, and the rest of the research staff to actually run the trials.
- Provide office space for all the research coordinators
- Research contracts, especially clauses dealing with publication (what is and is not allowed) indemnity, and other legal issues. (When she first came, the institution was not even signing the contracts)
- Extensive marketing – brochures, trade shows, individual department brochures (now that they had a track record)

She also managed to create a trusting relationship with pharmaceutical companies, especially with regards to budgets, and helped out in patient recruitment. She organized workshops for research staff/ investigators and training for nurses.

“I was there to help the researchers, to facilitate research, not to be self important. The idea is to lighten the paperwork load of researchers, and there is lots of it, as well as help with the legal, financial and ethical issues.”

Saskatchewan Drug Research Institute (SDRI)

SDRI is a not-for-profit Unit of the University of Saskatchewan, but all the funding comes from services provided. It was established in 1993, by Gordon Johnson, professor of

pharmacology. At the time the patent legislation was revised and pharmaceutical companies were committed to spending more research dollars. The intent was to help Saskatchewan position itself to benefit from this.

SDRI's mandate is *"to forge links between the pharmaceutical industry and Saskatchewan clinical and basic-science researchers, in order to recruit projects and grants and to increase the quality and quantity of pharmaceutical research and development conducted in Saskatchewan."*²²³

They offer site management organization services. This includes collecting all regulatory documents, making REB submissions, and do the required follow-up, and all serious adverse events report.

They have an arms length relationship with the REBs. But because they know the requirements, the formats, and have extensive experience with previous applications, they have a good understanding ahead of time of what is likely to be of concern to the REB. They can tell, for example, that "this compensation clause will not be accepted", and point to red flags ahead of time. There are three other REBs in Saskatchewan, one in Saskatoon, one in Regina, and one in Prince Albert. "Having a lot of different local REBs can be confusing, especially if you have 2 or 3 research sites doing the same trial."

SDRI does 95% of its work with CTs. In 94-95 the total contract value was \$0.9 million. In 2001-02, this number was \$6.59 million, they have been growing steadily each year, by 10-20% a year

Patient Networks: the Canadian HIV Trials Network

Another Best Practice would be the Canadian HIV Trials Network (CTN).²²⁴ A non-profit, national organization, the CTN was established in response to the needs and concerns of Canadian clinical investigators, persons living with HIV/AIDS, the pharmaceutical industry, community physicians, specialists, and laboratories. The CTN is funded by Health Canada, and jointly by the University of British Columbia and St. Paul's Hospital, Vancouver. The HIV/CTN has now been subsumed by the Canadian Institutes for Health Research (CIHR) and may provide a model for the CIHR to follow in clinical trials for other diseases. The HIV/CTN includes HIV patients in every phase of the clinical trials, from ethics review to the design of the trial, to a central registry leading to dissemination of information to the community. In the words of one patient network:

*"This is the hallmark of the HIV/AIDS community and puts us ahead of other patients groups."*²²⁵

In addition, the HIV/AIDS CTN ethics review panels have avoided the immediate post trial problem by stipulating on-going access to the drug as a condition of participation.

²²³ <http://www.usask.ca/sdri/>

²²⁴ <http://www.hivnet.ubc.ca/ctn.html>

²²⁵ Patient Network -6

The BC Cancer Care Program

Patients point to another best practice, an in-between service such as the *B.C. Cancer Agency Monthly* which provides fairly rapid updated report on treatments:

“The British Columbia Cancer Care Program is an example of best practices. Its Data Base is excellent and the Website broadcasts updated treatment guidelines on a regular basis. Treatment is more aggressive and better outcomes reflect this methodology. Strong leadership linking clinical care to good research has made the BC. Cancer Care Agency a source of pride to B.C.”²²⁶

²²⁶ Interview with Patient Network 5

8. Findings, conclusions and research questions

This report is a feasibility study, not a definitive analysis. Our original intent was to develop a full-fledged research proposal for a major research study aimed at examining innovation in the Canadian pharmaceutical sector, especially the clinical trials component of innovation, and to identify and adopt “best practices” that would streamline the clinical trials process.

Our objectives were --

- to identify the roles and contribution of the different stakeholders in the clinical research, testing and regulations of new medicines;
- to examine the interactions between the different stakeholders;

Our initial hypothesis was that improvements and time gains might be realized at **the interfaces** of the four nodes of the clinical trial system: the pharmaceutical industry, the clinics/hospitals/university faculties, the regulatory arm of Health Canada, and the patients. It was also our hypothesis that this problem could be considered in terms of a clinical trial/research *innovation system* or *technology cluster*, using the model of Harvard’s Michael Porter and others.²²⁷

Major findings

Based on our interviews, and review of numerous documents, a key finding is that the activities related to clinical trials and the testing and development of new drugs can be described as an integrated innovation system. A first attempt to capture the various interactions among the systems’ stakeholders is shown in Table 5 below.

We estimate that these activities are **significant**, representing an annual expenditure of \$800 million – \$1 billion. We do not have enough data to describe any clinical trials *clusters* that would have distinct geographical concentration in the Porter sense.

There is also strong evidence to indicate that both from a new medicine innovation and health care patient perspectives, ***clinical trials generate significant positive benefits to Canadian society.***

What is more problematic from a public policy or innovation perspective is that there is ***no single, integrated source of reliable information*** on this innovation system. There is no solid, verifiable or comprehensive data on *what* trials are being held, how many, where, by whom, and for what purpose. We don’t know how many investigators we have,

²²⁷ See, for example, *The Competitive Advantage of Nations*, by Michael E. Porter (1990) Free Press; also *The Economics of Industrial Innovation*, by Chris Freeman, Luc Soete, Paperback 3rd edition (July 1997), Pinter Pub Ltd

Table 5: Interactions between the components of the clinical trial system

Research Community													
	Patients	Regulators, Health Canada	Research Ethics Boards	Provincial Formularies	Nurses, allied health professionals, CRAs	Investi-gators	CIHR	Hospitals and univer-sities	Large Global Pharma firms	New Biotech firms	Clinical Research Organiza-tions (CROs)	Private Research Clinics	Site manage-ment organi-zations
Patients	Own health	P trust HC, but want faster access, beyond CTs	Patients want to participate in ethics decisions	P want access to new medicines, harmonized standards	Explain trials, consent form, recruitment	P want better involvement by GPs, and be informed of CT opportunities	Not enough \$, P would like it to play greater leadership in applied research		P suspicious of industry trials, especially non-reported data			Access to patients critical to success	
Regulators, Health Canada		Protection of public and patients	Streamlining of ethics process	Not enough links, two parallel processes									
Research Ethics Boards			Patient safety and research integrity				Tri-council policy	Need to put more money into REBs	Suspicion, need for streamlining ethics process			Drives creation of private ethics boards	
Provincial Formularies				Cost control					Limit market				
Research Community													
Nurses, allied health professionals, CRAs					Personal job and career	work as a team		need to hire & retain more			need to hire & train more		need to hire & train more
Investi-gators						Research Publications			Suspicious		CROs not liked by investigators		
CIHR							Advance-ment of knowledge, research	Could fund more CTs					
Hospitals and univer-sities								Overheads, research reputation	Overhead & facilities			Compete with hospitals for industry dollars	Can make hospitals more attractive for CTs
Large Global Pharma firms									Market and financial growth	Alliances for commercial-ization of new molecules	Rarely use CROs	Lge Pharma prefer private research clinics for speed	
New Biotech firms										Innovative development			
Clinical Research Organiza-tions (CROs)											Service contracts		
Private Research Clinics												Service contracts	
Site manage-ment organi-zations													Service contracts

how many sites that currently carry out clinical trials, and what level of capacity we have in this country for this research-based activity.

Throughout the study, we were faced with an absence of reliable metrics and basic data. But we did find many highly competent individuals who spoke passionately about the subject. The information we did find is fragmented, anecdotal, and qualitative.

We have been able to put together a composite picture of what in our view is a complex and dynamic system, which generates benefits to Canadians that are significant, although underestimated and under-reported. We are now able to describe some of the major players and their interactions. Instead of finding **four** stakeholder groups or nodes, as initially anticipated in our research proposal, we have been able to document at least **thirteen groups** with distinct interests, as mentioned in Chapter 2.

We can also point to some of the friction points in the system with some degree of reliability. Identifying the best practices which will eliminate these friction points or bottlenecks will be the subject of our major study.

Patients

Of all the groups in the clinical trials system, possibly the most pervasive and significant is that of patients. It is for their ultimate benefit that research in new therapeutics is being carried out, and it is only with their full and willing collaboration that clinical trials can even take place. As we discovered in Chapter 4, patients, patient networks and health charities have strong views on all aspects of clinical trials and drug development, largely because they have such a high personal stake in the successful outcome of the process. The patient and patient groups interviewed are fully convinced of the intrinsic value of clinical trials: in addition to adding to new knowledge on a given therapeutic, participating in a clinical trial may contribute to improved health outcomes. And most patients we talked to want **more and better access** to these clinical trials, to avail themselves of these benefits. We have identified some research questions as a result of our interview as follows:

Research Questions

Explore models for increased patient involvement at all stages of a clinical trials project, and how the whole clinical trial system could become transparent and accountable.

Identify ways for patients to have easier access to more trials, e.g. through a central registry, through better referrals by their physicians (both specialist and family practitioner).

Help patients have faster access to better and new drugs, through a regulatory system that is efficient, rigorous, yet timely and harmonized with that of other countries.

Regulators, Health Canada/TPD

Summary of findings

In reviewing the regulatory approval system in Canada, namely the Therapeutic Products Directorate (TPD) in Health Canada, it has to be stressed that we did not carry out any primary data collection and analysis, nor did we carry out an organizational review of TPD, but relied exclusively on secondary data and findings. There are clear signals from some stakeholders, namely patients and the pharma industry that approval times for medicines are too slow. International comparison data shows that Canada is in the upper mid-range of major industrialized countries, and is within a range of +/- 3 to 4 months. These are based on average or median times. There appears to be a trend over the last five years towards an increase in approval time by TPD by almost 30%, relative to 1997 levels. Some are suggesting that the current TPD model may not have the flexibility or resources to meet future challenges.

Research Questions

Explore as a priority options for an *optimal model* for Canada's drug approval organization. The model should include the following:

- **Flexibility in funding to attract top scientific talent,**
- **Ability to meet the challenges of new technology,**
- **Appropriate structure, organization, reporting and accountability,**
- **Balance between cost recovery from industry fees and government's stewardship role,**
- **Best practices from such countries as Sweden, the UK, and Australia, and generally help Canada take a leadership role internationally in clinical trials and drug development and testing.**

Research Ethics Boards

Summary of findings

Research Ethics Boards seem to be a major factor slowing the clinical trials process. But their fundamental role in protecting the safety of patients in clinical trials and the integrity of research is seen as important. Patients want more involvement in the process, industry and researchers want faster approval times, and more knowledgeable board members. Lack of funding, training, and absence of Canada-wide standards or guidelines are issues.

Research Question

Explore approaches that would increase coordination, provide uniform standards and accreditation for Research Ethics Boards, as well as ensure proper training and resourcing.

Provincial formularies

Summary of Findings

Both the pharmaceutical industry and the patients groups feel the process for inclusion in the different provincial formularies is unclear and lacks transparency. Patients want access to new drugs, firms want access to markets. Recent federal provincial discussions have moved towards a uniform review system, but there is still far from an equitable, harmonized National System.

Research Questions

Explore approaches --

- **To accelerate the process of harmonization of provincial formularies**
- **To ensure that there is an ongoing process of bringing new medicines to Canadians in an equitable way**

Research Community

Allied health professionals: nurses, coordinators and associates

Summary of Findings

The critical role of front line health professionals who run or oversee clinical trials has not always been fully appreciated. Challenges in terms of training and supply suggest a need for a broader human resources strategy approach for this group of stakeholders.

Research Question

Explore initiatives that would address the human resource strategy, i.e. shortage and need for training for allied health professionals (including CRAs and research nurses) involved in clinical trials, career paths, compensation, retention, etc.

Investigators

Summary of Findings

Investigators have a key role to play in leading clinical trials at a given site. Findings suggest that there may not be enough of clinical investigators with the right mix of leadership, scientific expertise, and access to patients, with a willingness to work with and collaborate with industry. Moreover, the role of family practitioners seems almost non-existent in the CT system.

Research Question

Explore means to improve communication between researchers and industry to increase trust and collaboration, encourage more academic entrepreneurs in clinical research, and greater involvement of family practitioners.

CIHR

Summary of Findings

CIHR is the major federal funder of health research in Canada, but spends less than 5% of its budget on clinical trials. There appears to be ample opportunity to increase not only funding but the priority of CTs in the CIHR portfolio, and internal resources and expertise within CIHR dedicated to CTs.

Research Questions

Explore further how CIHR's capacity in clinical trials could be enhanced, both in terms of peer review resources and in terms of funding, to allow them to play a stronger leadership role, particularly in areas not of interest to Pharmaceutical companies.

Hospitals and faculties

Summary of Findings

Hospitals and universities are currently the major performer of clinical trials. Some of their current administrative practices, while in the short term appear advantageous to the institution, may in the longer term reduce their attractiveness to funders of clinical trials, especially large pharmaceutical companies.

Research Questions

Explore ways

- **To increase the capacity and infrastructure (working conditions, space) of Canadian Hospitals and Schools of Medicine to carry out clinical trials and research, and**
- **To remove existing barriers (contracting services, and O/H) in order to make them more competitive in attracting more trials.**

The Industry – Large Global Pharma firms

Summary of Findings

As the major funder of clinical trials in Canada, industry plays a major role in the system. Many companies in Canada compete with their sister divisions around the world for attracting more clinical trials research money to Canada. This requires better collaboration with researchers, who at times view the industry with suspicion. There are opportunities for developing better partnerships among these different stakeholders, based on a better mutual understanding of each group's legitimate agendas.

Research Question

Examine mechanisms to provide greater openness and transparency between the academic research community and large pharmaceutical companies, and improve collaboration.

The Industry – The new Biotech firms

Summary of Findings

Canadian Biotechnology firms come in different stages of evolutions, with different types of products, and each category has different needs. These should be studied further to gain a proper understanding of the different categories in that industry, and its needs for specific assistance. In addition to the inevitable need for financing, there is a shortage of resources and skills in the early phases of drug development, both in terms of outsourcing (formulation, manufacturing) and in finding appropriate senior executives with the required experience. This particularly challenging when the new companies, generally founded by chemists or engineers, need to tackle the regulatory complexities of the health sector. Again, interaction with other stakeholders, e.g. university-based researchers in the health sector, could be better focused and improved.

Research Questions

Explore more systematically the needs of biotechnology companies in various stages of development, not only in terms of capital financing, but also in terms of other skills and resources, e.g. formulation, manufacturing, and early phase drug development, including clinical trials.

Clinical Research Organizations

Summary of Findings

The importance of Clinical Research Organizations (CROs) in the Canadian clinical trials system is not well documented, nor is their linkage to the Canadian research community fully established. This is an area that should be studied in more detail, as CROs are an important private sector stakeholder in the clinical trials system.

Research Question

Carry out an industry analysis of the role, importance, human resources dimension of CRO companies in Canada.

Private Clinical Research Clinics

Summary of Findings

Private research clinics are a growing phenomenon. There is little data as to how many there are, and how fast they are growing. While providing an efficient and cost-effective service to companies and taking good care of patients, little is known as to how well they are linked to the knowledge network of Canadian health research, and maximize benefits to Canadians as a whole. Of equal concern is the role of private REBs. It is not known at this stage whether these organizations can provide a viable alternative to university and hospital-based institutions, with the same benefits to Canadians.

Research Question

Carry out an analysis of the growth, distribution and scope of private research clinics, and probe their linkage into Canada's health research knowledge translation network.

Carry out a review of private REBs, examining their scope, practices, and equivalence to institutional REBs, in terms of standards, procedures and level of funding and resourcing.

Site management organizations

Summary of Findings

In our view, site management organizations can do a lot to improve over time the desirability of a hospital to become a clinical trial centre for industry, and should be studied in more detail as to whether and how this model could be propagated.

Research Question

Survey, compare and benchmark, where possible, various models of site management organizations, and identify best practices for hospital and university applications.

Canada's competitive position

Summary of Findings

A number of factors make Canada attractive to international firms for holding clinical trials: high quality of data, high quality of investigators, a public health care system, tax credits on R&D, proximity to US, and lower costs than US. But making Canada more attractive to global firms has not yet emerged as a government priority. One good example of a country that seems to have addressed this head on in an integrated way, for the good of patients and the economy, is the UK. Singapore is moving aggressively to position itself also as a leader.

Research Question

Explore how Canada might become a much bigger player in the field of clinical trials.

Identify market niches we could exploit based on our particular expertise, i.e. Alzheimer, HIV/AIDS, children, where we have world renown researchers and expertise.

Develop better policy coordination and incentives to build up Canadian clinical trial capacity, and attract more private sector investment.

9. List of Interviewees

5 individual patients

Alzheimer Society of Canada

Astra Zeneca

Aventis Pharma

Bristol-Myers-Squibb

Canadian Arthritis Patient Alliance

Canadian Cancer Coalition

Canadian Cystic Fibrosis Foundation

Canadian Diabetes Association

Canadian Institute for Child Health

Canadian Treatment Action Committee (CTAC) (HIV/AIDS)

Capital Health Centre for Clinical Research

CIHR

Endpoint Research

Glaxo-Smith-Kline

Lorus Therapeutics

Merck Frosst

National Network for Mental Health

Parkinson Society Canada

Purdue Pharma

Q&T Research

Saskatchewan Drug Research Institute

