

REPORT ON THE STATE OF CANCER CLINICAL TRIALS IN CANADA

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Canadian Cancer Research Alliance • Alliance
canadienne pour la recherche sur le cancer

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CONTRE LE CANCER

OCTOBER 2011

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EXECUTIVE SUMMARY

At a time when the greatest potential opportunity for translation of research discoveries to clinical testing, the possible threat to cancer clinical trials in Canada was considered a critical issue for action by the CCRA as part of its strategic plan.

Clinical trials are critical vehicles for evaluating novel therapeutics and biomarkers that emerge from basic biomedical research and vital in the quest to translate knowledge into clinical practice and public health policies. In February 2010 the Canadian Cancer Research Alliance (CCRA) established the CCRA Clinical Trials Working Group to examine the trends in clinical cancer research in Canada, to report on the issues identified and to examine models of international clinical trials support. Most important, the CCRA Clinical Trials Working Group was to develop recommendations to ensure that Canada remains a global leader in the discovery of new, personalized cancer therapies and the opportunities for cancer patients to be enrolled in clinical trials are increased.

Canada has an outstanding international reputation for its contributions to cancer therapeutics development, from first-in-human studies to randomized controlled trials that have resulted in improved patient outcomes, the identification of new biomarkers for individualizing therapeutic decisions, changed clinical practice and new international collaborations. Indeed, many have argued that Canada has had an impact far outstripping the size of its research community and the funding for clinical research. This reputation for leadership is largely, but not exclusively, related to the studies conducted by academically based cooperative clinical trials groups, such as the NCIC Clinical Trials Group (core funding from the Canadian Cancer Society), the Ontario Clinical Oncology Group (funding from Cancer Care Ontario and Hamilton Health Sciences), and the Princess Margaret Hospital Phase II Consortium (core funding from the National Cancer Institute (U.S.)).

In 2009, however, the CCRA consulted with researchers, patients, policy makers, and funders across Canada as part of the development of the Pan-Canadian Cancer Research Strategy and found that the ability to conduct cancer clinical trials in Canada was under growing threat. This was particularly the case for trials based on ideas developed by the academic sector (i.e., those from cooperative groups). It was also observed that pharmaceutical trials are increasingly moving to Eastern Europe or Asia, where rapid accrual at lower costs is possible. At the same time, it is clear that there is now an unprecedented opportunity to take the fruit of decades of molecular biology research into the clinic in the form of new agents and for the development of new biomarkers. Clinical trials developed and conducted by Canadian academic investigators are likely to answer the clinical and translational questions that are based on the most promising discoveries from Canadian laboratory researchers and that address the greatest concerns to the health and wellbeing of Canadians in a manner most relevant to the our health care systems.

This research is of profound importance to patients, clinicians, researchers, those who deliver health care and those who promote innovation. Without clinical trials, the outcomes of

cancer patients will not continue to improve. In response, the CCRA formed a working group of experts led by representatives of the CCRA Secretariat and the Canadian Cancer Society, to review the state of cancer clinical trials in Canada and to make recommendations based on its findings.

Major Findings of the CCRA Clinical Trials Working Group

The CCRA Clinical Trials Working Group identified substantial evidence that the cancer clinical trials system in Canada is indeed under threat.

Cancer clinical trial performance metrics are falling.

- Accrual to cancer clinical trials is declining.
- Time to trial activation has tripled from 50 to 150 days between 1999 and 2009.

Institutional clinical trials units are under stress.

- Clinical trials unit staffing has doubled while trial enrolment has levelled off or declined over the last 10 years. Staff time per patient has increased. (See trial complexity below.)
- Institutional cost recovery efforts for “non-standard of care” activities have increased. Also, most units are charged flat fees for protocol review by pharmacies, research ethics boards (REBs) etc. (while some exempt cooperative group studies, this, too, is disappearing).
- Institutional funding for key personnel in clinical trials units has declined or been eliminated. Increasingly it is expected that trials will fully fund themselves.
- The types of trials undertaken are changing. A decade ago the majority of trials in cancer centres were academically driven (cooperative group or investigator-initiated). Now the majority are pharmaceutical industry-sponsored studies. This shift is largely related to financial pressures noted. Although pharmaceutical industry-sponsored trials are often meritorious, the shift in the clinical research agenda away from academic studies is a concern.

Trial complexity has increased.

Today’s cancer trials are more complex than those in the past by almost every measure: more trial objectives, endpoints, tissue collection, inclusion and exclusions tests, baseline and on-study testing. Consent forms and protocol documents are, on average, twice as long as are the protocol documents themselves. These changes reflect the increased emphasis on translational science, enrolment of patient subsets, and integration of additional questions and endpoints (e.g., quality of life, economics) into therapeutic trials.

The regulatory environment has changed and is more onerous.

In 2001 the *Food and Drug Regulations* were amended and a clinical trials regulatory framework was added. It created the obligation to file a clinical trials application with Health Canada for any non-marketed drug and any marketed drug used in an off-label setting and to conduct the study according to Good Clinical Practice (GCP) standards. (Previously, only non-marketed investigational agents required filing.) GCP creates obligations around on-site monitoring of trial conduct, drug product dispensing serious adverse event reporting and more. These changes have led to an increase in infrastructure costs for academic trials since almost all trials utilizing a drug fall under the framework of the regulations. Data to support improved patient safety or

quality of trial conduct for marketed agents as a result of increased regulation was not found in the review conducted by CCRA.

The workload of research ethics boards is increasing.

Research ethics boards (REBs) have been affected by the change in regulatory framework. Most notably the numbers of serious adverse events being reported has increased substantially. More complex protocols, tissue collection issues and more pharmaceutical firm studies have also increased REB workload. Recent welcomed trends have been the development of specialized regional cancer REBs in some provinces.

Cancer clinical trials offer broad societal benefits.

An in-depth cost-benefit analysis of cancer clinical trials identified interesting findings: clinical care costs of cancer trial patients have not been shown to differ significantly from matched non-trial patients. At the institutional level, costs of conducting trials are primarily for data managers, nurses and others involved in direct trial participation but increasingly include cost-recovery for clinical services and flat fees for opening studies. Costs for cooperative group sponsors of trials are related to trial coordination and analysis, regulatory compliance, translational research and per-case support of patient recruitment in participating centres.

Benefits of cancer trials are multiple and include long-term societal gains through improved health outcomes. In the short-term, data show improved outcomes for patients treated in institutions with an active trial program. At the institutional level clinical trials yield substantial drug cost savings for institutions, provide incentives to recruit and retain clinical investigators (who also practise within their specialty area) and facilitate knowledge translation and innovation. Clinical trials offer patients opportunities to receive new therapies and to participate in generating knowledge to improve outcomes.

Vision for Canada's Leadership in 21st Century Clinical Cancer Research

With the dramatic increase in our understanding of fundamental molecular mechanisms of cancer initiation, progression and metastasis, novel therapeutics are moving more quickly into clinical evaluation. New treatments are increasingly expected to be most effective in molecularly defined subgroups of patients. Such a “personalized” approach will not only reduce the number of patients exposed to ineffective therapy (and its adverse effects), but also has the potential to reduce health care costs.

Clinical trials to assess efficacy while at the same time discovering and validating predictive biomarkers require the collaboration of clinicians, laboratory scientists, pathologists and those expert in diagnostics development. Tumour and/or blood samples are needed from all trial subjects. Access to high-throughput sequencing technologies, immunohistochemical analyses and mutational analyses has become a priority for 21st century clinical trials. Innovative, possibly adaptive, trial designs must be deployed to maximize the knowledge return on investment in trials. Quality of life assessments and economic analyses are now standard components of modern cancer trials.

Fortunately, Canada has established and supported a cooperative group system for cancer clinical trials that is highly regarded internationally. It provides a means of evaluating the therapeutic questions that our excellent network of clinician scientists develops. The threats identified, however, place this system at extreme risk. It is urgent that a coordinated approach be undertaken to address the issues identified and, most important, to realize our vision:

To improve the health and wellbeing of Canadians by ensuring that Canada is at the forefront internationally in clinical cancer research at a time of unprecedented opportunity for advances that are emerging from fundamental science.

Synthesis and Recommendations

Cancer clinical trials have three goals: to achieve better cancer control, to increase survival and to improve the quality of life for patients. Implementing recommendations across these areas will reinvigorate the cancer clinical trials system in Canada, allowing substantial increases in trial enrolment and in the numbers of academic-led trials within a few years, while continuing to protect patient safety. Efficiencies will be enhanced and resources will be deployed more strategically. Further, Canada will be poised to be a leader in 21st century cancer trials.

The cancer clinical trials system in Canada is indeed under threat. A variety of stressors are affecting multiple levels of the system. Addressing them will require a coordinated approach with the engagement of multiple stakeholders. Action in the areas of pan-Canadian clinical trials infrastructure and support, and clinical trial oversight (regulation and ethical review processes) is recommended, as is the reduction in non-added-value work in trial conduct and cost management.

Recommendation 1: Create a pan-Canadian infrastructure program that supports cancer clinical trials

This program should have the following components:

- **Stable Institutional Clinical Trials Support:** Create a model for stable clinical trials infrastructure funding in Canada that will substantially increase recruitment to peer-reviewed and cooperative group clinical trials. This model should be based on the highly successful U.K. National Cancer Research Network. That project includes infrastructure funding for key trial team personnel, tissue collection support and other common tools and resources. National, regional or provincial funding may be needed but the goal is to coordinate the program at a pan-Canadian level.
- **Trial Personnel Credentialing:** Working with national clinical trials leaders, reduce the duplication of effort in investigator and trial personnel qualification processes, such as GCP and ethics training, and Standard Operating Procedures. For example, creating a national repository of acceptable modules for an agreement among trial sponsors such that certification from one any is equivalent to certification from another.
- **Contract Language:** Working with key institutional stakeholders and partnering with others engaged in clinical trials, develop common contract language around confidentiality, tissue

access and intellectual property and indemnification for use by major universities and hospitals.

- **Trial Budgeting Tools:** Spearhead a coordinated effort to share best practices and tools for budget development and forecasting. Furthermore, standardize cost schedules for standard of care, pharmacy services, pathology, medical records, imaging, etc., across cancer centres so that the tools and processes are effectively utilized.
- **Trial Decision Making:** Encourage clinical trials units and cooperative groups to adopt and implement portfolio management tools to support a balanced and strong portfolio of potentially practice-changing cancer clinical trials.

Recommendation 2: Streamline the clinical regulatory environment

Engage with Health Canada and other key stakeholders to propose non-legislative changes to the *Food and Drug Regulations*, through guidance documents or other similar documents that will improve the efficiency of clinical trials and ensure or enhance safety while reducing work and costs.

Recommendation 3: Consolidate or develop reciprocity in research ethics boards

Working with the Canadian Association of Research Ethics Boards and other stakeholders, champion the consolidation of specialized cancer REBs and reciprocity between REBs to reduce any duplication of efforts and enhance content knowledge.

Recommendation 4: Reduce non-value added steps in trial development and conduct

Review of routine practices in trial development and conduct by cooperative groups, investigators and institutions to identify steps or protocol components that add work or cost but add little value.

In summary, conducting trials in which translational research and discovery of individualized treatments are goals represents a challenging new paradigm. It requires new investment and a different approach to infrastructure and regulatory issues. High expectations from funders, patients, clinical investigators and the public that Canada will continue to play a pivotal role, make it critical that the trials system not only be supported but also enhanced to enable more participation in and leadership of clinical trials rich in translational science that are part of 21st century research.

1. BACKGROUND

Cancer clinical trials are critical for evaluating novel therapeutics or biomarkers that emerge from translational research activities. Thus, they are critical in the quest to translate knowledge into clinical and public health policies. Through clinical trials, evidence is generated to inform optimal cancer prevention and care. In Canada, clinical trials may be initiated by individual investigators, academic clinical trials groups (also known as “cooperative groups” such as the NCIC Clinical Trials Group (CTG)) may develop and conduct them or they may be sponsored by the pharmaceutical industry. Canada has enjoyed an international reputation in conducting trials that establish new global standards of care. Studies initiated in Canada have led to improved outcomes in among others lung cancer, breast cancer and ovarian cancer. This internationally recognized excellence, particularly in the sphere of cooperative group and investigator-initiated academic clinical trials, is critical to maintain, as exciting new agents emerge from our increased molecular understanding of cancer.

A healthy clinical trials system that allows academic trials to flourish is key to improving cancer control because these trials ask questions not usually addressed by the pharmaceutical industry and they often have great impact in shifting practice and outcomes. Furthermore, patients interviewed during this work articulated that it is extremely important that trials be available as treatment options for cancer patients. For these reasons, the finding that many investigators perceive clinical trials are under threat, particularly those initiated by investigators and conducted by cooperative groups, made the investigation of the issue a high priority in the Pan-Canadian Cancer Research Strategy.

This section of the report gives background on the research funding agencies involved in the process, the clinical trials system in Canada, as well as international trends. A list of abbreviations and acronyms used in this report is provided in Appendix A.

1.1 The Canadian Partnership Against Cancer, the CCRA and the Impetus to This Work

The Canadian Partnership Against Cancer (the Partnership) is an independent organization funded by the federal government. Its purpose is to accelerate action on cancer control for all Canadians. The Partnership evolved from the Canadian Strategy for Cancer Control, a volunteer-driven coalition working to counteract the growing burden of cancer on Canadian society. The coalition drafted Canada’s first national cancer control plan and successfully advocated for its funding.

The Canadian Cancer Research Alliance (CCRA) comprises 31 organizations. Collectively, these organizations are the custodians of the majority of public funding and charitable donations devoted to investing in research that will lead to better ways to prevent, diagnose and treat cancer. Its membership includes federal research funding agencies (such as the Canadian Institutes of Health Research (CIHR)), provincial research agencies (such as the Fonds de la recherche en santé du Québec (FRSQ)), provincial cancer care agencies (such as Cancer Care Nova Scotia) and national cancer charities (such as the Canadian Cancer Society (CCS)). Each CCRA member has strategic objectives and accountability structures. CCRA and its Board act as the Research Advisory Group of the Partnership.

The CCRA has three major roles. Its first has been to identify, develop, and advise on investment in two large transformative cancer research initiatives now funded by the Partnership

with other partners (a 300,000-person cohort called the Canadian Partnership for Tomorrow Project (CPTP) and the Pan-Canadian Cancer Biomarker Initiative). Its second has been to document cancer research activity in Canada. Its third and most recent role has been to endeavour to coordinate cancer research at a pan-Canadian level.

In 2010 the CCRA completed an ambitious plan to develop a pan-Canadian cancer research strategy. Published in May of that year, this strategy was developed in consultation with research funding agencies, researchers, clinicians, patients, survivors, the public, and policy makers.¹ The document, grounded in the strengths of the Canadian cancer research community and highly connected to emerging priorities in the international research landscape, provides a framework that will guide cancer research investment in Canada. It sets as its agenda new collaborations between research funding agencies and creates a vision for Canadian cancer research achievement over the next five years.

The 24 “priorities for action” described in the strategy involve multiple research funders either as lead or participating agencies. Priorities include capitalizing on an area of research strength where collaboration could accelerate progress, responding to a gap in research investment where newly funded initiatives present an opportunity and addressing specific issues or concerns within the research system. The action item on cancer clinical trials would be an example of addressing a concern within the research system.

Regional consultations conducted during strategy development and other findings suggested that the ability to conduct cancer clinical trials in Canada is under threat. The reasons are multifactorial. Although no comprehensive study has systematically assessed the problem, the reasons may include the declining ability of hospitals/cancer centres to support core clinical trials infrastructure, emerging international competition, increasingly complex studies, changing regulatory and administrative environments and the lack of funding for clinician researchers.

For this reason Action Item 11 in the CCRA strategic plan was to report and make recommendations on cancer clinical trials in Canada. This work was intended to clearly outline the issues facing cancer clinical trials in Canada and to recommend how to resolve these issues. The lead agencies for this work are the CCS and the CCRA secretariat, which is fully funded by the Partnership. Partner CCRA agencies are the Alberta Cancer Foundation (ACF), the BC Cancer Agency (BCCA), the Canadian Association of Provincial Cancer Agencies (CAPCA), Cancer Care Ontario (CCO), the FRSQ, the Ontario Institute of Cancer Research (OICR) and the Terry Fox Research Institute (TFRI).

1.2 The Cancer Clinical Trials System in Canada: The Importance of Academic Trials and Cooperative Groups

Canada has an international reputation for its contributions to cancer therapeutics development from first in human studies (phase I) to randomized controlled trials aimed at changing practice (phase III). This work has resulted in improved patient outcomes, changed clinical practice and new international collaborations. This reputation has been earned largely, but not exclusively, from studies conducted by cooperative clinical trials groups such as the NCIC CTG (core funding from CCS with institutional members from across the country), the Ontario Clinical

¹ www.ccra-acrc.ca/PDF%20Files/Pan-Canadian%20Strategy%202010_EN.pdf

Oncology Group (OCOG) (funding from CCO and Hamilton Health Sciences), and the Princess Margaret Hospital (PMH) Phase II Consortium (core funding from the U.S. National Cancer Institute with institutional membership from across Canada).

About two decades ago, this area of national strength led the pharmaceutical industry to bring opportunities for clinical trials participation in their global studies to Canadian sites. Overall the number of trials conducted over that period increased. Accurate data on the percentage of cancer patients enrolled in clinical trials and the types of trials in which they are enrolled, however, remain elusive. A widely quoted estimate is that about 3% of cancer patients are enrolled in clinical trials. A recent report from the Partnership quotes a clinical trial participation ratio of 7% of new adult cases in 2009, using data submitted by nine provinces.² Not only are clinical trials important for evaluating novel therapeutics or biomarkers that emerge from translational research activities, but evidence suggests that institutions with high participation rates in academic clinical trials have better cancer outcomes than institutions with low participation rates.

Clinical trials require a coordinated approach. Most studies, because of sample size or recruitment needs, are conducted in multiple centres such as hospitals or cancer centres. Each participating institution must have qualified investigators and patient access but the appropriate infrastructure must also be in place such as specialized staffing for ethics submission, regulatory compliance, protocol conduct, pharmacy expertise, financial management and adequate space in which to work. In Canada, such cancer clinical trials units are found in almost all cancer treatment facilities and teams of experienced personnel are retained to work on a menu of trials available in that centre. Staffing includes data managers, research nurses, ethics coordinators, financial personnel and physician investigators.

Each multicentre trial requires a single data/operating centre to coordinate protocol development, regulatory submission to Health Canada, institutional monitoring, database development, safety monitoring and data collection, cleaning and analysis according to the clinical trial protocol. Staffing includes statisticians, computing and database development experts, ethics and regulatory specialists, data coordinators and administrative support. Academic clinical trials groups are networks of participating centres bound together by university-based coordinating centres. Groups such as NCIC CTG, OCOG and the PMH consortium also include faculty level investigators (MD or PhD) within their coordinating centres. They will be referred to as “cooperative groups” throughout this report.

Clearly the pharmaceutical industry must also fulfill the function listed above when conducting trials. In Canada many trials conducted by industry are part of global drug development activities. Canada will contribute 6 to 10 sites to an international study. The global office (usually not based in Canada) houses the database and is where analyses are carried out. The Canadian affiliate is responsible for aspects of trial conduct, including on-site monitoring, regulatory filing and other aspects of the study, but, generally, data cleaning and analysis happens in a central location. Often the pharmaceutical industry accomplishes these tasks through a contract research organization (CRO). Occasionally, investigator-initiated trials are conducted within one or a few institutions in Canada through a pharmaceutical company, but, in large part, the participation of Canadian sites in pharmaceutical industry studies is as part of global research studies. The pharmaceutical industry sometimes conducts studies through a contractual arrangement with

² www.partnershipagainstcancer.ca/wp-content/uploads/system_performance_2010_EN.pdf

cooperative groups. Often the cooperative group develops the trial concept and the pharmaceutical industry collaborator supports the activity through project funding under a contractual agreement with the academic trial sponsor.

Cooperative groups have been extremely important in Canada. They undertake important research in new therapeutics and in study health care systems issues that are highly relevant to the Canadian context. Moreover, they drive a research agenda that has changed practice and created an international reputation for Canadian scientists. The menu of trials conducted by such groups includes phase I to phase III evaluations of new therapeutics and studies of non-drug interventions, new technology assessment and more. Such research networks also require committee structures to facilitate investigator engagement and idea generation, workshops, meetings and a robust governance or decision-making structure. Core funding to support the institutional and coordinating centre activities is in the form of competitive peer reviewed grants from charitable or government sources. Because of sample size and time considerations, almost all randomized controlled cancer clinical trials led by Canadian cooperative groups are conducted with international partners, primarily cooperative groups from the United States, Europe and Australia. This factor adds further complexity to administrative and regulatory aspects of trial conduct, beyond the ones noted below.

Cancer clinical trials take place within the context of Canada's health care and ethical and regulatory environments. The skill sets required to navigate these complex systems are not readily found within academia, though are commonplace in the pharmaceutical industry. Thus, to be successful, cooperative groups have invested in training or recruiting specialized personnel to conduct trials. The growing complexity of this environment has created new stresses and costs on both cooperative group coordinating centres and those cancer centres and institutions that participate in cancer clinical trials.

The regulatory environment in which clinical trials are conducted in Canada has changed over the last decade. In 2001 the *Food and Drug Regulations* were amended with the addition of a clinical trials regulatory framework.³ Within this framework a clinical trials application (CTA) must be filed with Health Canada for any marketed drug used in an off-label setting. Before the amendments, such a filing was required only for trials of truly investigational agents (ones with no notice of compliance for any indication) or for agents that were being supplied free within a clinical trial. The extension of the requirement to all other types of drug trials, even for those using drugs in a manner consistent with standard of care guidelines, created the obligation not only to file the material with Health Canada but to conduct the study in compliance with the regulations. This latter has implications for on-site monitoring of trials, drug product dispensing as well as definitions for and reporting of serious adverse events.

Almost all cancer drug trials fall under these requirements, so in effect a legal sponsor who is knowledgeable about the Health Canada requirements and who can file the CTA must conduct the trial in accordance with guidelines and regulations. Health Canada also launched an inspection program to ensure that sponsors and institutions participating in trials complied with the regulations. Health Canada offers few documents on how aspects of the regulations should be

³*Food and Drug Regulations* - C.R.C., c. 870 (Section C.05.005), see http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.%2C_c._870/page-258.html#h-253

interpreted. Furthermore, phase I first in human trials and phase III trials of a drug given in accordance with published standards of care (but which may not be labelled as such) have the same requirements for sponsors and participating investigators or institutions.

Research ethics boards (REBs) in Canada review proposed human subjects research and must ensure that the research is well designed, the investigators are competent, harms and benefits for the patient or subject are balanced, the selection of subjects is equitable and the informed consent document and processes are appropriate.

1.3 Global Clinical Cancer Research Context and the Pharmaceutical Industry

Major shifts have and are continuing to take place in the global cancer trials environment. The pharmaceutical industry has looked outside Western Europe, the United States and Canada for trials participation because of increased competition, administrative demands, government regulation of trials, costs and decreased accrual. It favours Eastern Europe and Asia for many new studies, particularly large randomized trials, because of their growing market, easy patient access, limited regulatory oversight, lower costs and their ability to recruit large numbers of patients quickly. Nevertheless, complex early clinical drug studies (phase I and II trials), incorporating biomarkers, tissue acquisition and other specialized testing not available in emerging markets, are more likely to remain within the United States, Western Europe and Canada.

In the United States, concerns about the viability of the cancer clinical trials system have led to a number of recent studies. Focusing primarily on cooperative group (academic) trials, the Institute of Medicine⁴ made recommendations that will affect trial coordination and infrastructure over the next few years. To boost trial speed and efficiency, the report recommends consolidating some cooperative group operations and activities, harmonizing government oversight, incorporating new science and improving the process of trial prioritization.

Europe's adoption of the European Union Clinical Trials Directive, with its stringent regulatory and insurance requirements has restrained organizations, other than pharmaceutical industry, from conducting clinical trials, particularly trials that involve multiple partner institutions in different countries. Because most randomized trials require the participation of multiple sites to recruit large numbers of patients, Europe has struggled to remain competitive.

In spite of the strict administrative and regulatory requirements, international collaboration between cooperative groups and major cancer centres is strong; they are evaluating new agents and conducting key translational science, adjuvant studies and comparative studies of treatment effectiveness. Tissue and blood collection for research is a routine part of such academic cooperative group trials. This creates a valuable resource for exploring prognostic and predictive markers relevant to the study question and for discovery research that informs future studies. Additionally, innovation in trial methodology and design is largely driven by such groups. Academic biostatisticians within cooperative groups are a major source of innovation in trial design and conduct and are able to evaluate new methodologies using the large datasets that are at their disposal.

⁴ www.iom.edu/Reports/2010/A-National-Cancer-Clinical-Trials-System-for-the-21st-Century-Reinvigorating-the-NCI-Cooperative.aspx

1.4 21st Century Cancer Trials – Canada’s Leadership Role

A revolution is under way in how new cancer therapies are being discovered and developed. Led by a greater understanding of fundamental molecular mechanisms of cancer initiation, progression and metastasis, novel therapeutics are moving into clinical evaluation at an accelerated pace. New treatments are increasingly expected to be most effective in molecularly defined subgroups of patients. This personalized approach will reduce the number of patients exposed to ineffective therapy (and its adverse effects) and may reduce health care costs. This new era of molecular medicine and the high expectations of funders, patients, clinical investigators and the public that Canada will continue to play a leadership role, make it critical that the trials system remains robust and provide further impetus for this report.

Clinical trials assessing efficacy while discovering and validating predictive biomarkers require the collaboration of clinicians, laboratory scientists, pathologists and experts in diagnostics development. Tumour and/or blood samples are needed from all trial subjects. Access to high-throughput sequencing technologies, immunohistochemical analyses and mutational analyses has become a priority for 21st century clinical trials. Innovative, possibly adaptive, trial designs must be deployed to maximize the knowledge return on investment in trials. Quality of life assessments and economic analyses are also becoming standard. Within Canada, the track record has been established for capabilities in all these areas. Indeed some funding organizations (notably CIHR) are gearing up for even greater investment in clinical trials infrastructure to promote an even greater output.

2. METHODOLOGY

2.1 Purpose and Scope of the Clinical Trials Working Group

Upon the completion of the Pan-Canadian Cancer Research Strategy, representatives from each partner agency involved in the clinical trials priority action item formed a working group. Representatives of the two lead agencies (CCS and CCRA secretariat) lead the Clinical Trials Working Group (CTWG).

At its first meeting, the CTWG defined its overarching purpose—to respond to the widespread concern about a growing threat to the health of Canada’s cancer clinical trials activities by:

- Documenting the change in clinical trials activity over time in a variety of ways.
- Describing the factors that have led to this change.
- Exploring other jurisdictions for practices that have (and have not) contributed to a healthy clinical trials exercise.
- Recommending action to address the issues. These recommendations may be divided into short- and long-term activities.

In so doing, it acknowledged the variety of audiences for this report: clinical investigators, cooperative groups, hospitals and cancer centres where trials are conducted, government, research funders, the pharmaceutical industry and research ethics boards.

The CTWG developed a list of items for which data/information had to be gathered before the nature and scope of problems within the cancer trials system could be identified. The evidence gathered forms the basis for the actions recommended to reinvigorate the cancer clinical trials system in Canada.

2.2 Activities and Reviews

Since its creation in early 2010, the CTWG has undertaken the following activities and reviews:

- A review of accrual patterns in cooperative groups, and in two regions (British Columbia and Ontario)
- A review of 28 NCIC CTG cancer trial protocols and consent forms from two different periods, 1995–2000 (n=14) and 2005–2010 (n=14), to quantify changing patterns in trial complexity
- A survey (n=7) of major clinical trials units in British Columbia, Alberta, Ontario and Quebec, to understand changes in levels and types of clinical trial infrastructure support provided by host institutions (hospitals or cancer centres)
- A review of some trends in regulation and ethics review of cancer trials
- A structured review of the literature using (PubMed and EconLit databases, congress and symposium proceedings), focusing on the costs and benefits of cancer clinical trials

- Interviews with 35 key informant, representing a cross-section of cancer clinical trial stakeholders perspectives (patient, investigator, administrator, funders, etc.), to discuss costs, benefits, strengths, weaknesses, opportunities and threats and to respond to those challenges
- A targeted review of documentation concerning the reform initiative underway in the United States, United Kingdom and the European Union supported by interviews with key opinion leaders from those jurisdictions
- Review of the Partnership's System Performance report, specifically the section on cancer clinical trials
- Initial discussions with CIHR leadership about its Strategy on Patient Oriented Research (SPOR) initiative

2.3 Methods for Report Development

Individual working group members and a consultant gathered data and information identified as critical to the work noted above. After meeting twice to review the findings, the CTWG compiled a list of the major stressors affecting the Canadian cancer trials system. The CTWG formulated ways to deal with the stressors, based on lessons learned in other jurisdictions and developed the recommendations in this report to present to the CCRA for further discussion and action. During the process the leadership of this action item met with the leaders of the CIHR SPOR to align, as much as possible, the activities of CIHR with the processes of the CCRA and to provide CIHR with input on the cancer clinical trials based on the work of CCRA CTWG.

3. FINDINGS

3.1 Evidence of Stress: The Status of the Current System in Canada

Data from cooperative cancer trials groups, institutions participating in clinical trials, key informant interviews and other sources show that concern for the health of the cancer clinical trials system in Canada is warranted. This concern applies equally to the cancer centres and hospitals, where clinical investigators are based and patients are recruited for studies. It also haunts cooperative groups that not only research new therapeutics but also study health care systems issues that are highly relevant to the Canadian context. Evidence to support these conclusions was drawn from the various activities and reviews described in Section 2 and detailed in the subsections below.

Finally, based on the literature review and international key informant interviews, many of the issues raised are not unique to Canada: similar stresses have been and are being documented in the United States and in various European countries. Section 5 of this report will highlight the lessons learned from those jurisdictions.

3.2 Accrual and Other Metrics: Measures of Trial Conduct

At present, accrual to cancer clinical trials is not well tracked on a Canada-wide population basis, so data from several sources were examined to seek evidence of trends in accrual to clinical studies. There is no standard metric for reporting clinical trials accrual ratios: although all sources reviewed use the number of new accruals to trials in the numerator, the denominator may be new cancer cases, new treatment cases, or some other measure. Thus, results from one institution or region may not be comparable to another. To standardize the reporting language and to allow cross-jurisdictional comparisons over time, the Canadian Partnership Against Cancer, in its recently published System Performance Report, included a report on clinical trials participation rates in several Canadian provinces.⁵

Over the last several years, CCO has compiled data examining enrolment in cancer clinical trials in 12 Ontario cancer centres as a proportion of the number of cases undergoing systemic treatment. Two forces drove the data collection: firstly, the plan to invest in clinical trials infrastructure in cancer centres and, secondly, the need to determine whether a three-year infrastructure investment in clinical trials staff and other support planned by the OICR (in 2004: Ontario Cancer Research Network (OCRN)) would increase clinical trials enrolment, and if so, whether that growth could be sustained after the program was complete. The infrastructure funding began in 2005 and ended in 2007. In 2004, before the infrastructure program, the proportion of patients enrolled in clinical trials across all centres (as a proportion of treated cancer cases) was 8.9%. Data from 2001 suggests that the 2004 numbers had already begun to rise, perhaps in anticipation of the 2005 funding. Accrual had peaked at 12.4% in 2007 and had fallen to 8.5% by 2009 (see summary in Table 3.1.1 and details in Appendix B). These data have been interpreted as meaning that providing infrastructure support for key personnel and resources improved clinical trials accrual but it could not be sustained once the funding ended. Indeed enrolment on trials has been falling in subsequent years.

⁵ www.partnershipagaincancer.ca/wp-content/uploads/system_performance_2010_EN.pdf

TABLE 3.1.1
ONTARIO CANCER CLINICAL TRIALS ENROLMENT DATA, 2004–2009

Participation	2004	2005	2006	2007	2008	2009
Enrollees	4,067	4,856	5,043	5,469	4,392	4,287
Treated cases	45,662	43,511	42,404	44,151	48,721	50,555
% cancer patients recruited	8.9	11.2	11.9	12.4	9.0	8.5

Data from the BCCA’s Vancouver Clinic show an increase in accrual to cancer clinical trials between 2000/2001 and 2007/2008 with a drop in 2009/2010 (see Table 3.1.2 below). We do not know whether the decrease in accrual in 2009/2010 is unusual and we cannot predict whether it be sustained in subsequent years. Data from CancerCare Manitoba also demonstrate a gradual increase in accrual during the same ten-year period with a drop in accrual in 2008/2009 (see Table 3.1.3 below). Accrual in Manitoba did increase in 2009/2010 but, again, it is unclear if this represents an anomaly or the beginning of a trend.

TABLE 3.1.2
BC CANCER AGENCY’S VANCOUVER CLINIC: CANCER CLINICAL TRIAL ACCRUAL 2000/01 TO 2009/10

Summary	2000 /01	2001 /02	2002 /03	2003 /04	2004 /05	2005 /06	2006 /07	2007 /08	2008 /09	2009 /10	Total
Patient accrual	203	258	215	298	241	369	277	371	372	281	2,885
New studies opened	23	21	21	16	35	30	36	41	28	33	284

TABLE 3.1.3
CANCERCARE MANITOBA: CANCER CLINICAL TRIAL ACCRUAL 2000/01 TO 2009/10

Summary	2000 /01	2001 /02	2002 /03	2003 /04	2004 /05	2005 /06	2006 /07	2007 /08	2008 /09	2009 /10	Total
Patient accrual	138	243	290	287	311	352	372	464	302	389	3,148
New studies opened	28	24	19	37	51	51	52	47	33	53	395

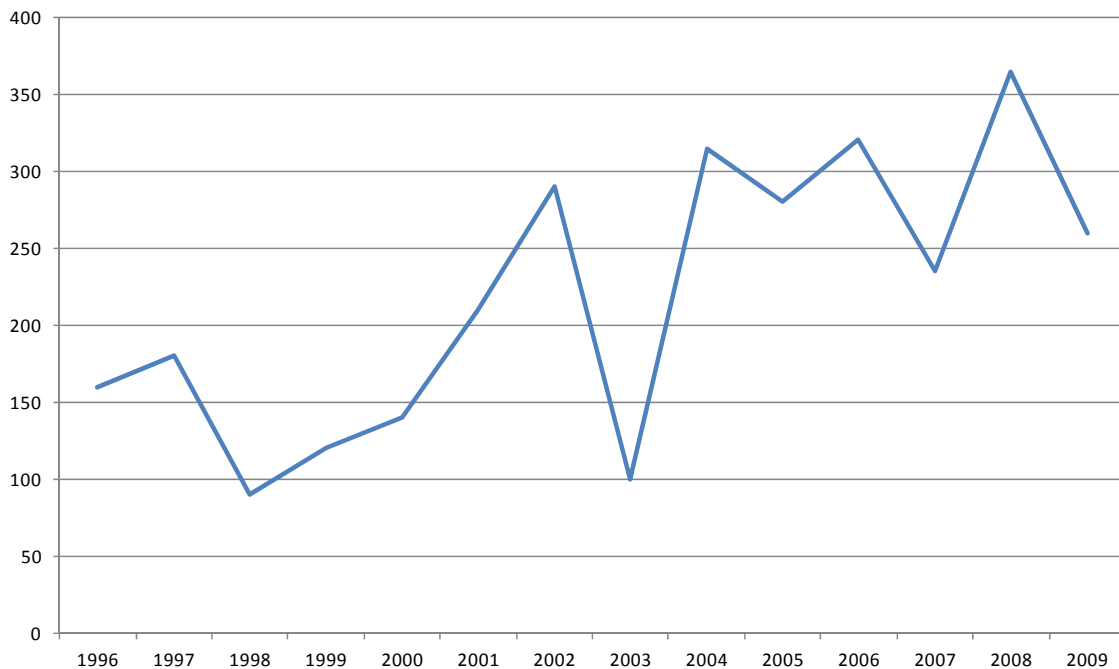
At the NCIC CTG, enrolment in its trials from within Canada was 2,618 in 2005 and fell to 1,462 in 2006. It gradually increased to 2,121 in 2009. Approximately the same number of trials was open for enrolment during the three time periods (between 70 and 78 accruing studies), but these observations are not easy to interpret. The mix of trials that were open may have affected accrual numbers. Trial complexity, competing industry trials and other factors may also have had an effect.

In the Partnership’s System Performance Report, clinical trials participation ratios (the number of adult or paediatric accruals divided by the number of new cases registered in cancer

centres) were reported for nine provinces. In terms of adult cancer trial participation, in 2009, the average national ratio was 7% with the provinces ranging from 2% to 11%.

Other metrics useful in assessing the efficiency of the cancer clinical trials environment include the number of studies opened for recruitment each year and the time taken to begin enrolment in new trials. The latter topic is demonstrated in data provided by the NCIC CTG (see Figures 3.2.1 and 3.2.2 below) and is also considered later in this section because it is a measure of ethical and other local and central review procedures.

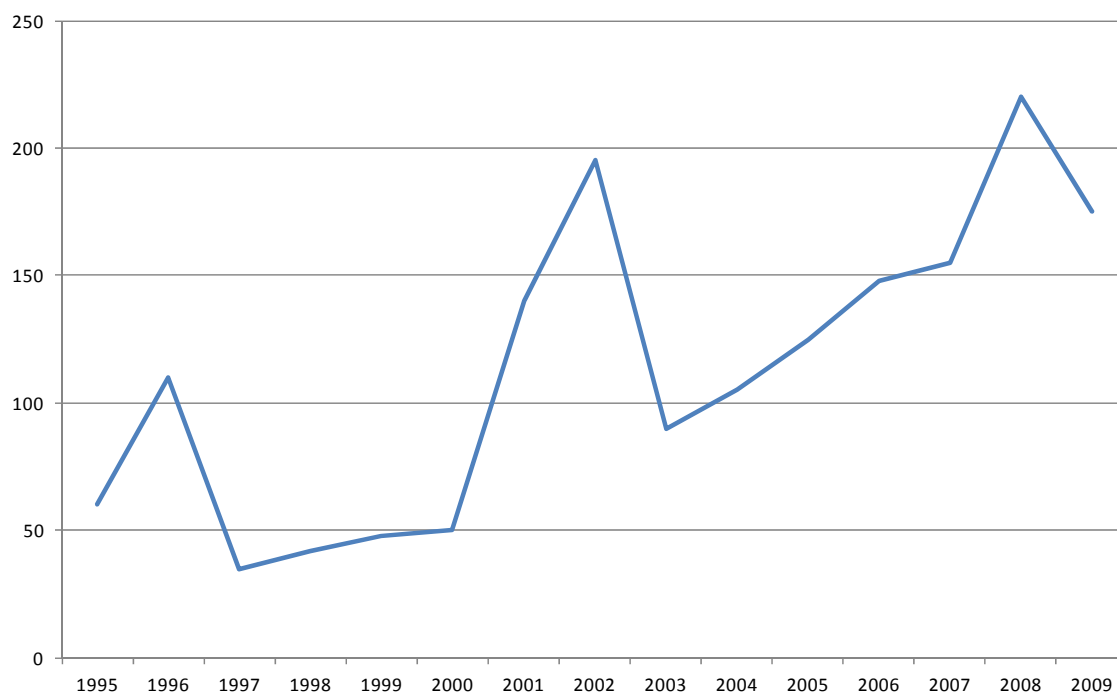
FIGURE 3.2.1
AVERAGE TIME TO FIRST PATIENT ENROLLED IN ALL ACTIVATED CENTRES
IN PHASE I-II TRIALS AT NCIC CTG, 1996–2009



Data not shown from the BCCA's Vancouver Clinic indicates that the number of new trials opened and the time to open new studies has been relatively constant over the last three years. Data from earlier years are not available.

In the NCIC CTG, for the 10 largest accruing member institutions, the average time for centres to become locally activated (i.e., have all pre-study procedures completed including ethics review) increased from about 50 days to around 200 days between 1999 and 2009. In early phase clinical trials, the mean time to first patient enrolment has likewise been increasing. In 2000 the first patient was enrolled in a new trial, on average, only two months after the trial was officially opened (had secured Health Canada approval). By 2009 this time had increased to approximately five months. Interestingly, delays in submitting study protocols for ethical review do not appear to have caused the increase in time: the time to REB submission actually became shorter over this time.

FIGURE 3.2.2
AVERAGE TIME (IN DAYS) TO LOCAL TRIAL ACTIVATION IN 10 LARGEST ACCRUING CENTRES
(ALL TRIALS) AT NCIC CTG, 1995–2009



In summary, although the measurements taken are not comprehensive and the data are not consistent with each other, enrolment on clinical trials seems to have declined in some areas over the last several years. Furthermore, the process for trials to move from Health Canada approval to the enrolment of the first patient is becoming more efficient. This latter observation suggests that more steps are required at the level of participating institutions to open studies for enrolment. This point will be explored later in this section. Finally, the Partnership's report provides a benchmark of national clinical trials participation against which future data can be assessed.

3.3 Clinical Trials Infrastructure and Support

Section 4 describes aspects of the costs and benefits of cancer clinical trials. Trends in providing infrastructure or programmatic support within health care institutions and cooperative group offices (academic trials coordinating centres) to maintain ongoing programs of clinical research are summarized. Stable, highly qualified teams need to be assembled to conduct the complex clinical research studies increasingly required for progress in cancer research. Thus, knowledge of the current environment in sustaining such teams is important.

Sophisticated knowledge of the science of oncology is required so that important questions for clinical investigation may be asked. Statistical skills are also necessary so that the research is appropriately designed. Analyses must be robust and data management skills are essential to collect

and clean data. Computing and technical knowhow are fundamental to create data capture systems and databases. Laboratory science expertise is imperative to develop and conduct correlative science questions on tumour samples. Clinical investigators, research coordinators, ethics and regulatory specialists, pharmacists, statistical and computing teams, biobanking and lab scientists and knowledgeable administrative staff are needed to collaborate and conduct studies. Finally, opportunities for educating the next generation of clinical scientists are an integral part of such teams.

Funding to support these experts is required at institutions that participate in clinical trials and at trial coordination centres in cooperative groups. At participating institutions funding covers human resources costs, such as nurses, data managers, and others directly involved in trial conduct, but it also supports equipment, facility rental, and fees to various hospital departments. Historically, institutional funding provided core support for clinical trials units. Added to that base was project-specific funding from pharmaceutical company contracts, peer-reviewed grants, or grants from other sources to expand the team and take on more research studies. Finally, university or cancer agency budgets generally account for clinical investigators (physicians) because these individuals also play key roles in both delivering cancer care and teaching.

Infrastructure trends in hospitals/cancer centres

For this review, major cancer centres and hospitals were surveyed about the infrastructure and operations of their cancer clinical trials units. Questions were directed to such topics as the current status of their unit's funding and activity and the changes experienced over the last decade. Seven major cancer centres or institutions responded from Quebec, Ontario, Alberta and British Columbia. Key findings:

- Over the last decade, institutional infrastructure support of key personnel (non-physician personnel) in clinical trials offices has declined or been discontinued.
- The number of trials opened per year has remained the same or grown.
- Although more trials have opened, when data was available, most centres indicated that the actual number of patients enrolled per year in trials had plateaued or was decreasing. Only one centre saw an increase in accrual.
- The number of staff at clinical trials units ranged from 12 to 121. For those centres that could provide information on personnel, the number of staff doubled from 2000 to 2010.
- Staff time per patient enrolled has increased. The primary reason is the greater administrative (non-patient) workload associated with clinical trials (REB communications, serious adverse event processing, on-site monitoring preparation and visits). A secondary reason is the trial conduct itself (more complex studies and a variety of electronic data capture systems require more time and queries than older paper forms).
- Trial costs and budgeting have garnered much more attention. Cost-recovery efforts for non-standard of care activities are commonplace, though most struggle to define "standard of care." It is also common for cancer centres and hospitals to look to the overhead from trials to fund other operations and fees for services (REB review, pharmacy review, etc.). Although most indicate that cooperative group studies have not been required to pay these fees, this may be changing. In general, many centres expect each trial to be self-supporting.

- Not surprisingly, because more funding is now needed to support core clinical trials operations, the mix of trials has changed over the last decade. Six of the seven centres indicated that a half to a majority of trials (50% to 75%) being conducted at their institutions are pharmaceutical industry-sponsored studies with the remainder being academic cooperative group or investigator-initiated studies. For the three sites with historical data, this pattern has been completely reversed; just a decade ago, more than half of all trials were academic cooperative group studies.

It appears that not only have many institutions reduced core support for clinical trials activity, but they also expect the trials to generate revenue for the institution. As the workload associated with individual trials has grown (see Sections 3.4 and 3.5 for the factors leading to this increase), so too has the cost to recruit each patient. Not surprisingly, the more lucrative pharmaceutical industry-sponsored studies help to offset these costs. Thus, more and more, trials that are a priority for the pharmaceutical industry sector are driving the clinical cancer research agenda in Canada.

Cooperative groups/Academic trials coordinating centres

Changes have also been noted at the operations or statistical centres for cooperative groups. In response to the change in the regulatory environment in Canada, infrastructure (primarily personnel) is being confronted with the larger volume of adverse event reporting, changing on-site monitoring processes and other activities. For example, data from the NCIC CTG shows that staffing doubled from 75 to 149 from 2001, when the *Food and Drug Regulations* were amended and the new clinical trials regulatory framework was added, to 2009. The number and the kinds of trial open have, however, remained relatively constant. Thus, to manage the change in the administrative and regulatory work, the number of people running the clinical trial program has doubled.

Progress in cancer biology and the rising interest in identification and validation of predictive markers as secondary endpoints within clinical trials have created the need for tissue banks and correlative biology committees. Networks of translational scientists have had to be formed and then integrated into the activities and structure of cooperative groups.

Finally, the pressures felt in many clinical trials units in cancer centres have had an impact on cooperative groups. With the academic sector of clinical research offering lower rates of per-case funding, participating centres have shifted their emphases to industry-sponsored trials, which, in turn, have delayed the activation and completion times of some cooperative group trials, as noted earlier. The slowdown increases the overall costs of the study in the coordinating centre: the longer it takes to complete a trial, the more full time equivalent-years are committed to it. Thus, if the funding for a given project has been fixed based on an estimated time to completion, that same funding must be stretched out as long as possible so that it is not exhausted before the study is completed.

3.4 Trial Complexity

A greater understanding of the genetic and other molecular drivers of cancer is becoming a driver for clinical cancer research. This knowledge has yielded numerous new targeted agents and putative biomarkers to select treatment options. These trends in science can make clinical research studies more complex: they demand an assessment of markers within patient subgroups, a collection of tumour or blood samples for correlative biology, more complex interventions and more challenging requirements for informed consent. By extension, the more complex a study, the more expensive and time-consuming it is.

To determine whether evidence supports the notion that trials are becoming more complex, protocols of NCIC CTG phase I, II and III treatment trials from 1995 to 2000 and from 2005 to 2010 were reviewed. Metrics evaluated include general study features, such as the number of protocol and consent form pages and the number of trial objectives, and specific features such as the number and type of correlative studies, economic analyses, quality of life analyses, the number of inclusion or exclusion criteria, the number of on-study tests and aspects of tissue collection.

Twenty-eight studies were reviewed, with 14 from each period. A full summary of the resulting data is found in Appendix C. Trials were a range of phase I, II, and III projects and were paired so that each 1995 to 2000 study was matched to a later study of the same tumour type and trial phase. A summary of the comparison of trials activated in 1995 to 2000 versus trials from 2005 to 2010 is provided in Table 3.4.1 below.

Metric	1995–2000	2005–2010
Objectives (mean number)	3.1	5.7
Protocol (mean number of pages)	39.5	53.9
Consent form (mean number of pages)	4.8	9.9
Efficacy endpoint (mean number)	1.7	3.4
Other endpoints (mean number)	1.9	4.3
Correlative studies (percent of trials)	50%	86%
Inclusion criteria (mean number)	17.6	20.1
Exclusion criteria (mean number)	8.8	14.0
Baseline tests (mean number)	22.6	30.4
Study tests (mean number)	19.4	26.4

By all measures that evaluate trial complexity, trials initiated during the 2005 to 2010 period were more complex than similar trials initiated a decade earlier. The phase I first-in-human trials were the main exceptions to this; these trials were scored as complex trials with multiple endpoints and tissue and blood collection during both periods. More testing, endpoints, correlative studies, protocol and consent form content in the recent trials mean that these trials are more labour-intensive in terms of clinical trials staff, investigator time and coordinating centre processes, than similar trials conducted a decade before. These findings help to explain why in cancer centres,

hospitals and cooperative group operations centres, more staff (time) is needed per patient enrolled in trials being conducted now than in those carried out a decade ago, and thus why today’s trials are more costly.

3.5 Trial Governance: Regulatory and Ethics Review and Challenges

As described in Section 1, changes in Canada’s regulatory framework environment have had a significant impact on the ability of cooperative groups – the NCIC CTG, the OCOG and the PMH Consortium – to conduct clinical trials. For example, data from the NCIC CTG over the past decade show an increase in amendments filed with Health Canada and serious adverse events (SAEs) processed (see Figures 3.5.1 and 3.5.2 below), though the number of trials being undertaken over the same period did not increase. As noted earlier, trials conducted under a CTA require more intense on-site monitoring and adverse event reporting than those not requiring a CTA submission. Thus, to manage the extra work, cooperative groups and clinical trials units have hired more regulatory staff and have altered procedures to ensure compliance with regulations. These measures have, however, considerably inflated the indirect costs of conducting research. Individual investigators or institutions without infrastructure support may be unable to undertake local clinical trials.

FIGURE 3.2.1
NUMBER OF INDIVIDUAL SERIOUS ADVERSE EVENT (SAE) REPORTS AND EXTERNAL SAFETY NOTICES (SUS) ON ALL NCIC CTG TRIALS, 2004–2009

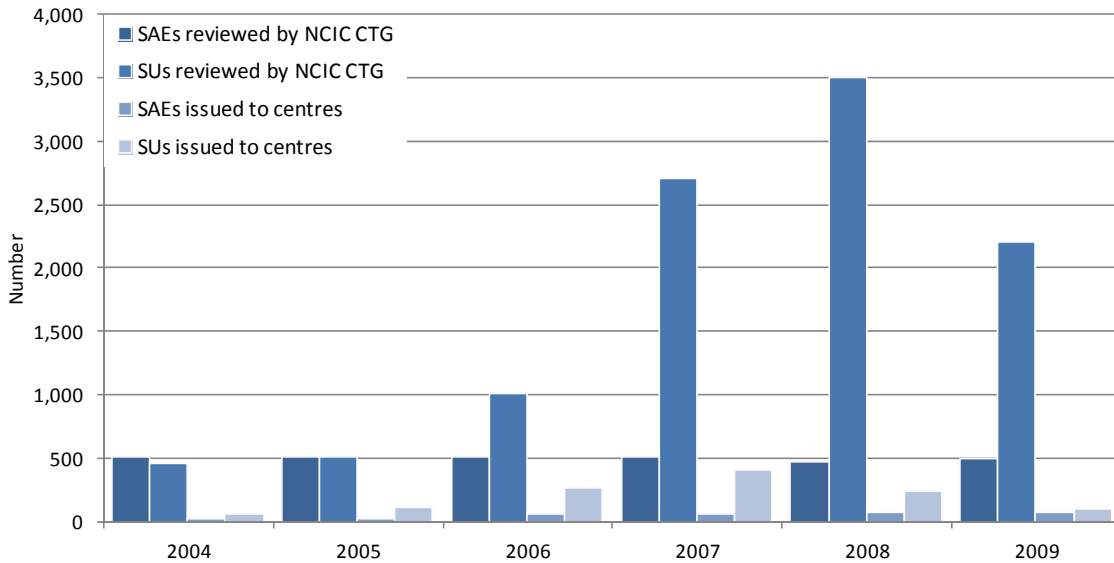
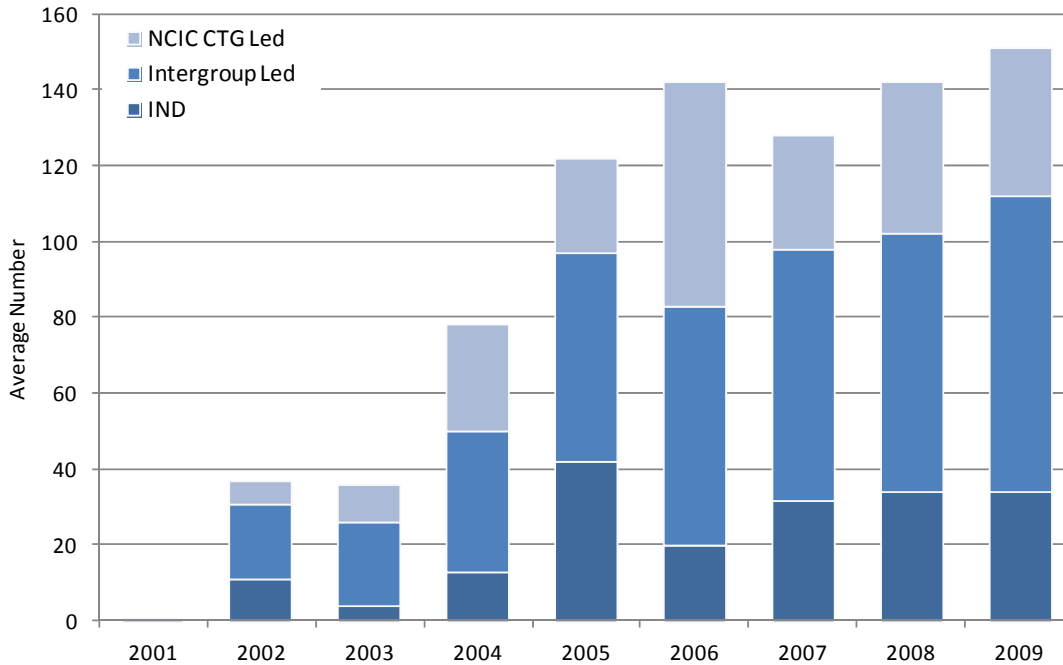


FIGURE 3.2.2.
AVERAGE NUMBER OF NOTIFICATION AMENDMENTS SUBMITTED TO HEALTH CANADA, 2001–2009



REBs in Canada review proposed human subjects research and are responsible for ensuring that it is well designed, that the investigators are competent to carry it out, that the harms and benefits for the patient or subject are appropriately balanced, that the selection of subjects is equitable and that the informed consent document and processes are appropriate.

The changing clinical trial and regulatory environment have affected REBs. Greater numbers of complex studies and a larger proportion of those being sponsored by the pharmaceutical industry have increased the workload for REBs in terms of protocol and amendment submissions and the number of SAE reports to review. For example, data from the BC Cancer Agency’s REB annual reports⁶ show that the number of SAE submissions has increased by more than 250% in just the last three years. This proliferation may, in part, be related to a higher proportion of industry-sponsored trials, which interpret reportable SAEs very conservatively.

The Canadian Association of Research Ethics Boards (CAREB) has called for action on this particular item. It has proposed that, for SAEs occurring on subjects or in trials outside the institutional REBs, only “unanticipated problems” (as is defined by CAREB in its report) should be subject to real-time reporting.⁷ If adopted, the workload of REBs would be substantially reduced.

⁶ www.bccancer.bc.ca/RES/REB/AnnualRep.htm

BC Cancer Agency’s published data show: 180 new projects in 2005–2006 and about 300 SAE reports per month (~3,600 per year) compared with 253 new projects in 2008–2009 (an increase of about 40%) and 9,667 serious adverse event reports (an increase of 270%).

⁷ www.careb-accor.org/files/CAREB%20DRAFT%20Guidance%20-%20Reporting%20of%20Unanticipated%20Problems%20including%20AEsv2010-02-05.pdf

The development and interpretation of guidelines regarding tissue collection and research as part of clinical trials are additional aspects that will be of concern to REBs.

One favorable trend under way in Canada is a movement towards centralizing REB review. In multicentre trials it is standard practice for each institution to have its own REB review the entire proposal and consent form. Many smaller institutions may have been reviewing projects without the relevant expertise present on the local REB. This factor, plus a desire to increase efficiency and reduce redundancy in reviews, has led several provinces to experiment with more centralized and specialized reviews of cancer clinical research. British Columbia, Alberta, Ontario and Quebec have all embarked on approaches that centralize REB review to some degree. The impact of this trend across Canada has not been comprehensively reviewed, but anecdotally, many investigators have found it saves time.

4. COST-BENEFIT ANALYSIS OF CANCER CLINICAL TRIALS

A detailed cost and benefit analysis of cancer clinical trials was undertaken as part of the background work to this report. This section summarizes some key findings and conclusions.

4.1 Cancer Clinical Trial Costs

The first challenge in discussing the costs of clinical trials is that each party involved in the process has unique perspectives. For example, society and general public, ministries of health, hospitals and cancer centres, patients, trial sponsors, and those working in clinical trials units may have differing views on costs.

Health care system perspective

Health care institutions across the country are tightening budgets and increasingly scrutinizing non-care activities, such as research. Clinical trials units are being treated as profit and loss centres. In this budgetary framework, overhead expenses (administration, physical plant occupancy and energy consumption) are charged back to clinical trials units and recovered through overhead charges, generally an additional 30% to 40% over budgeted costs. In addition, some departments such as radiology and pharmacy may charge fees for imaging, testing and other services related to clinical trials. With greater frequency, institutions are viewing on-site research activities, including clinical trials, as a source of revenue from overhead charges. Debate about the actual costs of clinical trials engenders much internal negotiation.

Patients in clinical trials are perceived as consuming more health care resources than patients receiving standard care. In fact, little evidence supports this belief. However, despite this generally held view, data from several American studies, summarized in the Table 4.1.1, have been inconclusive.

Reference	Study Population/Design	Time frame	Finding	Statistically Significant?
Wagner (1999)	61 Cancer Patients in Phase II/III with matched case controls	5 years	Trial patients costs were 5-11% higher	No
Fireman (2000)	135 patients in NCI sponsored trials with matched case controls	1 year	Trial patient costs were 10% higher largely from chemotherapy administration costs	No
Bennett (2000)	35 patients on Phase II trials and controls matches based on gender, age, tumour type and stage	6 months	Total mean charges for treatment were 9% lower for trial patients (\$57,542.00 for trial patients vs. \$63,721 for controls)	No
Bennett (2001)	377 patients on Phase II/III clinical trials matched with controls on standard care – a review of 5 pilot studies	Varied (6 months to 5 years)	Costs ranged from 10% lower for trial patients to 23% higher in a review of 5 studies	No
Goldman (2003)	A representative sample of 932 non-pediatric patients enrolled in 1 of 35 different trials, Phases I-III, matched with 696 non-participants	2.5 years	Treatment costs, excluding administration, for clinical trial patients were 6.5% higher (3.8% higher for phase III trials)	No

In no study were clinical care costs significantly different between trial patients and matched non-trial patients—actual differences in costs over periods of six months to five years ranged from 9% lower to 23% higher. In the largest study (932 trial patients and 696 controls), clinical care costs of trial patients were, on average, 6.5% higher (not statistically significant). It is not clear how or if that study accounted for drug cost avoidance (see Benefits of cancer clinical trials below).

There are, to date, limited data from Canada assessing actual consumed health care costs on trial patients versus matched non-trial patients. A recent pilot study from Alberta showed that cancer centre resource utilization for 44 patients enrolled in phase II or III prostate cancer trials were not increased significantly over a 52-week period as compared to matched non-trial patients receiving standard of care. This single study finding supports the U.S. data cited earlier and should spark interest in further investigation.

In summary, clinical care costing data available, to date, show that trial patients do not consume significantly more health care resources than matched non-trial patients. Indeed, as described in the next subsection of this report, significant cost savings may result from an active clinical trials program through free drug supply for trial patients.

Clinical trials unit perspective

Clinical trials units in cancer centres and hospitals operate three types of trials: directly sponsored by industry (more than 50% of the portfolio in many institutions), cooperative group sponsored (some of which are indirectly supported by industry through the provision of drug or funding) and investigator-initiated studies often with fewer, or even one, study site.

Human resources required to conduct trial-related procedures are the major expense in running clinical trials. People are needed for study initiation and ethics review preparation, patient enrolment, data collection, preparing for audit and monitoring visits by the sponsor and SAE and other reporting. Additional costs through institutional fees have been added to this list. These include charges for non-standard of care patient management and flat fees for protocol review (most commonly pharmacy and REB). The process of developing the budget to account for these fees is complex since there is no national agreement or costing template for (non)standard of care. Furthermore, the data on clinical care costs referenced above suggests that trial patients in general do not consume substantially more resources than non-trial patients.

Costs of clinical trials are steadily rising. Trial complexity, increasing administrative and regulatory work (leading to the need for more human resource) and cost recovery and fees are all contributing factors.

Trial sponsor perspective

The trial sponsor is the organization responsible for the overall trial conduct and, if applicable, files the CTA with Health Canada. Pharmaceutical industry and cooperative groups are the main sponsors of clinical trials in Canada, although, in some settings, individual investigators or institutions will sponsor a trial conducted within their institution.

Regardless of who sponsors the trial, the costs from the sponsor perspective broadly fall into two categories:

1. The costs of central operations for the trial (regulatory, statistics, computing, data management, drug distribution, safety oversight, audit and monitoring and other activities related to Good Clinical Practice (GCP)). These costs are primarily human resources but include the costs of meetings, travel, communications, and technological infrastructure (databases, biobanks).
2. The costs paid to participating institutions to support their clinical trials units in the recruitment of patients (per case funding).

For cooperative groups, costs of both these categories of activity have been increasing throughout the past decade. Central operations costs have risen to allow compliance with Health Canada requirements and the change in the *Food and Drug Regulations* such that almost all drug trials require CTA submission, audit, monitoring and safety reporting. In addition, more complex studies require more central operations coordination (tumour banking, specimen shipping, etc.). Per-case funding has also risen (although most would say not sufficiently) to address the need for enhanced funding by clinical trials units given the increased costs.

A relatively new cost for trial sponsors is related to laboratory testing and correlative biology studies embedded in clinical trials. Many trials have integrated molecular endpoints and, thus, whether through peer-reviewed or contract funding, the cost of doing such research must be covered.

Finally, an important but difficult to quantify cost for clinical trials sponsors is the cost of delayed trial conduct and slow accrual. Pharmaceutical companies may measure this cost in terms of loss of patent time and market access. Cooperative groups see it somewhat differently: most projects are funded over a fixed period, so if the trial is not completed by the planned end-date, expenses continue while revenue has been exhausted.

Patient perspective

For many patients, the potential to enrol in clinical trials is seen as a very important option in the course of their care. Patients may incur direct (for example, some oral medications) and indirect costs (child-care, lost wages, transportation) related to trial participation that are not reimbursed. Although almost all clinical trials protocols supply drugs to patients free of charge, out-of-pocket expenses, particularly related to transportation costs for those residing outside major treatment centres, can be significant and are a potential barrier to participation in clinical trials. For example, one interviewee for this report enrolled on a phase II trial, reported non-reimbursed out-of-pocket expenses of \$12,500 over the course of a year after the \$125.00 per day travel allowance was deducted through her insurance policy.

4.2 Benefits of Cancer Clinical Trials

As was the case for clinical trial costs, the benefits of cancer trials may be viewed from many different perspectives.

Societal perspective

Cancer clinical trials provide information that enables medical and public health practice to be improved by identifying efficacious interventions. The ultimate benefit can be described in

terms of both “life years” or “quality-adjusted life years” gained and enhanced cancer control. As noted earlier in this report, trials led by Canadian groups have substantially contributed to improved survival outcomes in several cancers including breast, lung, colorectal, prostate and ovarian cancers.

Institutional and research funder perspective

From the institutional (academic institutions, in particular) perspective, clinical trials and translational research results disseminated in the form of peer-reviewed publications are critical to knowledge translation. They are a measure of research or researcher performance from the perspective of employers (institutions) and research funders such as CIHR and CCS. The impact of the publications from Canadian clinical research has been evaluated empirically and found to be higher than any other country in the world.

In addition, a healthy clinical trials program enhances the ability of an institution to recruit and retain highly qualified investigators and other human resources who have roles in the health care and educational systems beyond their research activities. Of course, the institution also benefits from revenue and overhead from contracts and grants related to clinical trials.

Finally, strong evidence from the literature shows that significant drug cost avoidance is a benefit of participating in clinical evaluations of investigational drugs in general (across diseases) and, in particular, cancer clinical trials, as shown in Table 4.2.1 below.

TABLE 4.2.1 SUMMARY OF FINDINGS OF STUDIES ON DRUG COST AVOIDANCE			
Reference	Study Population/Design	Episode	Finding
Bredin (2010)	101 oncology clinical trials from Alberta	1992-1997	Drug cost avoidance had a median range of \$1,377 to \$23,751 per patient (varied by tumour group).
Lafleur (2004)	Review of 139 protocols at a single institution	2 Fiscal Years	Annualized cost avoidance was \$2.6 million.
MacDonagh (2000)	Review of records of two hospitals. Costs were assigned to drugs contributed by sponsor/through trials and compared to hospital payments for non-trial drugs for the same period.	1 Fiscal Year	Cost avoidance from drugs provided through trials was \$2.9 million representing 8% of the hospital drug budget. The two diseases categories with the largest cost-avoidance were HIV/AIDS and cancer.
Uecke (2008)	Analyzed 88 oncology clinical trials led by 29 researchers in 11 German hospitals	3 Fiscal Years	Potential costs avoidance over 3 years was \$6.7million based on accrual targets. Actual cost avoidance was USD\$2million.

As noted in the table, an Alberta study confirmed the studies from U.S. and Europe in finding substantial savings from drug cost avoidance. A review of the administrative records of the BCCA found drug avoidance costs for the province, as a result of clinical trial participation, ranged from \$2 million to \$5 million per year.⁸ The cost savings from drugs is tied mostly to phase III studies, in which the standard of care treatment arm is a marketed drug, the cost of which is covered by the budget of a cancer agency or hospital formulary. These cost savings are a compelling argument for a business case—supporting clinical trials from institutional budgets is an important method of drug cost avoidance and results in overall net savings in health care costs.

⁸Personal communication, S. O’Reilly, VP Clinical Care.

Patients' perspective

Benefits described from the patients' perspective (from interviews conducted for this report) include access to experimental therapy not yet on the market, improved quality of life and an opportunity to contribute to medical science and ameliorate the suffering of future generations.

Beyond this, literature from Europe suggests ovarian cancer patients treated in institutions with active cooperative group clinical trials programs experience better cancer outcomes than those treated at institutions without such programs. In a report from Quebec, authors found that women with breast cancer who were treated in centres with either on-site radiotherapy, research activity, or teaching status had significantly better outcomes, even after adjusting for caseload (Hazard ratio 0.68; 95%CI, 0.50-0.92). This benefit resulted regardless of whether the patients were actually enrolled in trials. The premise that active institutional involvement in clinical trials improves the outcomes of all patients treated at an institution was the impetus for the U.K. Department of Health's funding of a cancer trials infrastructure program in England as part of its plan to improve cancer outcomes. Furthermore, the Partnership has recently started to report on clinical trials participation ratios as a measure of the cancer system performance. Thus, evidence that patient outcomes are improved by treatment in a centre that is active in clinical research is gaining acceptance, though more data to support this assertion are needed.

Cancer control and cancer systems perspective

Some benefits to a vigorous clinical trials program are noteworthy. Involvement of clinicians in trials facilitates knowledge translation. New practices are adopted more quickly and practitioners gain important knowledge about proper use of new agents in the controlled trial environment.

Why clinical cancer outcomes appear to be better in institutions with active clinical research programs is not clear. It may, however, relate to the extension of standard of care aspects of clinical trial protocols to non-trial patients in terms of processes and safety monitoring in the treatment centres.

Finally, extending the continuum of clinical evaluation methods to the health services setting can further improve the innovative capacity of the system with respect to service delivery and clinical policy. For example, the clinical trials infrastructure of U.K. National Cancer Research Network (NCRN) is linked to and built upon the cancer clinical care networks that existed *a priori*.

Community Perspective

It has been estimated that for every job created by the bioscience sector, an additional 5.7 jobs are created in supporting industries such as packaging, accounting, law, etc. This is known as the "direct-effect employment multiplier."⁹ Trials foster the growth of communities of science and create the social capital that generates innovation, health benefits and wealth.

Clinical trials pay "economic rent" in various ways, including tax revenue from employment income and royalties from patents, which also sometimes accrue to academic

⁹ Biotechnology Council of Ontario, *Investing in the Life Sciences Sector: A Proposed Strategy for Innovation in Ontario, Volume 1* (August 2006), p. 18.

institutions or philanthropic funders that share intellectual property and tax revenue from industry corporate taxes.

Finally, institutions, charities and foundations rely on the tangible findings and outcomes of clinical trials and on the credibility of clinical trials leadership to raise philanthropic revenue.

4.3 Summary of Cost-Benefit Analyses

In summary, cancer clinical trials costs are variable but benefits are numerous. Of note, clinical care costs of cancer trial patients do not significantly differ from matched non-trial patients. The costs of conducting trials at the institutional level include funding the personnel required in clinical trials units for activities directly related to trial participation but also, increasingly, cost recovery for clinical services and flat fees for opening studies. Sponsors of trials incur costs related to trial coordination and analysis, regulatory compliance, translational research and per-case support of patient recruitment in participating centres.

Long-term societal gains through improved health outcomes are among the benefits of clinical trials, as are, in the short term, improved outcomes for patients treated in institutions that have an active trial program. In addition, clinical trials save institutions substantial drug costs, provide an incentive to recruit and retain clinical investigators (who also practise within their specialty areas) and facilitate knowledge translation and innovation. Finally, clinical trials offer patients the opportunity to receive new therapies and participate in the generation of knowledge that has a goal of reducing the burden of cancer.

5. LESSONS LEARNED

In this section, case studies of clinical trials units and systems in Canada and abroad are presented.

5.1 Ontario: Clinical Trials Infrastructure Project

In 2001 the OCRN (later part of the OICR, funded by the Ontario Ministry of Research and Innovation) undertook a review and a needs analysis for cancer clinical trials with the help of PricewaterhouseCoopers. From this analysis a program of infrastructure funding was developed that aimed to enhance cancer clinical trials enrolment in the province. Institutions and centres participating in the program created business plans for how the funding would be used to increase accrual and to build a balanced and sustainable portfolio following three years of funding. The institutions and centres used the funds largely for human resources, in particular, specialized personnel such as nurses and data managers. From 2005 to 2007 (and apparently even as the program was ramping up in 2004) accrual increased across the province. It has since fallen to close to 2004 levels (see Appendix B). Because of the need for sustainability at the end of the program, the increase in accrual was largely due to industry-supported trials, not investigator-initiated or cooperative group studies. These data suggest that, although infrastructure funding is associated with greater participation in clinical trials, this growth could not be sustained after the funding ended. The inability to maintain these numbers could have been related to unrealistic business models, but during that time, other changes in the cancer system in Ontario may have played a role as well. Some informants suggested that to sustain increased capacity, longer periods of funding are needed, as are better tools to plan clinical trials portfolios (see, for example, the U.K. National Cancer Research Institute experience below). Other innovations by OCRN and OICR have included the formation of a central cancer-specialized REB (Ontario Cancer Research Ethics Board), ethics training modules, standard operating procedures (SOPs) around GCP for clinical trials personnel and tools for trial costing and monitoring.

5.2 United Kingdom: The National Cancer Research Network

In 2001 U.K. Department of Health established the NCRN. The network provides the National Health Service (NHS) with an infrastructure to support prospective trials of cancer treatments and other well-designed studies to integrate and support research funded by cancer charities. Its aim is to improve the speed, quality and integration of research, which would ultimately result in improved patient care.

The initial goal of the network was to double the enrolment of cancer patients in the trials funded by government and charitable research agencies such as Cancer Research UK and the Medical Research Council by 2004. In fact, it achieved this goal in less than three years. At that time the portfolio of trials for which the infrastructure could be used was extended to integrate a few industry trials as well.

In England, 32 Local Research Networks (LRN) have been established. They are closely aligned to the NHS Cancer Networks that were established to drive change and improvement in cancer services for the population in a specific geographical area. Each LRN is required to appoint a clinical and administrative lead (Clinical Lead for Research and Research Network Manager) who

is responsible for the overall leadership and management of the local networks. Each research network receives funding to appoint research staff and to give them access to pharmacy, pathology, radiology and other areas of support, such as information systems and training, all of which are integral to high quality research. In addition, the U.K. has established Clinical Studies Groups to discuss, develop and coordinate cancer trials that are run through coordinating units throughout the country and which draw participants from within the NCRN system.

Unlike the OCRN/OICR infrastructure program, the Department of Health initially established the NCRN and its program on the basis of recruitment to “portfolio trials,” which excluded industry studies. Furthermore, funding to each network continued, contingent on its performance.

With an annual investment of £20M per year, overall accrual to clinical trials rose from a baseline of less than 4% of new cases to 14% of new cases by 2006. About half the recruits were enrolled in randomized studies. By this measure the NCRN has been a resounding success. In fact, this success led the Department of Health to expand this approach to therapeutic areas outside cancer by creating the National Institute for Health Research Clinical Research Network (NIHR CRN) that, until recently, was co-directed by Dr. Peter Selby, the inaugural director of the NCRN.

5.3 Germany: Coordination Centres for Clinical Trials

In Germany the platform for cancer clinical trials are the Coordination Centres for Clinical Trials (KKS) and the KKS Network. Cancer(s) are specific “competence” areas within the network.¹⁰ Established in the late 1990s, the KKS comprised 17 institutions by 2009, with 400 employees working as scientific service providers for universities, study groups and the pharmaceutical and biotechnology industries. The network was established to improve the quality of clinical trials, provide training and increase the number of trials. The federal ministry of education and research funds the network through a grant.

Cancer networks include paediatric cancers, acute and chronic leukemia, and malignant lymphoma. The network employs trial personnel (research and administration), develops internet portals, supports study centres with central protocol development and review and provides standardized case report forms and protocol templates.

No data could be found on the impact of this model on trends in accrual or on numbers of trials conducted. Anecdotally, however, pharmaceutical industry representatives indicated that they viewed Germany as a strong performer with respect to accrual. On the other hand, its decentralized model (different networks for different diseases) and high costs were detractors.

5.4 European Union: Clinical Research Infrastructures Network

In addition to the country-specific initiatives noted above, the European Clinical Research Infrastructures Network (ECRIN) was established in 2004. As of 2009, 13 European Union member states were participants. This initiative was developed, in part, in response to the European Union Clinical Trials Directive in member states, because the fragmentation of the health and legislative systems in Europe was hampering multinational clinical research. This was a significant

¹⁰ A “competence centre” is local whereas as “network” includes more than one centre.

issue for organizations such as the European Organization for Research and Treatment of Cancer (EORTC), whose primary goal is to conduct multinational cancer treatment studies. Thus, ECRIN's main mission was to create and operate a sustainable infrastructure for multinational clinical research.

ECRIN is based on the connection of national hubs for national networks of clinical research centres and clinical trials units. So, for example, the U.K. contact would be an individual at the NIHR CRN, which is the overarching body where the U.K. NCRN sits. ECRIN's goals are to facilitate, promote and accelerate clinical research across Europe. The network provides information, consulting and services to investigators and sponsors in the preparation and conduct of multinational clinical studies for any category of clinical research and disease area. This was felt to be particularly important for investigator-initiated or small and medium enterprise-sponsored clinical trials and for clinical research on rare diseases where international cooperation is a key success factor.

ECRIN is in its early days and seems to provide many of its services through national networks and infrastructure. The total funding for the network is not clear (multiple governments support its activities) and, thus, its success will ultimately depend on national commitments to clinical research. ECRIN's role may be the value added by working towards more harmonization, addressing gaps in tools and education, and providing help to investigators and small companies in doing multinational research.

6. SYNTHESIS, VISION & RECOMMENDATIONS

6.1 Synthesis of Findings

Cancer clinical trials offer individual patient and health system benefits

Interviews with key informants and literature reviews underscore that, in spite of the cost of cancer clinical trials, the health care system and cancer patients benefit from cancer clinical trials activity. A growing body of evidence supports this argument, and the framework for studying and monitoring the positive effect of cancer clinical trials on an ongoing basis is robust.

The ways in which the benefit is realized are multiple and include cost savings from free drug supply, access to highly qualified personnel for non-clinical trial-related care delivery and the influence that regular participation in cancer clinical trials has on clinician behaviour and health care norms or standards. For example, clinicians are exposed to new agents and procedures. As a result, they can learn and practice innovative approaches to care before those agents and procedures are marketed and disseminated. In addition, the discipline of protocol compliance appears to promote adherence to standard of care and treatment guidelines.

Environmental stressors on cancer clinical trials system

The stressors on the cancer trials system described by clinical researchers, cooperative groups and key stakeholders are largely a function of cost dynamics. Greater trial complexity as translational research questions are embedded in studies, decreasing infrastructure support from institutional base budgets, more institutional efforts at cost recovery and higher regulatory and administrative demands have driven the budget for maintaining clinical trials units upward. More staff is needed to do the work, but sources of revenue have diminished or not kept pace with the real cost of clinical research. As a result, well-funded pharmaceutical industry trials are dominating the trial mix in cancer centres and hospitals, an important shift from the situation of a decade ago. Correspondingly, the level of commitment that these same institutions can make to academic cooperative group or investigator-initiated studies has declined.

Cooperative groups are also under strain. Increased regulatory and other administrative requirements related to Health Canada's clinical trials regulations have increased the staff to trial ratio. Delays in trial activation and slower recruitment from participating centres (related to many of the same pressures) have extended the life of a trial. Thus, when a trial budget is based on delivery of a final analysis and the time to deliver this analysis has increased, the expenses to produce the same work product are higher, but the budget remains the same.

Finally, key informants from the pharmaceutical industry noted that efficiency is their priority. They defined efficiency as the speed at which patients could be recruited while keeping costs contained. Informants highlighted the need to avoid the scenario where trials open with no accrual. In addition, they acknowledged the administrative burden of trials in North America, particularly with respect to the budget and contracting process. It is, they suggested the single biggest rate limiting factor in the time taken to open new trials.

Moving to address the issues in the cancer clinical trials system

The cancer clinical trials system itself is not a formal entity but a broadly distributed enterprise. Cancer trials are collaborative efforts with numerous parties working for different

organizations supported by multiple sources of funding. In such a system, no single intervention is likely to strengthen performance. For that reason key stakeholders, who live in different geographical areas and who have different functional roles within the system, must coordinate their approach.

International successes on which to model a coordinated approach

Looking outside Canadian borders, the most instructive model of organizational design comes from the NCRN (U.K.). It has achieved a new standard for the proportion of patients enrolled on clinical research studies (14% of new cancer cases) and the principles on which they have focused their reforms, such as good governance, improved efficiency and, in particular, stable infrastructure for institutions to recruit to a specified “portfolio” of studies.¹¹ Although the tools and programmatic mix to act on these principles may be different in Canada, the challenges experienced in the U.K. are more or less the same and the principles by which they have tackled these challenges can be imported to Canada. Political will has, in part, enabled the success in the U.K. and a commitment to clinical research has been made concrete in policy through funding by the NHS, the sole publicly funded health care provider. A coherent and compelling vision of how a reinvigorated Canadian cancer clinical trials system will realize a better future for cancer care and cancer patients is needed to mobilize the same improvements in Canada.

The situation in the United States is also noteworthy because recent reports (for example, Institute of Medicine report) suggest that many stressors similar to those in Canada are at play. The issues in the U.S. are, however somewhat different from those in Canada. The U.S. Government, through the Cancer Therapy Evaluation Program at the NCI, the comprehensive cancer centre programs and other initiatives, plays a fundamental role in the U.S. cancer trials enterprise in a way yet to be realized in Canada. The approaches taken to improve the clinical trials systems may therefore be quite different.

In Canada missing opportunities to coordinate, harmonize, standardize and consolidate reduces effectiveness and makes it uncompetitive. Moreover, the clinical trials system in Canada is so closely wired to its American counterpart through funding arrangements and regulatory umbrellas that it is critical to understand the operating assumptions that underpin the reformative ambitions articulated in the Institute of Medicine report.

Designing a coordinated approach – the principles and recommendations for action

At a minimum a coordinated approach in Canada to reinvigorate the cancer trials system must include pan-Canadian mechanisms for clinical trials infrastructure and other supports and good clinical research oversight, but it must also reduce non-added-value work in clinical trials conduct. It must take into account the demands of the Canadian federation, like the federal and provincial responsibilities in health care delivery, build on existing organizational (NCIC CTG, PMH Phase II Consortium, OCOG) and regional strengths, including clinical cancer research programs at key institutions and identify pragmatic and pan-Canadian solutions.

¹¹ Portfolio studies for the NCRN were initially clinical trials that had received peer-reviewed funding from cancer research funding agencies. After initial success in enhancing recruitment to peer-reviewed trials, NCRN initiated a process to include select high priority industry-sponsored trials in the portfolio.

The strategy for action must also embrace the ethos of bringing the highest standard of care, which includes access to clinical trials, as the preferred program of treatment to cancer patients in both urban and rural areas. More patients recruited to the right trials in more communities will increase and distribute the benefits of cancer clinical trials as measured by improved survival and adherence to the standard of care and treatment guidelines

6.2 Vision for 21st Century Clinical Trials

With a greater understanding of fundamental molecular mechanisms of cancer initiation, progression and metastasis, novel therapeutics are moving into clinical evaluation at an accelerated pace. New treatments are expected to be most effective in molecularly defined subgroups of patients. Such a personalized approach will reduce the number of patients exposed to ineffective therapy (and its adverse effects) and it may reduce health care costs.

Clinical trials to assess efficacy while simultaneously discovering and validating predictive biomarkers require the collaboration of clinicians, laboratory scientists, pathologists and experts in diagnostics development. Tumour and/or blood samples are needed from all trial subjects. Access to high throughput sequencing technologies and immunohistochemical and mutational analyses have become priorities for 21st century clinical trials. Innovative, possibly adaptive, trial designs must be deployed to maximize the knowledge return on investment in trials. Quality of life assessments and economic analyses are standard components of modern cancer trials.

Canada's track record in all these areas has been strong, but the issues identified in this report must be addressed and clinical research strengthened to realize the vision of the CCRA working group:

To improve the health and wellbeing of Canadians by ensuring that Canada is at the forefront internationally in clinical cancer research at a time of unprecedented opportunity for advances that are emerging from fundamental science.

The goal of improving the environment for the conduct of academically-driven cancer clinical trials is to achieve better cancer control, increase survival and enhance the quality of life for patients. Furthermore, a stronger cooperative group/academic clinical trials program will indirectly benefit the pharmaceutical industry in Canada because such a program will be more efficient and globally competitive.

6.3 Recommendations

Recommendation 1: Create a pan-Canadian infrastructure program that supports cancer clinical trials

A healthy and re-invigorated cancer trials system can accelerate the pace of knowledge translation into the clinic and identify biomarkers to select patients most likely to benefit from treatment. Such a system will require stable funding and common tools to manage and account for direct and indirect costs. In addition, efficiencies and standard approaches to tissue collection, contract development and SOPs common to major clinical trials groups and units across Canada should be aspirations and products of a pan-Canadian clinical trials infrastructure. This program should have the following components:

Stable institutional clinical trials support

- Create a model for stable clinical trials infrastructure funding in Canada that will substantially increase recruitment to peer-reviewed and cooperative group clinical trials. This model should be based on the highly successful U.K. NCRN that includes infrastructure funding for key trial team personnel, tissue collection support and other common tools and resources. National, regional or provincial funding may be needed but the goal is to coordinate the program at a pan-Canadian level.

Trial personnel credentialing

- Work with national clinical trials leaders to reduce the duplication of effort in investigator and trial personnel qualification processes, such as GCP, ethics training and SOPs. For example, create a national repository of acceptable modules for an agreement among trial sponsors such that certification from one any is equivalent to certification from another.

Contract language

- Work with key institutional stakeholders and partner with others engaged in clinical trials, to develop common contract language around confidentiality, tissue access and intellectual property and indemnification for use by major universities and hospitals.

Trial budgeting tools

- Spearhead a coordinated effort to share best practices and tools for budget development and forecasting. Furthermore, standardize cost schedules for standard of care, pharmacy services, pathology, medical records, imaging, etc., across cancer centres so that the tools and processes are effectively utilized.

Trial decision making

- Encourage clinical trials units and cooperative groups to adopt and implement portfolio management tools to support a balanced and strong portfolio of potentially practice-changing cancer clinical trials.

RATIONALE

1. Costs

In addressing the costs of clinical research, it is important to state the true costs and identify who is bearing them. Although there is general agreement on what is driving the costs (trial numbers, increased trial complexity in the era of molecular medicine, increased regulatory and administrative work), bias was observed in the interviews undertaken for this report in two respects. First, few people would or could speak to the overall cost dynamics in the cancer trials system, which is not a surprise, given its distributed nature and complexity. Thus, most informants and participants in this process viewed costs through the lens of their own place in the system. Second, no consensus could be reached on how to contain costs, although it was agreed that a cost-management strategy should have the following four components:

1. Transparency: Make costs at institutions and cooperative groups transparent by diligently tracking them. Standard tools would be helpful.
2. Better budgeting and forecasting methods and tools.
3. Streamlined process: Eliminate redundancy and non-value-added steps in the trial activation, monitoring and reporting process.
4. Optimal funding levels to cover the real costs of clinical trials.

Some organizations (institutions that participate in trials) have already made strides with the first three components and returned to a balanced budget in their clinical trials units. Thus, those behaviours, models and processes may be replicated at clinical trials centres across the country.

All those engaged in clinical trials development should reflect on whether each activity contributes value, either by ensuring patient safety or by generating knowledge that will benefit patients and the health care system. Component (3) is clearly tied to the governance/regulations recommendation because many actions in trial activation can be traced to the interpretation of regulations. That being said, many procedures are also self-imposed by cooperative groups, the pharmaceutical industry, investigators and institutions themselves and a hard look must be taken at all of these.

It was universally agreed that the budgeting and contracting process added time and costs to the system but had limited value. Contracting processes, given the high potential value of intellectual property attached to both trial processes and the products they assess, tend to be onerous. In addition, indemnification issues, reimbursement for standard care and insurance are areas where negotiations chronically and repeatedly stall. In fact, even when two parties reach agreement on a one contract, the same two parties may start from the beginning with new issues on a second contract initiated shortly after signing the first.

Clearly, a system with many non-value-added, but time-consuming steps and processes translates into a high cost and lost opportunities resulting from human resources that could be better deployed elsewhere. Thus, organizations at all levels of the system should be working together to manage costs through improved efficiency within and among organizations.

Other options to improve cost management include:

- Consolidate the contracting and negotiating process between clinical trial centres. (This could be accomplished through regional consolidation. Not all provinces need a dedicated office and some provinces, like Ontario, will likely need more than one.)
- Reduce opportunity costs by carefully choosing the trials in which one participates. This will, in turn, reduce the amount of effort spent on trials that do not accrue patients but still incur significant costs at the front end of the process.
- Develop a reasoned and standard approach to charging indirect costs and overhead. As a matter of principle, host institutions should be transparent—able to articulate the underlying assumptions and defend the rationale for the percentage charges. Policies to charge a fixed cost for all trials, as is done in some Radiology and Pharmacy Departments, must be challenged unless an activity-based formula underpins those charges. These costs should therefore be viewed as highly variable.

Equally important is the need to recognize the substantial cost savings from clinical trials. They are considerable, but are seldom acknowledged by institutions housing clinical trials units. Indeed, an understanding of the cost savings will be important in building the business case that investment in clinical trials infrastructure will gain savings in pharmacy budgets and allow highly qualified clinical trials personnel, like clinical investigators and research nurses, who participate in other health care-related activities, to be employed by the institution.

2. *Core infrastructure support for clinical trials units*

Cooperative groups and institutions are relying on project funding (as a per capita payment) more often to support the core infrastructure (nurses, data managers and administrative staff) required for clinical trials programs. When project funding is obtained, it must be budgeted to cover the true cost of the research. But stable clinical trials teams are needed to undertake such projects, and to do this, core program funding is needed. Over the last decade the proportionate (and in some cases absolute) amount of core program support for clinical trials units and operations offices from institutions and funding agencies has diminished, or, in some cases, disappeared.

Although costs have risen, core support has been reduced. Therefore, even if costs are reduced, the survival of some clinical trials programs remains precarious. This problem must be addressed if Canada is to continue to contribute important knowledge to cancer control through its internationally regarded trials activities.

This type of core support has been generally described as infrastructure funding. Such funding refers to clinical trials personnel (data managers, administrators, nurses, and statisticians) but may also include physical plant costs incurred in cancer clinical trials (occupancy costs in host institutions for care related to trials, examination rooms or chemotherapy chairs and beds, administrative and laboratory services) and costs related to modern clinical trials (core technologies and platforms for communications, data management and the processing, handling and transportation of biological specimens).

The right approach to addressing infrastructure costs is likely a composite of the following:

- When full project funding is available, per-patient funding levels requested should reflect the real costs of the study. This point will most likely to apply to pharmaceutical industry-funded studies.
- A non-pharmaceutical industry-driven research agenda must be maintained in Canada; therefore funding is needed for a stable pool of human resources to support the trials system and to undertake less well-funded projects from peer-reviewed or academic sources that will drive improved cancer outcomes. Funding for this stable pool of clinical trials personnel can come only from host institutions themselves, peer-reviewed programmatic research funding from government or the charitable sector.

Host health care institutions, with their own budgetary restraints, are unlikely to identify large amounts of new funding within their budgets. Data showing cost savings from clinical trials (noted above) may persuade some institutions to remove, at minimum, some of the charges levied against trials units, which might place some units in a better financial position. But it is more likely that funds to support core clinical trials infrastructure via institutional budgets will happen only if provincial health ministries flow additional monies specifically for this purpose to, at the very least, major tertiary care hospitals and cancer centres. They must, however, first accept the evidence gathered in this report that cancer outcomes are optimized by active clinical trials participation, that cost savings may come from trial participation and that patients/public expect their health care system to include opportunities for innovation and improving outcomes through research.

Programmatic research funding is another important source of core funding support for clinical trials units and cooperative groups from government or charitable research funding agencies. Indeed, the NCIC CTG, PMH Phase II Consortium and OCOG each receive some core infrastructure for their program of trials through a research grant or contract with charitable agencies or government funders. The planned CIHR SPOR initiative is highly relevant, because it is proposed to include institutional funding and funding for research coordinating centres. Thus, engagement with CIHR as the SPOR program is developed is important to maximize the opportunities for support of an already well-established, but faltering, clinical trials system in cancer. From the CIHR perspective, this could be an early win for SPOR because costs related to building units and training investigators or research managers are not required. Funds to bolster existing clinical trials centres would be sufficient. Other funding agencies with which these issues should be discussed include those at the CCRA table and provincial ministries with a research, innovation or educational mandate.

To determine how much core infrastructure is required, the minimum number of personnel required across the country to sustain and grow clinical trials participation and recruitment should be estimated. Using the U.K. experience with NCRN as a benchmark, approximately 750 personnel have been funded to increase clinical trials enrolment on portfolio trials (largely trials supported through a peer-review process) from less than 4% to 14% of incident cases. A similar number in Canada (based on relative population size) would be about 300 to 350 personnel. Funding might also be concentrated in the 8 to 12 major centres or institutions across Canada that recruit over half the cancer trial patients. Closing these centres would have an

enormous impact and, by corollary, strengthening their core support would likely have the greatest favourable impact on trial accrual and conduct. Those centres, in turn, could reach out to smaller institutions within their catchment area. The U.K. NRCN experience suggests this framework works best when clear directions are given regarding the kind of trials the infrastructure is intended to support and standard tools for costing and other infrastructure activities are developed. Finally, infrastructure investment should look to the lessons of Ontario and the U.K. where different models were rolled out. The combined experience suggests we should strive for a performance-based, rather than time-limited, infrastructure program. Furthermore, as in the U.K., the infrastructure support might best be directed to those trials supported through peer-reviewed processes and cooperative groups because they suffer most from cost containment, their trials have created the international reputation Canada enjoys in clinical research, and their studies, some argue, are most likely to have the greatest impact on cancer control.

Recommendation 2: Streamline the clinical regulatory environment.

Engage with Health Canada and other key stakeholders to propose non-legislative changes to the *Food and Drug Regulations*, through guidance or other similar documents that will improve the efficiency of clinical trials, ensure or enhance safety and reduce the amount work and the costs.

Recommendation 3: Consolidate or develop reciprocity in research ethics boards.

Working with the CAREB and other stakeholders, champion the consolidation of specialized cancer REBs and reciprocity between REBs to reduce the duplication of efforts and enhance content knowledge.

RATIONALE

The work associated with clinical research oversight is a key area for strategic action. The impact of compliance with federal regulations (as currently interpreted) and ethical due diligence has substantially increased the workload associated with clinical trials activities in Canada. Research oversight is intended to ensure the safety and interests of research subjects/patients. A detailed examination of the safety of cancer clinical trials in Canada was outside the scope of this review. Ideally, however, Health Canada should make such data available as it reviews the impact of the regulations of clinical trials. Many scientists and clinicians involved in clinical trials believe that enhanced safety reporting and other changes brought about by addition of the clinical trials regulatory framework to the *Food and Drug Regulations* in 2001 have increased the workload but have not clearly improved trial conduct or safety. Indeed, some have proposed that the massive rise in SAE reports may obscure true safety signals lost in the noise. These recommendations also encourage further streamlining and consolidation of REBs.

The goal of the recommendations 2 and 3 is to retain the protective effect of the current regulatory framework, while apportioning the costs and work in a manner related to the risk of various types of trials. In other words, if the outcomes are acceptable then the goal is simply to improve efficiency.

1. Clinical trials' regulations

Although a change in the regulations themselves may be desirable, at the very least, Health Canada should develop guidance documents in collaboration with appropriate stakeholders to ensure that the degree of oversight relates to the degree of risk of the particular study being conducted. For example, on-site monitoring, safety reporting and other GCP activities for trials that are using commercially available products are unlikely to require the same level of intensity as first-in-human studies of new chemical entities. The level of monitoring should be linked to the body of evidence of human safety that exists before the trial commences. Clearly, the engagement of Health Canada, REBs and other stakeholders in the community of interest in this topic (patient advocates, research organizations and the pharmaceutical industry) is important for action in this area.

2. Research ethics board (REB) efficiencies

There has been some progress in Canada in consolidating institutional REBs into regionally based cancer-focused REBs (for example, at the BCCA, in Ontario and in Alberta). In some cases the boards have been consolidated and in others a reciprocity agreement has been reached such that another board becomes the “board of record” for a particular institution. The impact on REB times and on investigators workload has been beneficial: the work of REB submission and response to reviews has been delegated to one institution on behalf of many. In addition, consolidated REBs also increase the enhanced content knowledge in the review process, because specialized review boards are able to recruit appropriate numbers of cancer experts. Engagement with CAREB to examine how these models might be further extended is warranted.

A critical issue for REBs themselves is the burden of work related to safety reporting, processing of amendments, etc. Their growing workload is linked not only to the numbers of trials under their purview, but also to the change in clinical trials regulatory framework discussed above.

Recommendation 4: Reduce non-value-added steps in trial development and conduct.

Cooperative groups, investigators and institutions should review their routine practices in trial development and conduct to identify steps or protocol components that add work and/or cost but little value.

RATIONALE

Clinical trials today are more complex than those a decade ago. Although the changing landscape of clinical research may be driving complexity – biomarker selection and discovery embedded in protocols and the desire to include companion quality of life and economic analyses in trials that might be practice-changing – some of the complexities introduced into trials are non-value added. These steps may relate to entry or exclusion criteria, methods of disease assessment, on-study monitoring, data collection and many more. Their presence in trials may be dictated more by tradition and caution than a requirement to address the study questions.

Beyond the factors associated with trials themselves, cooperative groups, pharmaceutical companies and institutions often deploy many process-related steps in protocol review, approval, initiation and analysis that could more efficiently be done at the same time or not at all. Thus, wherever possible all those engaged in cancer trials must examine where and how they may save time and gain efficiencies in their work.

6.4 Summary

The cancer clinical trials system in Canada is under threat. Multiple stressors have been identified that are affecting multiple levels of the system. Addressing them will require the coordinated approach of multiple stakeholders. The recommended approach should include actions in the areas of pan-Canadian mechanisms to support clinical trials infrastructure and support, clinical trials oversight (regulation and ethical review processes), and reduction in non-added-value work in trial conduct.

Implementing recommendations across these areas will re-invigorate the cancer clinical trials system in Canada and continue to protect patient safety. Within a few years, trial enrolment should substantially increase, as should the numbers of academic-led trials that may change practice. Efficiencies will be enhanced and resources will be deployed more strategically. The importance of cancer clinical trials to the health care system will be underscored by improved patient outcomes in the short term. In the medium to long term, Canada will be a leader in 21st century cancer trials that have as their goals better cancer control, higher rates of survival and an enhanced quality of life for patients.

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Appendix A. Abbreviations and Acronyms

ACF	Alberta Canada Foundation
BCCA	BC Cancer Agency
CAPCA	Canadian Association of Provincial Cancer Agencies
CAREB	Canadian Association of Research Ethics Board
CCRA	Canadian Cancer Research Alliance
CCS	Canadian Cancer Society
CIHR	Canadian Institutes of Health Research
CPTP	Canadian Partnership for Tomorrow Project
CRO	Contract Research Organization
CTA	Clinical Trials Application
CTWG	Clinical Trials Working Group
ECRIN	European Clinical Research Infrastructures Network
FRSQ	Fonds de la recherche en santé du Québec
GCP	Good Clinical Practice
IND	Investigational New Drug
KKS	Coordination Centres for Clinical Trials (Germany)
LRN	Local Research Networks
NCIC CTG	NCIC Clinical Trials Group
NCRN	National Cancer Research Network (U.K.)
NIHR CRN	National Institute for Health Research Clinical Research Network (U.K.)
OCOG	Ontario Clinical Oncology Group
OCRN	Ontario Cancer Research Network
OICR	Ontario Institute for Cancer Research
PD	Pharmacodynamic
PK	Pharmacokinetic
PMH	Princess Margaret Hospital
REB	Research Ethics Board
SAE	Serious Adverse Events
SOP	Standard Operating Procedure
SPOR	Strategy on Patient Oriented Research
SU	External Safety Notice
TFRI	The Terry Fox Research Institute

Appendix B. Ontario Cancer Clinical Trials Enrolment Data, 2004-2009 – Details

Percentage of cancer patients treated at cancer centres recruited to treatment-based clinical trials, Ontario, 2004 to 2009

	REGIONAL CANCER CENTRE												
	All reporting cancer centres	Windsor RCC	London RCP	Grand River RCC (Kitchener)	Juravinski (Hamilton)	Carlo Fidani (Peel)	Odette (Toronto Sunnybrook)	UHN/PMH (Toronto)	MDRCC (Oshawa)	Southeastern RCC (Kingston)	Ottawa RCC	HRSRH/KCP (Sudbury)	Northwestern RCC (Thunder Bay)
2004	Enrollees	58	328	30	433		956	1,484	92	85	432	105	64
	Treated cases	2,186	5,627	1,198	7,147		7,048	7,204	1,361	2,655	6,844	3,094	1,298
	%	2.70%	5.80%	2.50%	6.10%		13.60%	20.60%	6.80%	3.20%	6.30%	3.40%	4.90%
2005	Enrollees	109	385	66	591		901	1,826	118	81	562	158	59
	Treated cases	2,031	4,996	1,605	6,805		6,356	8,091	1,752	2,361	5,641	2,692	1,181
	%	5.40%	7.70%	4.10%	8.70%		14.20%	22.60%	6.70%	3.40%	10.00%	5.90%	5.00%
2006	Enrollees	104	393	80	639		1,147	1,883	60	111	514	80	32
	Treated cases	1,821	4,537	1,873	6,804		5,999	8,679	1,883	2,173	5,006	2,548	1,081
	%	5.70%	8.70%	4.30%	9.40%		19.10%	21.70%	3.20%	5.10%	10.30%	3.10%	3.00%
2007	Enrollees	61	412	109	699		700	2,541	130	98	569	73	77
	Treated cases	1,840	4,837	2,036	6,987		5,944	9,609	2,069	2,074	5,058	2,583	1,114
	%	3.30%	8.50%	5.40%	10.00%		11.80%	26.40%	6.30%	4.70%	11.20%	2.80%	6.90%
2008	Enrollees	66	300	110	567	76	678	1,768	113	58	489	85	82
	Treated cases	1,908	5,794	2,062	7,170	2,571	6,698	7,863	2,488	2,137	5,324	3,342	1,364
	%	3.50%	5.20%	5.30%	7.90%	3.00%	10.10%	22.50%	4.50%	2.70%	9.20%	2.50%	6.00%
2009	Enrollees	85	603	59	644	85	483	1,482	101	72	466	83	123
	Treated cases	1,868	5,245	2,456	7,636	2,906	6,819	8,313	2,706	2,272	5,439	3,421	1,470
	%	4.60%	11.50%	2.40%	8.40%	2.90%	7.10%	17.80%	3.70%	3.20%	8.60%	2.40%	8.40%

Report Date: February, 2010

Data sources: Clinical Trials Program (Ontario Institute for Cancer Research), Cancer Program Scheduling System (PMH), Activity Level Reporting

Appendix C. Trial Complexity Methods and Results

Methods

Protocols and consent forms from 28 NCIC CTG trials were reviewed, 14 from each period (see Table 1). Only trials that were activated in this period were selected. They represented a range of phase I, II, and III projects and were paired so that each 1995 to 2000 study in a given tumour type was matched to a later study of same tumour type and phase.

Phase	Disease	1995–2000 Trial number	Agent(s)	2005–2010 Trial number	Agent(s)
III	Breast (adj)	MA.17	letrozole	MA.32	metformin
III	Colorectal (advanced)	CO.10	FU/FA	CO.20	cetuximab/brivanib
III	Lung	BR.12	marimastat	BR.26	PF-804
III	Ovary (IG)	OV.10	paclitaxel	OV.19	bevacizumab
II	Breast	IND.132	temozolomide	IND.197	foretinib
II	Endometrial	IND.126	letrozole	IND.192	ridaforolimus
II	Melanoma	IND.104	bryostatin	IND.189	IL-21
II	Ovary	IND.116	ISIS5132	IND.185	sunitinib
II	Prostate	IND.111	ISIS5132, 3521	IND.195	SB939
II	Renal	IND.119	troxacitabine	IND.161	triapine
II	Glioma	IND.94	gemcitabine	IND.162	TMZ, RAD001
II	NSCLC	IND.120	troxacitabine	IND.196	foretinib, erlotinib
I	all	IND.101	RPR taxane	IND.188	SB939
I	all	IND.107	BAY12-9566	IND.181	AT9823

General and specific measures of complexity were identified. General measures included number of objectives and protocol pages. Specific measures include number of inclusion/exclusion criteria, whether or not correlative studies were included and number of tests at baseline and on-study. Metrics identified for tabulation for each trial are shown in Table 2.

The following comparisons were made:

- For paired trials of the same design and disease, the differences in numeric metrics were tabulated (the “delta”) and the mean delta (positive or negative) for each metric was tabulated. They were further subdivided by phase I, II and III trials
- Means of numeric metrics were also calculated for “old” (1995–2000) and “new” (2005–2010) trials
- The numbers of old and new trials with certain measures (for example, tumour collection, blood sampling for PK or PD testing, correlative study endpoints) were also described by trial type and by period.

TABLE 2. METRICS ABSTRACTED FROM EACH TRIAL PROTOCOL		
Trial code		
Disease/drugs		
Phase		
General:	Number of objectives	
	Number of protocol pages (to end of references and excluding appendices)	
	Number of main consent form pages	
Endpoint types:	Number of efficacy endpoints	
	Number of other endpoints:	economic QoL correlative (#)
Eligible by histology?		
Number of inclusion criteria		
Number of exclusion criteria		
Tumour collection	Any?	
	If yes:	required? archival? fresh?
Other special collections	Blood?	
	Urine?	
Tests	Number at baseline	
	Number on follow-up on treatment	
Frequency Follow-up on Rx	q 3-4 wks	
	q 5-8 wks	
	q > 8 wks	
Duration of Follow-up	fixed period	
	progression/relapse	
	death	

Results

Mean of the differences seen in measures of paired trials (trials of the same phase and disease in both time periods)

	All trial pairs	Phase III pairs	Phase II pairs	Phase I pairs
No. of objectives	mean of 3 more objectives	mean of 5 more objectives	mean of 2 more objectives	mean of 0 more objectives
No. of protocol pages (to end of references, excluding appendices)	mean of 16.9 more pages	mean of 32.3 more pages	mean of 13.4 more pages	mean of 16 fewer pages
No. of main consent pages	mean of 4.5 more pages	mean of 6.3 more pages	mean of 4.25 more pages	mean of 0 more pages

Means of actual individual trial data by time period

Mean	Trials 1995–2000 n = 14	Trials 2005–2010 n = 14
No. of objectives	3.1 per trial	5.7 per trial
No. of protocol pages	39.5 per trial	53.9 per trial
No. of consent pages	4.8 per trial	9.9 per trial

Protocol endpoints

Mean	Trials 1995–2000 n = 14	Trials 2005–2010 n = 14
No. of efficacy endpoints	1.7	3.4
No. of other endpoints	1.9	4.3

In general, protocols and consent forms in 2005–2010 were longer. In addition, recent trials have incorporated, on average, several more objectives and efficacy and other endpoints.

Correlative studies, biomarkers and tissue

	Trials 1995–2000				Trials 2005–2010			
	All	Phase III	Phase II	Phase I	All	Phase III	Phase II	Phase I
Total	14	4	8	2	14	4	8	2
No. of trials with:								
Correlative studies	7 (50%)	1	4	2	12 (86%)	4	6	2
Tumour tissue collection	5 (36%)	2	2	1	11	4	6	1
Blood collection (for PK or other markers)	6 (43%)	1	3	2	10	4	4	2

Tissue or blood was collected in a higher proportion of phase II and III trials for markers or PK in 2005–2010 compared to 1995–2000. There was no difference in the tissue and blood collection in phase I trials when comparing both periods.

Patient eligibility

Mean numbers of:	Trials 1995–2000 n = 14	Trials 2005–2010 n = 14
Inclusion criteria	17.6	20.1
Exclusion criteria	8.8	14

On average, the recent studies had more inclusion criteria and exclusion criteria.

Molecularly defined disease for patient entry

In the 1995–2000 protocols only one (MA.17) required marker criteria for study entry (ER or PgR positive or unknown). In the trials from 2005–2010, 3 of 14 required marker definition of disease (IND.197, CO.20, IND.196)

Study tests

Mean numbers of:	Trials 1995–2000 n = 14	Trials 2005–2010 n = 14
Baseline tests	22.6	30.4
On study treatment tests	19.4	26.4

The number of tests (blood work, imaging, other measures) at baseline and on protocol therapy was higher on average in the 2005–2010 studies compared to those done a decade earlier.

Follow-up

Follow-up frequency on treatment and after treatment was similar in protocols from 1995–2010 and 2005–2010.

Summary

On almost every metric selected to assess trial complexity, trials initiated in 2005–2010 were more complex than similar trials conducted a decade earlier. The exception was phase I first-in-human trials. In both periods they scored as complex trials with multiple endpoints and tissue and blood collection. In general they were slightly broader in inclusion and exclusion criteria than disease-oriented phase II or III trials from the same periods.

More testing, endpoints, correlative studies, protocol and consent form content in more recent trials required more clinical trials staff and investigator time when compared to similar trials done the decade before.

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