



November 2012



# CANADA'S CLINICAL TRIAL INFRASTRUCTURE:

*A Prescription for Improved Access to New Medicines*

Standing Senate Committee on Social Affairs,  
Science and Technology

The Honourable Kelvin K. Ogilvie, *Chair*

The Honourable Art Eggleton, P.C., *Deputy Chair*





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## ORDER OF REFERENCE

Extract from the *Journals of the Senate*, Tuesday, November 22, 2011:

*The Honourable Senator Ogilvie moved, seconded by the Honourable Senator Frum:*

*That the Senate Standing Committee on Social Affairs, Science and Technology be authorized to examine and report on prescription pharmaceuticals in Canada, including but not limited to:*

- (a) the process to approve prescription pharmaceuticals with a particular focus on clinical trials;*
- (b) the post-approval monitoring of prescription pharmaceuticals;*
- (c) the off-label use of prescription pharmaceuticals; and*
- (d) the nature of unintended consequences in the use of prescription pharmaceuticals.*

*That the committee submit its final report no later than December 31, 2013, and that the committee retain until March 31, 2014, all powers necessary to publicize its findings.*

*The question being put on the motion, it was adopted.*

Gary W. O'Brien  
*Clerk of the Senate*

## MEMBERS

The Honourable Kelvin Kenneth Ogilvie, Chair  
The Honourable Art Eggleton, P.C., Deputy Chair

The Honourable Senators:

Catherine S. Callbeck, Jane Cordy, Jacques Demers, Lillian Eva Dyck, Elizabeth Hubley, Yonah Martin, Judith Seidman, Asha Seth, Josée Verner, P.C., John Wallace

Ex Officio Members:

The Honourable Senators Marjory LeBreton, P.C. (or Claude Carignan) and James Cowan (or Claudette Tardif).

Other Senators who have participated from time to time in the study:

The Honourable Senators Campbell, Hubley, Housakos, Merchant\*, Peterson, Plett, Rivard.

*\* See Minutes of Proceedings - May 9, 2012*

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# EXECUTIVE SUMMARY

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## INTRODUCTION

On 22 November 2011, the Senate adopted an Order of Reference authorizing the Senate Standing Committee on Social Affairs, Science and Technology to examine and report on prescription pharmaceuticals in Canada. The study includes four components, each to be studied separately, which are: the process to approve prescription pharmaceuticals with a particular focus on clinical trials; the post-approval monitoring of prescription pharmaceuticals; the off-label use of prescription pharmaceuticals; and the nature of unintended consequences in the use of prescription pharmaceuticals.

This report is on this first phase of the study, for which the committee heard from witnesses between 28 March and 30 May 2012. Over the course of 11 meetings, the committee heard testimony from Health Canada and Office of the Auditor General of Canada officials, representatives from the pharmaceutical and clinical trial industries, patient advocacy groups, medical, ethical and legal academics and finally, representatives of research ethics boards.

## ISSUES OF CONCERN

The safety and efficacy of new drugs are thoroughly tested in human clinical trials, which are the final stage of drug development. This phase of development provides not only the data that is needed to assess safety and efficacy, but it can also provide, in some instances, early access to new medicines. Unfortunately, the proportion of global clinical trials being conducted in Canada has declined over the past decade. For companies seeking clinical trials the major factor, beyond the quality offered by clinical trial centres, is cost. Although financial factors such as currency, taxes and tax credits are elements of the cost

consideration, they are largely beyond the committee's scope in this study. However, time is also an important element of cost, and while it is essential that trials be conducted thoroughly, the committee identified a factor that significantly impacts the time required to start up clinical trials in Canada - the absence of a standardized approach to research ethics review. This deficiency results in companies having to submit multiple research proposals to meet the requirements of research ethics boards at numerous trial sites. Thus, considerably more time and effort is needed to get clinical trials designed, approved and started in this country. As a result, the cost of testing drugs in clinical trials is high in Canada, making it less desirable to the industry as a destination for clinical trials.

Canada's role in clinical trials of new drugs is critically important for attracting research dollars in the short term and improving access to new drugs in the longer term. The committee heard from witnesses about their concerns regarding clinical trial infrastructure and their suggestions for improvements. In response, this report makes recommendations that address issues such as: enhanced leadership of the federal government; transparency of the clinical trial process; standards and accreditation of research ethics review; barriers to patient recruitment; inclusion of vulnerable sub-groups of the population; drugs for rare diseases; and, the need to assess patent protection and tax incentives.

In the context of leadership, the committee is calling on the federal government to take initiatives that will position Canada more favourably on the global stage as a preferred jurisdiction for clinical trials. To that end, the committee recommends the creation of a National Framework for Coordinating Clinical Trials that will help to attract clinical trials



to this country. Further, it envisions this Framework as one that will promote the importance of clinical trials and the benefits of participating in them. The Framework will also identify a point of contact between the pharmaceutical industry and the research community.

The committee heard considerable testimony regarding the lack of transparency and the need for increased public disclosure about ongoing clinical trials. It calls on the Minister of Health to authorize the necessary changes so that Health Canada has the authority to require the registration of a comprehensive set of clinical trial data on a publicly accessible database. This would include foreign trials that support submissions for drug approval in Canada. It is essential that the new requirements be strictly enforced.

The need for standardization of the research ethics review process and the accreditation of research ethics boards was raised frequently during the study. Ethics review is essential for all research involving humans. The committee heard from many witnesses that the ethics review of clinical trials lacks consistency since many trial sites can establish their own research ethics review board and can operate under their own guidelines. As such, the research ethics review process is in need of standardization. The committee acknowledges that there have been attempts in this regard but it suggests that success will only be achieved if all relevant stakeholders are involved in the process. Once research ethics review has been standardized, an accreditation program for research ethics boards must be developed. Additionally, the committee urges that adherence to such standards must be enforced with a requirement that ethics review of clinical trials must be obtained from an accredited research ethics board.

In terms of facilitating and increasing patient recruitment into clinical trials, witnesses spoke of the benefits associated with the creation of research

networks. The committee recommends that the National Framework for Coordinating Clinical Trials promote the creation of research networks and provide guidance on centralizing ethics review and establishing internal databases to facilitate patient recruitment.

Further, witnesses described how research networks can be helpful in promoting inclusion of vulnerable sub-groups of the population in clinical trials. It is essential that this information be available to Health Canada when it assesses new drugs for safety and efficacy. The committee calls for changes to the drug regulatory regime such that there is a requirement for clinical trial design to reflect the population that can reasonably be expected to consume the drug once it is on the market. Further, market approval must only be granted by Health Canada if clinical trial data is available about all relevant population sub-groups.

The issue of rare diseases and the need for specific policy measures aimed at encouraging drug development and improved drug access for patients with rare diseases (an Orphan Drug Policy), were also examined by this committee. The committee notes that the issue of an Orphan Drug Policy has been raised previously at this committee, most recently during its study on the 2004 Health Accord, and that Health Canada has recently taken action. On 3 October 2012, the Minister of Health announced the creation of an Orphan Drug Framework to encourage research and development as well as facilitate authorization of new drugs. This report calls on the Minister of Health to ensure that this new framework addresses additional concerns such as clinical trial design and reducing or eliminating user fees. In addition, the National Framework for Coordinating Clinical Trials must promote Canada as a preferred site for conducting clinical trials for orphan drugs and facilitate the work of stakeholders to develop strategies for maximizing patient recruitment into such trials.



Representatives of the pharmaceutical industry voiced frustration over patent protection for prescription pharmaceuticals and emphasized that Canada has fallen behind other countries in terms of patent life. They suggested that the shorter patent life granted in Canada compared to other jurisdictions is a disincentive to pursue innovation in this country. In terms of tax incentives, these witnesses suggested that recent changes to the Scientific Research and Economic Development Tax Incentive Program, which reduced the general tax credit available to industry from 20% to 15%, will similarly discourage clinical trial activity in Canada. As potential deterrents to clinical trial investment, the committee would like these concerns addressed comprehensively by an expert advisory committee.

Officials from the Office of the Auditor General, which reported on Health Canada's performance regarding the regulation of pharmaceuticals in November 2011, discussed their concerns about Health Canada's role in clinical trial regulation. In its report, the Auditor General highlighted issues with: Health Canada's inspections of clinical trial sites; the department's handling of adverse event reports from clinical trials; and, the transparency of authorized clinical trials. The committee wants the recommendations of the Auditor General addressed immediately. It is also recommending that Health Canada increase its inspection activity in order to meet its target of conducting inspections of 2% of clinical trial sites and accelerate the implementation of electronic reporting of adverse drug reactions so that manual data entry can be eliminated. The Auditor General's report had raised these concerns, but had not issued recommendations related to them.

Several witnesses mentioned that the *Food and Drugs Act* requires updating and that this has been attempted in the past. The committee heard, for example, that the penalties provided in the Act are not sufficient to deter non-compliance and

that they should be increased. It also heard that additional authorities should be granted to the Minister of Health in order to increase the level of transparency in terms of the information that the department can make available to the public. The committee recommends that the necessary statutory changes be pursued in order to modernize drug regulation in Canada.

Finally, the committee would like Health Canada to regularly monitor and publicly report on the impact that implementing these recommendations has on clinical trial activity in Canada.

## CONCLUSION

Canada can no longer rely on an international reputation for conducting good quality research to attract clinical trials to this country. Declining clinical trial activity means lost opportunities for Canada to be a global leader in drug innovation. It must act now to improve clinical trial infrastructure so that efficiencies can be realized and this critical phase of research can proceed swiftly. While the committee acknowledges that attracting research dollars by improving the clinical trial infrastructure is important, it emphasizes that patient safety cannot be compromised.

This committee is calling upon the federal government to bring Canada's clinical trial requirements and obligations in line with other countries and to engage all stakeholders so that the needed infrastructure improvements can be accomplished. Implementation of the recommendations in this report will result in an increase in Canada's global competitiveness in the clinical trial sector and ultimately to improved access to innovative medicine for Canadians.





# 1. INTRODUCTION

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On 22 November 2011, the Senate adopted the following Order of Reference:

That the Senate Standing Committee on Social Affairs, Science and Technology be authorized to examine and report on prescription pharmaceuticals in Canada, including but not limited to:

- (a) the process to approve prescription pharmaceuticals with a particular focus on clinical trials;
- (b) the post-approval monitoring of prescription pharmaceuticals;
- (c) the off-label use of prescription pharmaceuticals; and
- (d) the nature of unintended consequences in the use of prescription pharmaceuticals.

That the committee submit its final report no later than December 31, 2013, and that the committee retain until March 31, 2014, all powers necessary to publicize its findings.

As suggested by the Order of Reference, the study includes four components, to be conducted individually in four separate phases. From 28 March until 30 May 2012, the committee heard from witnesses on the first phase of this study; clinical trials in the context of drug approval with a view to determining whether Canada should change the way clinical trials are approached in this country.

Over the course of 11 meetings, the committee heard testimony from officials from Health Canada as well as the Office of the Auditor General of Canada, representatives from the pharmaceutical and clinical trial industries, patient advocacy groups, medical, ethical and legal academics and finally representatives of research ethics boards.



## 2. CONTEXT-THE ROLE OF CLINICAL TRIALS IN THE DRUG APPROVAL PROCESS

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### A. HEALTH CANADA'S RESPONSIBILITY FOR DRUG REGULATION

All pharmaceuticals, or drugs, must be approved by Health Canada before they can be marketed in this country. The *Food and Drugs Act* (the Act) defines “drug” as:

- Any substance or mixture of substances manufactured, sold or represented for use in
- the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
  - restoring, correcting or modifying organic functions in human beings or animals, or
  - disinfection in premises in which food is manufactured, prepared or kept.<sup>1</sup>

Therefore, any substance that makes a health claim is considered a drug under the Act.

Health Canada uses the following categories to classify drugs for human use: prescription drugs, non-prescription drugs, radiopharmaceuticals, and biologics. These categories are described below.

#### i. Prescription Drugs

Prescription drugs are those for which an order from a practitioner stating the amount of that drug and for whom the drug is intended is required. This category can include patented and generic prescription drugs, drugs required for extraordinary use, and drugs requiring priority review.

#### ii. Non-prescription Drugs

Non-prescription drugs, also often referred to as over-the-counter drugs, are those which can be

sold without an order from a physician but do not include radiopharmaceuticals and biologics. Natural health products are also included within this group although they are regulated under their own *Natural Health Products Regulations*.

#### iii. Radiopharmaceuticals

Radiopharmaceuticals are radioactive drugs that can be used for diagnostic purposes as well as treatment. For example, there are radiopharmaceuticals that are used in diagnostic imaging and others that can destroy cancerous tissues.

#### iv. Biologics

Biologics are products used in the prevention, treatment or cure of diseases or injuries in humans and include vaccines, products of biotechnology, viruses, blood and its derivatives, proteins, etc. Due to their nature, more information must be provided to the regulator pertaining to the chemistry and manufacturing of these products than is required for traditional pharmaceuticals.



<sup>1</sup> *Food and Drugs Act*, section 2.



## B. OVERVIEW OF DRUG APPROVAL WITHIN HEALTH CANADA

All regulatory and enforcement activities, and most policy activities, associated with pharmaceuticals are conducted within the Health Products and Food Branch (HPFB) of Health Canada. Directorates within HPFB include one each for food and veterinary drugs and four for drugs, namely; the Biologics and Genetic Therapies Directorate, the Marketed Health Products Directorate, the Natural Health Products Directorate and the Therapeutic Products Directorate (TPD). HPFB also includes an Inspectorate which is responsible for compliance and enforcement activities associated with drugs and medical devices.

Reviews of prescription drug submissions are carried out within the following four bureaus of TPD depending on the type of drug being reviewed: the Bureau of Cardiology, Allergy and Neurological Sciences; the Bureau of Gastroenterology, Infection and Viral Diseases; the Bureau of Metabolism, Oncology and Reproductive Sciences; and the Bureau of Pharmaceutical Sciences. The drug approval process follows the steps laid out below for new drugs, with some modifications allowed for other categories of drugs.

### 1. Approval Process for New Drugs

#### a. Pre-submission Meeting

Once the developer and/or manufacturer of a new investigational drug is confident that it has produced a compound that can successfully gain Health Canada's approval, a pre-submission meeting is encouraged by TPD, but is not essential. The pre-submission meeting between TPD and the drug's sponsor provides an opportunity to notify the TPD reviewers of the upcoming submission and allows them to become familiar with it. It also allows the directorate to make adjustments to their review resources in order to accommodate the new submission. For

the sponsor of the drug, the meeting can identify submission package deficiencies or concerns, including concerns relating to the clinical trials which form the basis of safety and effectiveness assertions. The pre-filing meeting allows the sponsor the opportunity to optimize their submission package and reduces the burden on TPD by minimizing the number of submissions that must be returned as deficient.

#### b. Submission Filing

This is the first step in the approval process. Submission filing involves submitting to TPD a New Drug Submission, or NDS. The NDS must contain information that: describes the drug<sup>2</sup>; asserts its quality<sup>3</sup>; summarizes investigational studies and clinical trials pertaining to the drug including adverse reactions observed during clinical trials, and finally includes raw data from pre-clinical studies.

#### c. Screening

When TPD receives an NDS, it first screens the package to ensure that the submission is complete and in the proper format. Health Canada aims to meet a target of 45 calendar days for screening NDSs. Upon a successful screening, the submission proceeds in the approval process to the technical review. If, however, deficiencies are identified in the submission filing, the sponsor is sent a screening deficiency notice to which it has 45 calendar days to respond and address the noted deficiencies. Unsuccessful candidates are sent a Screening Rejection Letter.

#### d. Technical Review

Upon successful completion of the screening process, the submission passes to the technical review component. TPD has established a target of 300 days for this phase of the drug approval process. Evaluation of the submission involves a detailed review of all the material submitted in

<sup>2</sup> Description of the drug can include such elements as its structural formula, how it relates to other drugs, route of administration, dosage, indications and contraindications, proposed label and product monograph and any prior related submission.

<sup>3</sup> Quality of the drug can be established through manufacturing details, properties, impurities, reference standards, stability, etc.



the filing in order to produce a comprehensive analysis of the quality, safety and efficacy of the candidate drug and ensures that the risks associated with taking the drug do not outweigh the benefits. Clinical trial data is central to determining the safety/efficacy profile for a candidate drug. At any point during the review TPD can request clarification, re-evaluation or expansion of the submitted material.

There are several possible outcomes from this review. Similar to the situation described above for screening, a reviewer may find deficiencies in the submission. In this case, a Notice of Deficiency is issued to the sponsor and the review process stops. A sponsor must respond to all deficiencies identified within 90 calendar days. Once TPD receives the response, the submission must once again be screened, and if acceptable the review process can be reinstated. If TPD finds that the response is insufficient, it will notify the sponsor that they must withdraw their submission. This is done with a Notice of Deficiency-Withdrawal letter. At the completion of the review process, if TPD finds that the submission is incomplete or deficient, it can issue a Notice of Non-compliance which lists all deficient or incomplete aspects of the submission. The sponsor has 90 calendar days to respond and, if acceptable to TPD, the submission can be screened and reviewed again. If the response is unacceptable, or if the sponsor does not respond, TPD can issue a Notice of Non-compliance-Withdrawal letter and the submission will be considered withdrawn. Sponsors issued rejection letters or notices of non-compliance or deficiency can submit Requests for Reconsideration to TPD.

Successful submissions are issued a Notice of Compliance (NOC) which certifies that the drug complies with all requirements of the Act and its regulations. At this time a Drug Identification Number (DIN) is also issued which authorizes the drug to be marketed in Canada. The DIN

is an eight digit number which identifies: manufacturer; product name; active ingredient(s); strength(s) of active ingredient(s); pharmaceutical form; and method of administration (injected, inhaled, swallowed, etc.). Finally, Health Canada issues a Notice of Decision and a Summary Basis of Decision for each approved drug outlining its risk-benefit analysis. These are made publicly available on Health Canada's website, although no information is made available regarding unsuccessful submissions.

When TPD issues a NOC for a new drug, the approval extends only as far as the specifics for which the manufacturer initially requested approval. The dosing information, route of administration, labelling, formulation, method of manufacture and indications for use are specified in the NOC and any deviation from these requires a new approval, in which case the manufacturer must file a Supplemental New Drug Submission.

## 2. Variations of the Approval Process for Certain Categories of New Drugs

Under certain specified conditions, the approval of drugs can be shortened from the standard 300 day review. Submissions for generic versions of new drugs, for example, include material similar to that required for a NDS except that there is not the same need for clinical trials since a pharmaceutically equivalent product is already on the market. Instead, there is a focus on chemistry and manufacturing information to ensure the quality and equivalence of the drug. Submissions for generic drug approval include bioavailability data as opposed to traditional clinical trial data.

Health Canada also provides expedited review for drugs for serious and life-threatening conditions. Priority review of a submission may be granted for drugs that are intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating illnesses



or conditions where there is either no product currently marketed in Canada or the new product represents a significant increase in efficacy and/or significant decrease in risk such that the overall risk-benefit profile is better than that of existing therapies. Priority reviews are subject to the same requirements as NDSs but are processed more quickly, whereby the target for screening is reduced to 25 days and the target for the review is 180 days. There is also a process for expedited review in which the threshold of evidence required under the NDS process is reduced, that is, that the amount of clinical trial evidence may be reduced. Under this category of drug review Health Canada can issue a NOC with Conditions which requires that the manufacturer continue to collect data on the drug's safety and effectiveness, essentially supplementing the clinical trial evidence base to bring it up to the standards required for NDSs. Similar to priority review, the NOC with Conditions process can be applied to drugs for serious and life-threatening conditions where there is either no product currently marketed in Canada or the new product represents a significant increase in efficacy and/or significant decrease in risk such that the overall risk-benefit profile is better than that of existing therapies. This process allows for a screening target of 25 days and a review target of 200 days.

There is the possibility that new drugs may be approved by Health Canada when the safety, efficacy and quality data on them is limited. Under extraordinary circumstances a drug may be given market authorization with less information from clinical trials than would normally be permitted. These circumstances include emergencies such as exposure to a chemical, biological, radiological or nuclear substance which requires action to treat or prevent the resulting condition. The nature of these circumstances makes it impossible to design and conduct controlled clinical trials to first test the new drug. Therefore, Health Canada's Extraordinary Use New Drug policy allows approval of these drugs with little or no clinical trial data.



### 3. Drug Approval within Health Canada's Biologics and Genetic Therapies Directorate

The approval of biologics, radiopharmaceuticals and genetic therapies is carried out within the Biologics and Genetic Therapies Directorate (BGTD) of HPFB and the process is similar to that for new drugs within TPD, with some differences due to the unique nature of these products. Examples of products regulated by BGTD include cells, tissues and organs (for transplant), vaccines, blood and blood products, gene therapies, and radioactive pharmaceuticals, or radiopharmaceuticals.

Before a biologic can be considered for approval, sufficient scientific evidence must be collected to show that it is safe, efficacious and of suitable quality, as is the case with other drug submissions. Biologics differ from other drugs for human use, however, in that they must include more detailed chemistry and manufacturing information than is required for other drug submissions. Additional information is required for these products in order to ensure their purity and quality because they are more susceptible than other classes of drugs to contamination and variation from one production batch to the next. For example, detailed information about the manufacturing process must be submitted and the manufacturing facility is inspected to assess the production process since



these aspects also have a significant impact on the safety and efficacy of the product.

As with other classes of drugs described above, biologics and genetics therapies are granted NOCs and DINs once approved by BGTD. However, marketing of these drugs differs from the other drug categories in that lot batches must be indicated on the packaging. In addition, lots are tested for purity and the frequency of the testing depends on the risk category of the drug.

#### 4. Access to Unapproved Drugs

TPD offers a Special Access Programme (SAP) for drugs not approved for sale in Canada. SAP allows practitioners to request access to an unapproved drug for patients with serious or life-threatening conditions on a compassionate or emergency basis in those instances where conventional therapy is not available, has failed or is unsuitable. Drugs accessed through SAP have not been reviewed for safety, efficacy or quality and practitioners are responsible for reporting on the results from its use, including adverse reactions. TPD emphasizes that the SAP is not a mechanism by which manufacturers can circumvent the drug approval process.

### C. REGULATION OF CLINICAL TRIALS OF INVESTIGATIONAL DRUGS

As noted above, considerable information is required when submitting a drug for approval to Health Canada. The submission must include details of pre-clinical trials, which involve testing the effects of the investigational drug on animals, in tissue cultures or in cell cultures. This pre-clinical stage of testing is essential so that as much information as possible can be collected on a drug's effectiveness and toxicity before it is tested in humans. Following the pre-clinical stage, if positive results were obtained, the substance proceeds to clinical trials in humans, which are conducted in various phases designed to thoroughly test it for

safety (relative to harm) and efficacy. The human testing spans three or four phases:

- Phase I – Involves a small number of healthy subjects to test the toxicity, absorption, distribution and metabolism of the drug.
- Phase II – Involves trials with a larger set of individuals suffering from the condition for which the drug was developed, to test efficacy and safety.
- Phase III – Involves a greater number of people also with the condition in question, to test the drug's performance in relation to a placebo and/or standard therapy.
- Phase IV – Involves monitoring an approved drug for adverse events in the general population or within a specific sub-population.

Part C, Division 5 of the *Food and Drug Regulations* pertains to clinical trials. Before any trials of unauthorized drugs can be conducted in humans, the manufacturer or sponsor of an investigational drug must apply to TPD's Office of Clinical Trials (OCT) for authorization. The clinical trial regulations aim to ensure: the safety of the participants; the integrity of the study; the validity of the data; and strict controls over use of an unapproved drug. Clinical trials that must obtain authorization include phases I, II and III trials, comparative bioavailability trials, studies using approved drugs where the dosage, method of administration or indication for use is different from the specifics indicated in the NOC, trials studying specific population groups for whom the drug is not currently approved for use and trials pursuant to NOC/c requirements. Phase IV clinical trials do not require authorization from OCT provided they are conducted within the parameters of the NOC.

Sponsors seeking authorization must submit a clinical trial application (CTA) to the OCT which specifies: the sponsor of the trial and



the Investigator involved; the goal or intent of the clinical trial; documentation supporting the objectives of the clinical trial including its protocols; pre-clinical data in support of using the drug within the context of the proposed trial; and data in support of the drug's quality (chemistry and manufacturing). Although a sponsor does not have to have received approval from a research ethics board at the time of application submission, an attestation to such an approval must be submitted to OCT before the trial can get underway. Changes to an approved clinical trial must be approved before such changes can be implemented by submitting a Clinical Trial Application-Amendment.

In much the same way as applications for drug submissions are reviewed, OCT verifies the completeness of the submission (screening) and can issue requests for clarification or can reject the application by issuing a Screening Rejection Letter. CTAs that proceed to review, once any requested additional information has been submitted, can then be authorized by issuance of a No Objection Letter if Health Canada finds that the proposed protocol is scientifically sound and there is no undue risk to participants. Alternatively, CTAs may be rejected with a Not Satisfactory Notice. OCT has set a target of 7 days for review of CTAs for some Phase I trials and comparative bioavailability trials, while the regulations set a default of 30 days for all other CTAs. That is, if there has not been an issuance of a Not Satisfactory Letter within 30 days of the CTA submission, then the trial may proceed by default.

Under the clinical trial regulations, all clinical trials for investigational drugs must adhere to Good Clinical Practices including ethics review, and there is a requirement to maintain and retain records as well as report all serious unexpected adverse reactions to Health Canada.

## D. CLINICAL TRIALS OF INVESTIGATIONAL DRUGS WITHIN THE BROADER CONTEXT OF CLINICAL RESEARCH

Clinical research is defined by the Canadian Institutes of Health Research (CIHR) as “research with the goal of improving the diagnosis, and treatment (including rehabilitation and palliation), of disease and injury; and improving the health and quality of life of individuals as they pass through normal life stages” and includes “research on, or for the treatment of, patients.” Within this broad category of research, the CIHR defines a clinical trial as “a prospective controlled or uncontrolled research study evaluating the effects of one or more health-related interventions assigned to human participants.”<sup>4</sup>

Thus, clinical trials encompass more than just investigational drugs and can include any health-related intervention such as medical devices or techniques with medical or surgical applications. The definition of clinical trial in the *Food and Drug Regulations* relates strictly to unapproved drugs, which is the focus of this study. *The Food and Drug Regulations* define a clinical trial as:

“an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.”<sup>5</sup>

<sup>4</sup> CIHR definitions are derived from CIHR's Glossary of Funding Related Terms available at: <http://www.cihr-irsc.gc.ca/e/34190.html>

<sup>5</sup> *Food and Drug Regulations*, C.05.001



Clinical trial design traditionally includes a control arm and a treatment arm to which participants are randomly assigned, and both participants and those involved in conducting the trial are unaware as to which arm people have been assigned. This constitutes the double-blind, randomized, controlled study. The control arm of the study could be placebo, standard therapy or other supportive measures.

Clinical trials in which drugs that have been developed but require testing in human subjects thus comprise only a portion of the clinical research carried out in Canada. They are, however, the only category which is subject to federal regulations under the *Food and Drugs Act*. This is because pharmaceuticals must be approved by Health Canada before they can be sold in this country. Health Canada therefore requires that

sponsors of clinical trials for unapproved drugs apply for authorization from the regulatory agency<sup>6</sup> and are subject to the regulatory requirements set out in Part C, Division 5 of the *Food and Drug Regulations*.

A significant proportion of clinical research in Canada, as much as 80%, is publicly funded through the CIHR and the majority of that research is carried out in academic institutions and hospitals throughout the country. However, clinical trials (phases I through III) of investigational drugs are exclusively funded by pharmaceutical companies. In addition, about two-thirds of clinical trials of investigational drugs is carried out within the community at privately owned and operated facilities, as opposed to academic or hospital settings.

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<sup>6</sup> Clinical trials of investigational medical devices are also subject to regulation under the *Medical Devices Regulations*.





## 3. CLINICAL TRIALS IN CANADA-ISSUES OF CONCERN

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### 1. DECLINING CLINICAL TRIAL ACTIVITY

Health Canada's *Therapeutic Products Directorate Drug Submission Performance Annual Report-January-December 2010* reveals that the number of clinical trial applications (excluding the bioequivalence trials for generic drugs) submitted to the directorate has been steadily declining since 2007 from 776 to only 596 in 2010. The number fell further to 537 in 2011. Indeed, the committee heard from the Canadian Stroke Consortium that there has been a shift away from large pharmaceutical trials due to the complexity of setting them up. Of all clinical trial applications, approximately 20% relate to phase I trials, 37% to phase II trials and 43% to phase III trials. As much as 80% of phase II and III trials are multinational with foreign sponsors, and for clinical trials in Canada there are usually multiple sites across the country. Health Canada estimates that there are as many as 4,000 active clinical trial sites in Canada at any one time.

In 2010, the pharmaceutical industry invested \$110 billion in research and development globally, of which only \$1.3 billion was in Canada, and of that about \$1 billion was invested in clinical trials. While clinical trials were frequently described as a global activity, stakeholders from the pharmaceutical industry (eg. Rx&D and BIOTECanada) cited speed, cost and quality as critical factors in determining which countries should host clinical trials of their investigational drugs. They emphasized that Canada has many strengths such as a highly trained workforce, world class investigators, a good standard of medical care and a heterogeneous population which is desirable for testing new drugs. These aspects speak to the high quality of clinical trials that the drug industry

expects in Canada. However, with respect to cost and speed associated with clinical trials, Canada is lagging behind many other countries.

Brazil, Russia, India and China were cited as countries that the pharmaceutical industry has looked to to host clinical trials due to the vast population base from which to draw participants and the reduced operating costs associated with running clinical trials in those countries. However, it was pointed out that these countries have presented challenges as well. In Brazil, standard of care is lacking and drug companies have been asked to cover health care costs for participants outside of those associated with the condition for which the drug is being tested. In China, the barrier relates to employing people to run clinical trials, in that it is difficult to find and retain people who speak English and who are knowledgeable of the global environment. India presents a challenge to the pharmaceutical industry due to its policy to purchase only generic products. As a result, industry's desire to invest in R&D in that country is reduced. Russia was described as being very disciplined in pursuing clinical trials and to improving speed, cost and quality.

While the quality of clinical trials has always been high in Canada, the drug industry suggested that this is no longer sufficient to give Canada a competitive advantage. Other developed countries have caught up to Canada in this regard as they have realized the benefits of increased clinical trial activity in their jurisdictions. The aspects of cost and speed were described as aspects where Canada falls short and are reasons for the declining clinical trial activity in this country. The high cost and slow implementation of clinical trials was attributed



to the lack of a clinical trial infrastructure in Canada. For example, BIOTECCanada informed the committee that companies frequently have a finite amount of cash with which to accomplish a given phase of their clinical trials, making it necessary that the company carry out the trials in a country where the start-up time is optimal. These aspects are discussed further under the section on research ethics review.

## 2. TRANSPARENCY-REGISTRATION OF CLINICAL TRIALS

In 2004 the International Committee of Medical Journal Editors (ICMJE) issued a statement that in order to be considered for publication in any of the member journals, a clinical trial would have to be registered in a publicly accessible trials registry that met specified criteria.<sup>7</sup> The “clinical trials” referred to by the ICMJE are similar to the CIHR definition of clinical trial. The statement defines a clinical trial as:

“any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome.”<sup>8</sup>

Medical interventions include drugs, surgical procedures, devices, behavioural treatments, process-of-care changes, etc. Phase I clinical trials are exempt from this policy. The ICMJE indicated that an acceptable registry must include at minimum: a unique identifying number, a statement of the intervention and comparison studied, a statement of the study hypothesis, definitions of the primary and secondary outcome measures, eligibility criteria, key trial dates

(registration date, anticipated or actual start date, anticipated or actual date of last follow-up, planned or actual date of closure to data entry, and date trial data considered complete), target number of participants, funding source, and contact information for the principal investigator. It should be noted however that the ICMJE does not include trial results in its list of required data for registration. Regardless of the registration specifics of the ICMJE statement, several witnesses stated that the drug industry is not interested in publishing all the clinical trials it conducts.

In 2005 the World Health Organization (WHO) indicated its support for the requirement to register clinical trials by developing worldwide standards for trial registration under its International Clinical Trials Registry Platform (ICTRP). The ICTRP also aims to facilitate prospective registration of all clinical trials by providing a portal of entry to acceptable registries. The WHO standards for registration include 20 items of information for each clinical trial. In the United States (U.S.), the *Food and Drug Administration Amendments Act* of 2007 implemented a requirement for registration of all clinical trials (except Phase I) within 21 days of commencement. The registration must include information about the target number of people for enrolment, where the trial is located, the study design, contact information, the expected duration of the trial and outcome measures including results. The registry in the U.S. is called ClinicalTrials.gov which is run by the National Library of Medicine. All clinical trials performed in the European Union (EU) must be registered in a database called EudraCT. EudraCT is a confidential database of information on the content, commencement and termination of all clinical trials in the EU. The database was established in accordance with Directive 2001/20/EC, and is managed by the European Medicines Agency (EMA). Clinical trial information is made public through the EU Clinical Trial Register which contains information extracted from EudraCT.

<sup>7</sup> ICMJE, “Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication”, October 2004, available at: [http://www.icmje.org/2004\\_urm.pdf](http://www.icmje.org/2004_urm.pdf)

<sup>8</sup> *Ibid*, page 10.



There is no requirement in the *Food and Drugs Act* or Division 5 (Clinical Trials) of the *Food and Drug Regulations* to register clinical trials in Canada. Health Canada informed committee members that since 2007 it has encouraged clinical trial sponsors to make the data available by posting on publicly accessible registries recognized by the WHO but that it has no authority to compel this transparency. Department officials acknowledged that there is a global consensus that registration of study protocols and disclosure of clinical trial results are key to improving access to clinical trial information in order that patients and health care professionals are better able to make informed decisions.

Health Canada has been exploring options with regard to implementing greater transparency, including requiring clinical trial registration. The committee was told that proposed legislation in 2008, Bill C-51, contained authorities that would have permitted the introduction of required registration of clinical trials; however it did not progress beyond second reading in the House of Commons. Since that time, the department has continued to voice its support for clinical trial registration and has consulted with stakeholders on options to achieve it.

In its fall 2011 report, the Office of the Auditor General (OAG) assessed Health Canada's progress at increasing the level of transparency regarding clinical trials. The report noted the department's commitment to increasing public access to information about authorized clinical trials but confirmed that there had been no policy change in this regard. Further, the report highlighted that public access to an official listing of authorized trials would allow Canadians a way of verifying whether a trial had been authorized or not and assist potential participants in making fully informed decisions.<sup>9</sup>

In its testimony to the committee, the CIHR discussed the *Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans*, which was revised in December 2010 (the TCPS2). Under the TCPS2, all clinical trials funded by, or conducted within an institution receiving funds from, the CIHR must be registered in a public registry before the first participant is recruited. However, members heard that this is not adequate to ensure registration of clinical drug trials for two reasons. First, drug trials of unapproved drugs are exclusively funded by industry and frequently conducted in private facilities thus outside of the jurisdiction of CIHR. Secondly, CIHR has no means of enforcing the TCPS2.

Another issue of concern that was raised by some witnesses had to do with CIHR's 2011 issuance and subsequent withdrawal of its policy on clinical trial registration entitled *Policy on Registration and Results Disclosure of Controlled and Uncontrolled Trials*. Witnesses voiced concern about CIHR's removal of the policy within months of announcing it, and suggested that replacing it with the TCPS2, which pre-dated the clinical trial registration policy, was insufficient as they described it as being more vague on the specifics of registration. Ann Silversides, an independent health policy journalist, described the withdrawal of the policy as a lost opportunity for increased transparency.

Representatives from the pharmaceutical industry suggested that there is no need to implement a registration requirement in Canada. They indicated that this would be a duplication of efforts given the requirements that already exist in the U.S. and the EU, and the global nature of clinical trials such that clinical trials registered in these jurisdictions would likely have Canadian sites. These stakeholders also voiced concern with the amount of information that should be included in the registry, stating that there are proprietary issues when dealing with the discovery of new therapeutic substances.

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<sup>9</sup> Office of the Auditor General of Canada, Chapter 4, "Regulating Pharmaceutical Drugs – Health Canada," *2011 Fall Report of the Auditor General of Canada*.



Industry witnesses reinforced their support for the TCPS2 and also indicated that their commitment, as members of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), to the *Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases*.<sup>10</sup> This Joint Position states that members of IFPMA agree to register clinical trials, although there are fewer information items to be included than are required under the WHO standards. It was argued that several of the items required under the WHO standards have a proprietary component, and therefore they should not be required to release that information publicly. As well, the IFPMA Joint Position states that companies may register their trials on their own company websites, which IFPMA can make available through a portal, and that trial results need only be posted within one year of the drug being approved for use within at least one country.

In contrast, most other stakeholders urged a change to the Canadian requirements, and requested that clinical trial registration be mandatory in this country, as it is in most other developed countries. Among the stakeholders who support this approach were patient advocates, health professionals, academics, health researchers, ethical and legal specialists, who spoke of the need not only to make clinical trial registration mandatory, but that registration should include all aspects of the trials such as trial design, manner of patient recruitment, data collection approach, as well as all results and their analysis. Mandatory registration of a comprehensive set of information was described as essential to enable patients and health providers to make informed decisions, to increase access to new medicines for patients seeking options, and for academics to perform comprehensive analyses of all trial data in order to produce informed benefit/risk profiles for new drugs.

The requirement to register clinical trial information could extend to providing updates on trials that have been prematurely terminated, or truncated, and on the removal of participants from ongoing trials. The committee heard that this is necessary in order to reduce the amount of information that companies chose not to disclose. Witnesses offered examples of trials that had been truncated and from which patients had been dropped, due to negative results. By holding back such information, the clinical trial data that was submitted to regulatory authorities for drug approval presented a more favourable benefit/risk profile than would have been the case had all information been made available to them. However, the committee was told that this additional information is valuable not only for a more accurate reflection of the benefits versus the risks but it can also provide specifics on the population base for whom a drug may show more benefits by analysing those individuals eliminated from trials. It can also reduce duplication of research efforts by registering failed trials. Witnesses also explained that while there may be a lot of information currently registered on clinical trial sites, as emphasized by industry stakeholders, that information is often incomplete, and in some cases, inaccurate.

The pharmaceutical industry suggested in its testimony about clinical trial registration that there are proprietary constraints on disclosing some of the information items that many stakeholders have insisted should be included as part of the desired transparency. However, as other jurisdictions have implemented mandatory registration of several of the contested information items, and Health Canada voiced its support for such a requirement, it would seem that this concern could be resolved. In fact, the committee was told that the barriers to transparency were primarily institutional within the department and that despite Health Canada's claim

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<sup>10</sup> The IFPMA Joint Position is available at: [http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/EN/November\\_10\\_2009\\_Updated\\_Joint\\_Position\\_on\\_the\\_Disclosure\\_of\\_Clinical\\_Trial\\_Information\\_via\\_Clinical\\_Trial\\_Registries\\_and\\_Databases.pdf](http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/EN/November_10_2009_Updated_Joint_Position_on_the_Disclosure_of_Clinical_Trial_Information_via_Clinical_Trial_Registries_and_Databases.pdf)



to support greater transparency, there have been few measures taken to implement it.

### 3. THE SYSTEM OF RESEARCH ETHICS REVIEW

Most clinical trials approved by Health Canada, primarily phase II and III, are multi-national, and within the Canadian arm of approved clinical trials there are often several sites across the country. The committee heard that there could be upwards of 4,000 active clinical trials sites in the country testing almost 700 new drugs. However, despite the similarities of clinical trials between sites for a given entity and despite being subject to federal regulation, clinical trials were described as occurring within “silos”. Each clinical trial site operates independently, is limited to its patient population, and is restricted to ethics review within its own institution.

Canada’s clinical trial regulations (Part C, Division 5 of the *Food and Drug Regulations*) stipulate that approval is contingent on clinical trial protocols receiving approval from the research ethics board of each site at which the trial is to be conducted. However, the regulations do not specify standards for this review other than some requirements for the mandate and overall composition of each board. Federally-funded research involving human participants is subject to CIHR’s TCPS2, as discussed above (see “Transparency-Registration of Clinical Trials”). Industry-sponsored clinical trials are not bound by these guidelines unless the trials are performed within an institution that receives CIHR funding. Institutions that conduct clinical research (not just clinical drug trials) have each established their own research ethics review process, and these have therefore evolved with slight differences and requirements between them. Despite the differences that might exist between research ethics boards, they each hold patient safety as paramount and they all review the following components: the consent form to be signed by participants; the protocol of the trial; the contracts

between the sponsor and the institution and/or investigator, which include provisions regarding compensation; and reports of adverse reactions. These boards provide ongoing oversight of the trials they have approved and can retract their approval should serious concerns about the trial surface.

Witnesses spoke of the duplication of efforts when submitting protocols for ethics review at multiple sites, and the frustration of receiving different responses for seemingly identical submissions. There is broad consensus among stakeholders that the work of research ethics boards needs to be streamlined in order to improve efficiency and reduce costs. While the need for streamlining has been acknowledged for some time, witnesses spoke of an underlying mistrust among research ethics boards that has hampered attempts in the past to modify the ethics review infrastructure in order to improve efficiency. Continued efforts however appear to have paid off and the committee learned that there now appears to be a willingness among all players to come together in the interest of promoting clinical trials in this country. For example, CIHR indicated that, in partnership with Rx&D and the Association of Canadian Academic Healthcare Organizations, it had developed a common clinical trials agreement to be used by the drug industry when entering into contractual arrangements with an institution or investigator.

The committee heard about two parallel systems for research ethics review. Joel Lexchin, a professor at the School of Health Policy and Management within York University, explained that research ethics boards were originally created within academic institutions, where all clinical research was carried out early on. Over time, many clinical trials of new drugs have moved into the community, are led by community-based physicians and are run through Contract Research Organizations (CROs). The move out of the academic healthcare institutions was a result of



the realization that many drugs do not need to be administered within a hospital setting.

Concerns were raised that the research ethics boards created within the CROs operate under different standards than institutionally-based ones. The committee heard from Jack Corman from a CRO called IRB Services. Mr. Corman indicated that there was a different standard of operation between healthcare institution-based trials and CRO run trials as well as increased scrutiny of the private sector. The committee was told that there are fewer barriers with respect to contracts and centralized review within the private setting than is experienced in the public sector.

In regard to reducing such barriers, efforts have been undertaken in Ontario and British Columbia with respect to condition-specific networks and industry sponsored clinical trials to centralize ethics review. The Ontario Cancer Research Ethics Board (OCREB), which evolved out of the Ontario Cancer Research Network (now the Ontario Institute for Cancer Research), operates under the principle of “do it once and do it well” and provides ethical approval for most cancer trials in the province. This research includes more than just testing of new drugs. With respect to approaches specific to industry-funded clinical drug trials, Clinical Trials Ontario, a recent creation of Ontario’s Ministry of Economic Development and Innovation, aims to create a streamlined approach to multi-centre trials and in so doing, attract more pharmaceutical industry investment in the province. With respect to standardizing ethics review, OCREB, in partnership with the National Cancer Institute of Canada and the British Columbia Research Ethics Board, recently agreed on a common consent form for participants. However, the Canadian Association of Research Ethics Boards cautioned members that efforts to standardize research ethics across Canada must be sensitive to privacy legislation within the different jurisdictions.

A broader approach to standardizing ethics review that was developed by the Canadian General Standards Board (CGSB) was mentioned by several witnesses, who acknowledged CGSB’s work to develop voluntary standards for research ethics boards, including their composition and behaviour. Witnesses were generally not supportive of CGSB’s recently developed standards however, suggesting that they will add to the complexity of the research environment and that they fail to meet the multiple sets of regulations and policies to which clinical trials are subject.

#### 4. ASSESSMENT OF THE VALUE-ADDED OF NEW DRUGS

Health Canada’s approval process for new drugs involves a review of the drug’s safety, efficacy and quality. The department does not measure incremental benefit of a candidate drug over existing therapies but rather whether the new drug achieves the outcome claimed in the submission filing. Health Canada referred to incremental benefit as a “payer issue” and one that is addressed by the Canadian Agency for Drugs and Technologies in Health as well as by insurers. Although, the committee heard from the Reformulary Group that once a newly approved product is considered for listing decisions, the clinical trial data that is available does not reflect ‘real world’ use and does not offer comparative information over existing drugs. In this regard, the Canadian Medical Association urged that market approval include an assessment of a candidate drug’s performance in relation to existing drugs. In fact, Health Canada indicated that it favours clinical trial design that uses existing therapies as the control where ever possible. Trials conducted in this manner would provide evidence that would be readily available in order to securely identify reasonable alternatives in the event of a drug shortage.

In this context, the notion of “comparative effectiveness” was raised by several witnesses.



While the committee heard that placebo-controlled trials have traditionally been considered the gold standard, others urged only very limited use of placebo as the control measure in clinical trials. Arguments against the use of placebo-controlled trials include the ethics of removing patients from a standard therapy, or offering something that is less than the standard of care, in order to test a therapy of uncertain benefit. With respect to outcome measures, the use of a placebo-controlled trial would not reveal if a new drug is actually less effective than a standard or existing therapy. In addition, the effectiveness of these trials is undermined by the high proportion of both participants and investigators who successfully guess who is on placebo and who is on the investigational drug. Witnesses suggested that industry-sponsored trials favour the placebo-controlled design whereas “head-to-head” trials that compare a new drug to an existing drug are often investigator driven.

Discussion of the “me-too” drugs, those drugs that have little or no added-value over existing drugs, involved questioning whether they provide a societal benefit, and whether it was a social good to invest time, money and limited research resources into these drugs. The committee was told by the Association of Canadian Academic Healthcare Organizations (ACAHO) that academic institutions have little interest in hosting trials that test drugs that will not lead to improved health care or do not improve scientific knowledge. It also heard from IRB Services that about 70% of clinical trials are done within the community and only 30% within academic institutions. It was not clear from the testimony given whether there is a link between the large proportion of clinical trials being conducted within the community and the preference at academic institutions to limit their role in conducting trials to innovations, or breakthroughs, as opposed to minor enhancements of existing drugs. However, Health Canada’s 2010 performance



report on drug reviews indicates that such drugs make up a small proportion of all drug reviews and approvals, that is, drugs that are the first for a given condition or which provide a significant improvement over existing drugs (priority review and NOC with conditions submissions).<sup>11</sup>

## 5. INCLUSION OF VULNERABLE GROUPS IN CLINICAL TRIALS

Traditionally, clinical trials are designed in such a way as to optimize the outcome measure. Therefore, when measuring the effect of an investigational drug, all other variables are minimized such as the metabolic and developmental variables introduced in pregnant and nursing women as well as children, and the complicating variables of additional health conditions and medications associated with older participants. There is also an ethical component to excluding certain sub-groups of the population due to exposing vulnerable participants to untested drugs. Once clinical trials are complete, Health Canada’s approval of a new drug will extend only as far as the population in whom clinical trials were performed. While there may be scientific and ethical rationale for excluding these vulnerable sub-groups from clinical trials, witnesses emphasized that once approved, these drugs will be prescribed off-label<sup>12</sup> to them and, as such, it is essential that relevant clinical trial data be collected. The committee heard that the *Food and Drug*

<sup>11</sup> Health Canada, “Therapeutic Products Directorate Drug Submission Performance Annual Report: January-December 2010”

<sup>12</sup> Off-label refers to the use of a drug beyond the parameters of the specified conditions of the marketing authorization, or NOC, including the population for which it has been approved.



*Regulations* provide some incentive, in the form of an additional six months of market exclusivity, for performing clinical trials in children.

#### a. Children

Since 2009, Health Canada's Paediatric Expert Advisory Committee has provided the department with advice on how to protect the health and safety of children, and of pregnant and nursing women. With respect to drugs, the Advisory Committee acknowledges the need to develop, test, evaluate and label them appropriately for these groups.

Witnesses stressed that as much as 75% of drug therapy in children is done without any clinical evidence of the efficacy of the drug in the child population. Furthermore, where there are paediatric clinical trials being conducted, they are done post-approval and are not usually sponsored by industry as, for the most part, it is uninterested in pursuing what it perceives to be a small market. In the U.S. and in the EU, drug companies are required to conduct trials in children, when it is deemed appropriate. Thus, when the drug receives approval in those jurisdictions, the authorization and labelling reflect whether or not the drug is indicated for use in children. Members were told that companies do not routinely submit to Health Canada for a change to the approved conditions of use of the NOC reflecting the new information and therefore a change to the label. This may be due to the costs associated with submitting for the change relative to the profits associated with the expanded market. Without specific approval and associated labelling for the use of drugs in children and without access to the results of paediatric clinical trials, witnesses stated that children are put at undue risk.

#### b. Pregnant and Nursing Women

The committee heard that, as with children, the automatic assumption about clinical trials is that pregnant and nursing women will be excluded.

It was suggested that the assumption should be one of inclusion, unless the sponsor of the drug has a compelling argument not to include them. Françoise Baylis, Professor at the Faculty of Medicine at Dalhousie University, made the observation that “[p]regnant women get sick and sick women get pregnant”, and that they deserve the same level of evidence-based healthcare as any other Canadian.

Health Canada recently released a draft guidance document entitled *Considerations for Inclusion of Women in Clinical Trials and Analysis of Data by Sex* for comment from stakeholders. Pregmedic, the Canadian Alliance for Safe and Effective Use of Medication in Pregnancy, is supportive of Health Canada's efforts to encourage the inclusion of women in clinical trials but urges the department to amend the guidance document so as to establish two distinct policies: one for drugs intended for both male and female consumption and another for drugs intended for women only.

#### c. Older Canadians

Clinical trials have traditionally excluded older participants because this population often has multiple health issues, in addition to the condition for which a drug is being tested. Along with the high rate of frailty, this makes them more vulnerable to changes in their drug regimen. Witnesses concurred that, as with other vulnerable groups, clinical trial design must be done carefully in order to maximize safety but that all sub-groups in whom a drug can reasonably be expected to be prescribed should be included in clinical trials.

## 6. PERSONALIZED MEDICINE

Personalized medicine is a new area of research and innovation. Personalized medicine refers to tailoring an individual's treatment so as to optimize its success. It involves the identification of biomarkers within an individual that allows accurate predictions to be made about that person's





susceptibility of developing disease, the course of disease, or their response to treatment. Biomarkers, short for biological markers, can include the presence or absence of specific genes, proteins, etc. Health Canada is promoting the development of such products through its \$67.5 million investment with Genome Canada.

The committee heard from Nita Arora of Hoffmann-La Roche Ltd. who stated that personalized medicine has already arrived. The committee heard that Hoffmann-LaRoche has committed that by 2020, 50 per cent of all its drugs will have a personalized health care component to them. In that regard, the company has recently received tandem regulatory approval for the diagnostic kit and therapeutic product for metastatic melanoma.

Health Canada stated that while there are currently no clinical trials in this area, it is working with industry to develop procedures appropriate to personalized medicine. However, the department pointed out that it is the responsibility of the sponsor to determine the hypothesis and develop the protocol to test that hypothesis. Health Canada has the authority to scrutinize their protocol. Witnesses suggested that clinical trial design will have to adapt to meet the needs of personalized medicine and be more focussed with fewer participants. Some cautioned that this may be accompanied with calls for more flexible regulation with respect to what evidence of safety and efficacy should suffice for market approval.

## 7. REPORTING ADVERSE REACTIONS

Under the clinical trial regulations, sponsors are required to report serious unexpected adverse reactions to Health Canada. Because clinical trials being conducted in Canada often have sites in other countries, this obligation to report applies not only to Canadian sites but to sites in other countries as well. The regulations stipulate that sponsors must report to the department within 15

days of becoming aware of non-fatal and non-life-threatening reactions, but within seven days for fatal and life-threatening incidents.

In its 2011 report, the OAG reviewed the number of serious unexpected adverse drug reactions that had been reported to Health Canada. The report indicated that the number of incidents has steadily increased since 2007, with 95% of reported adverse reactions originating from other countries. The report noted that 115,000 adverse reactions had been reported to Health Canada in 2010, up significantly from 43,000 adverse reactions in 2007. It noted that Health Canada's method of manually entering all reports of adverse reactions into a database consumes considerable resources; resources that the OAG stated would be better allocated to assessing the safety issues. Health Canada described its risk-based approach to monitoring adverse reactions from investigational drugs as focusing resources on the highest risk drugs or on trials done on the most vulnerable populations. The Auditor General raised concerns about the lack of standard operating procedures for the department's monitoring activities and about the lack of criteria for prioritizing which adverse reaction reports are subject to thorough assessment.

Adverse reactions that are noted during the course of a trial by the trial investigator or other health provider charged with assessing the participants are not immediately reported to Health Canada. As noted above, clinical trials are conducted with some participants in the experimental arm and others in the control arm, where participants as well as those conducting the trial are unaware as to what treatment each participant is receiving. As such, adverse reactions cannot immediately be attributed to the investigational drug. Therefore, adverse reactions are reported to two bodies, each of which is independent of the trial. First, adverse reactions are reported to the research ethics board that approved the trial. Second, they are reported to data safety monitoring boards (DSMBs) which



have been instituted particularly for large trials where there is a perceived risk involved to the patients. DSMBs were described as independent of the investigator and of the institution in which the trial is conducted. Members of the DSMB have access to the data of all sites for a particular trial in order to make observations and attribute causality about adverse reactions and, if necessary, recommend that a trial be stopped. Adverse drug reactions therefore are subject to the scrutiny of research ethics boards and DSMBs, which make decisions about whether to forward the report on to Health Canada.

Despite the regulatory requirement to report adverse reactions to Health Canada, Miriam Schuchman, chair of the research ethics board at Women's College Hospital, pointed out that neither the department nor the ethics board or DSMB disclose this information to the public. Several witnesses specified that the mandatory clinical trial registration they were seeking should include adverse reactions within the results reporting so that adverse reaction information is available to the public.

## 8. CLINICAL TRIAL OVERSIGHT

Health Canada's Health Products and Food Branch Inspectorate is responsible for compliance and enforcement activities associated with drugs and medical devices, including inspection of the clinical trials regulated by the department. In this regard the department's compliance and enforcement activities are intended to protect the safety of trial participants and verify the quality of the data generated from the trials. Similar to its approach to reviewing adverse reaction reports, the department applies a risk-based approach to inspection activities. Health Canada stated that inspection activities must be appropriate and proportional to the risk posed by the product being tested.

The strategy developed by Health Canada and used by inspectors in deciding which clinical trial sites should be inspected involves determining the number of trials at a site, the number of subjects enrolled, the number of adverse reaction reports received, and observations from past inspections. However, the 2011 OAG report noted that Health Canada does not always have the information required to make this risk assessment since the regulations do not require sponsors to provide it with up-to-date information.. The report also found that Health Canada had not met its oversight target of inspecting 2% of all clinical trial sites, but had realized inspection of only 1.3% of sites. Also of concern is the OAG's finding that when inspections turned up non-compliance issues with the regulations, it took Health Canada between 56 and 142 days to notify the parties of the deficiencies. The OAG also noted that it took Health Canada an unsatisfactory length of time to review proposed corrective measures in response to non-compliance issues.

Witnesses frequently commented on the need for oversight of clinical trials. In contrast, industry representatives emphasized that they are currently subject to sufficient regulatory oversight. The committee heard testimony that clinical trials that occur within the community, that is, within CROs, are subject to greater scrutiny than are clinical trials within the public sector. However, it was not clear whether a larger proportion of Health Canada inspections had in fact been carried out on clinical trials within the community. On the contrary, Health Canada stated that the risk-based approach used to determine which clinical trial sites should be inspected suggests that breakthrough drugs would attract greater scrutiny and these are carried out predominantly within academic institutions.



## 9. DRUGS FOR RARE DISEASES

A rare disease is defined by the Canadian Organization for Rare Disorders (CORD) as one which affects less than 1 person in 2,000. Drugs used to treat rare diseases are often referred to as orphan drugs. Often, because the market is very small for orphan drugs, companies are resistant to investing in research in this area. CORD informed the committee that Canada is the only developed country without an orphan drug policy and that this is having an impact on the clinical trial activity in this country. It is also having an effect on the proportion of orphan drugs that seek approval in Canada, compared to other jurisdictions such as the U.S. and EU, where less than half of the approved drugs in those jurisdictions have been submitted for approval in Canada.

Members were told that an orphan drug policy could provide incentives to companies to develop and test orphan drugs in this country. The lack of incentive combined with Canada's small market has often resulted in companies leaving Canada in order to test their drug and Canadians are denied access in the clinical trials. Further, once a drug obtains approval elsewhere, the company frequently will not seek approval here because there had been no trial sites and therefore no clinicians familiar with the treatment.



CORD suggested that Canada could adopt an orphan drug policy that includes incentives similar to those provided in the U.S. and EU such as: financial incentives to develop orphan drugs; assistance in designing clinical trials appropriate to the population base and nature of the condition; extended market exclusivity; reduced fees for submitting for approval, etc. Such a policy could improve access to drugs for those Canadians suffering from rare diseases.



## 4. INCREASING CANADA'S GLOBAL COMPETITIVENESS IN CLINICAL TRIALS-THE ROUTE TO IMPROVED ACCESS TO PHARMACEUTICALS

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Why should Canadians be concerned that Canada is failing to attract clinical trials to this country? While some might say that clinical trials potentially expose people to unnecessary risk from untested drugs and that they are not sympathetic to the increasing costs that the drug industry faces, this narrow view fails to recognize the benefits to Canada and Canadians of promoting clinical trial activity in this country, which are outlined below. As stated by David Moher, senior scientist in the Clinical Epidemiology Program at the Ottawa Hospital Research Institute, “Clinical trials are hugely important building blocks for managing the health of all Canadians.”

The financial investment made by drug companies when operating clinical trial sites in Canada puts money back into the research environment and helps to train and retain investigators and other skilled professionals associated with conducting trials. Both the Best Medicines Coalition, an organization that represents the interests of patient and condition-specific groups and CODR urge the government to promote increased clinical trial since this provides early access to promising therapies, and familiarizes health professionals with new treatments so that, once approved by Health Canada, uptake of the new drug is easier. Finally, whether a manufacturer has conducted a clinical trial in Canada can affect the decision to seek approval for the drug's use from Health Canada. Health Canada does not control which drugs are submitted for approval following the completion of clinical trials. This decision is at the discretion of the manufacturer, and factoring into that decision

is how ‘friendly’ Canada has been to the product, including whether it hosted clinical trials. That is to say that, while it is not necessary to conduct clinical trials in this country in order for a drug to receive approval by Health Canada, it can have an impact on the decision to seek approval from the department. For all of these reasons, Canada must improve clinical trial infrastructure with the goal of becoming a country of choice for developing and testing innovative pharmaceuticals that provide significant improvements over existing therapies.

In terms of population, and by extension participant pool, Canada cannot hope to compete with those countries where clinical trial activity has increased in recent years, such as China and India. However, while it generally costs less to run clinical trials in countries such as India and China, the committee heard that the inconsistency in quality control of the health systems and medical facilities, the less rigorous training of the trialists and scientists, and frequent language barriers can be problematic. These are all potential areas in which Canada could be promoted as a more desirable host country for clinical trials. In addition to promoting Canada's existing strengths, Canada must take decisive steps in improving its clinical trial infrastructure and in so doing, streamline the process and reduce overall costs.



Regardless of the steps that should be taken to increase Canada's desirability as a host country for clinical trials, it is critical that the protection of participants remain a central and primary concern underlying all efforts to increase clinical trial activity in Canada. This sentiment was affirmed not only by academics and health professionals who appeared before committee but also by industry representatives such as Amgen Canada. Many witnesses advised that in order to provide needed incentives as well as proper oversight to ensure that all stakeholders are operating from the same set of rules, the renewed approach to clinical trials will require a "carrot and stick" approach.

## 1. A CALL FOR FEDERAL LEADERSHIP

While this study focussed exclusively on the clinical trials of prescription pharmaceuticals, which are subject to federal regulation and are funded by industry, it is important to note that 80% of all clinical research receives federal funding through CIHR. This means that the federal government plays a significant role in all clinical research. It is therefore in the best interest of the federal government to implement the changes needed in order that Canada's clinical research yields the most value for investment.

In this regard, several efforts have been made already. CIHR's Strategy for Patient-Oriented Research (SPOR) was launched in August 2011. In partnership with the drug industry, academic healthcare institutions and the provinces and territories, CIHR's SPOR was created with the goal of addressing the lack of clinical research infrastructure, difficulties relating to patient recruitment and the requirement for numerous ethics reviews for multi-centre trials. Under

this initiative, the federal government recently announced an investment by CIHR of up to \$150 million over five years. This amount will be matched by Rx&D, and will help both to promote Canada as a preferred site for clinical research and to translate research findings into clinical practice. The committee commends CIHR's stated efforts to develop, in partnership with ACAHO and Rx&D, a standard clinical trial agreement as a significant step in streamlining the system. However, it should be noted that this partnership leaves out a major stakeholder when considering clinical trials of investigational drugs: the clinical research organizations.

The committee heard about the Clinical Trials Summit held in September 2011 from the summit's hosts, CIHR, Rx&D and ACAHO. The summit included breakout presentations by these organizations to representatives of government, academia, clinical sites and industry; participation from representatives of research ethics boards or CROs, however, appears to have been limited. In fact, the committee was told by IRB Services that the private sector was not invited and that this approach will only perpetuate the problem of working in silos. This summit resulted in the development of an action plan increase clinical trial activity called *To Your Health and Prosperity... An Action Plan to Help Attract More Clinical Trials in Canada*.<sup>13</sup>

With respect to efforts to improve protection of clinical trial participants, some witnesses spoke about the 2008 report issued by the Experts Committee for Human Participant Protection in Canada entitled *Moving Ahead*.<sup>14</sup> This report recommended an accreditation system for research ethics review and the creation of the

<sup>13</sup> The Action Plan is available at: [http://www.achho.org/docs\\_new/CT%20Summit/Final/ActionPlan-FinalDraft\(March31\).pdf](http://www.achho.org/docs_new/CT%20Summit/Final/ActionPlan-FinalDraft(March31).pdf)

<sup>14</sup> The Moving Ahead report is available at: [http://www.novelttechethics.ca/files/files/Policy/Research\\_Ethics/Moving\\_Ahead.pdf](http://www.novelttechethics.ca/files/files/Policy/Research_Ethics/Moving_Ahead.pdf)



Canadian Council for the Protection of Human Research Participants to implement and oversee the new system. This approach would have included both the public and private research ethics boards and could have represented a step forward in eliminating silos and establishing a single national approach to clinical trials.

This report's recommendations have not been implemented and in fact, the committee was told that CIHR pulled out of such an approach. CIHR did, however, speak optimistically about the efforts of the CGSB with respect to establishing standards of ethics review. As mentioned earlier however, witnesses were generally hesitant about adopting the CGSB standards and in fact, the terms of reference used to develop them were not made clear to the committee.

The committee commends the efforts that have been made to date to improve the clinical trial infrastructure in Canada, but is concerned that these efforts have met with limited success. In order to bring about the needed change, the committee agrees that an integrated, Canadian approach to clinical trials requires clear federal leadership, given the federal role in funding and/or regulating clinical trials.

The committee therefore recommends that the federal government assume a leadership role in facilitating, coordinating and encouraging a comprehensive clinical trials infrastructure by:

- Establishing a National Framework for Coordinating Clinical Trials to; provide leadership, promote the importance of clinical trials and the benefits of being a participant, help to establish Canada as a preferred site for clinical trials, and provide a point of contact between industry and networks;
- Convening the Federal/Provincial/Territorial Conference of Health Ministers to discuss initiatives in their respective jurisdictions with a view to sharing best practices and reducing duplication of efforts; and
- Encouraging the inclusion of all relevant stakeholders in discussions, consultations and events held in respect of establishing that infrastructure. [Recommendation 1]



## 2. MANDATORY REGISTRATION OF CLINICAL TRIALS

The committee heard compelling evidence as to the importance of registering clinical trials on a publicly accessible website, as this would improve transparency. Matthew Herder, an assistant professor at the Health Law Institute at Dalhousie University, enumerated three reasons why greater transparency with respect to clinical trials is critical. First, secrecy violates a fundamental principle of research ethics by denying participants the benefit of access to the knowledge generated by their participation, thereby producing an unacceptable benefit to harm ratio for them. Second, he argued, shifts in scientific knowledge and product development such as those seen recently in advances in personalized medicine demand greater transparency in order that the knowledge base is strengthened. Third, he proposed that increased transparency will create opportunities for innovation. This, he suggests, will be because there will be a decrease in the amount of redundant research and development efforts, and will allow drug manufacturers to compile their own data with data generated by other companies with a view to making predictive assessments about products they have under development. The committee was told that industry concerns with respect to allowing competitors access to their data are addressed by existing patent rights and data exclusivity protection.

In addition to the reasons listed by Mr. Herder, greater transparency through clinical trial registration would also help to reduce many of the concerns raised by witnesses. Mandatory registration of all WHO data items would allow

stakeholders access to information on all trials performed with a candidate drug, including those that ended prematurely, gave negative results or in which patients were removed due to non-response or adverse reactions. In addition, full transparency would allow access to information on specific age-groups in whom a drug had been tested, regardless of whether it had gained approval in that age-group.

The committee agrees that drug development, as with all health research, must be carried out with the goal of generating an evidence-base upon which policy makers and health professionals can make the most informed decisions regarding the allocation of health resources. The transparency required in order to accomplish this will not be attained through ‘soft governance’, as Trudo Lemmens, Scholl Chair in Health Law and Policy at the University of Toronto, emphasize when he appeared before the committee. Transparency will only be achieved by making registration of clinical trials mandatory. With respect to where Canadian clinical trials should be publicly registered, the creation of a Canadian clinical trial registration website is unnecessary given the level of international interest and the number of existing WHO recognized sites. Given Canada’s proximity to the U.S., and the observation that the American [clinicaltrials.gov](http://clinicaltrials.gov) website hosts the greatest number of clinical trials, preference might be considered to requiring registration on that site.





The committee therefore recommends that the Minister of Health:

- move to immediately require clinical trial registration to the greatest degree permitted under its existing legislative and regulatory authorities;
- determine and propose the necessary amendments to the *Food and Drugs Act* and/or the clinical trial regulations contained in Part C, Division 5 of the *Food and Drug Regulations*, to require that manufacturers register a comprehensive set of data for clinical trial phases II and III on a WHO recognized website prior to recruiting any participants. Registration must include, but not be limited to, all results, adverse reactions, withdrawal of participants (non-identifying), and prematurely ended trials;
- require that all foreign clinical trials that are used to support applications for market authorizations in Canada have met equivalent registration standards; and,
- implement measures to strictly enforce this recommendation in order to ensure transparency of the clinical trial process and of the processes at Health Canada. [Recommendation 2]

### 3. ESTABLISH STANDARDS AND ACCREDITATION OF RESEARCH ETHICS BOARDS

It appears that research ethics boards have moved past their earlier mistrust of each other and now acknowledge the need and have demonstrated a willingness to work towards a standard for ethics review in order to break down the silos that have discouraged investment in clinical trials in this country. The committee commends stakeholders for the efforts undertaken in recent years to achieve this goal but finds it troubling that efforts to date, had they been adopted, may have still resulted in inconsistent approaches because discussions have not included all players. As a result there are two streams of clinical trials: one in the academic setting, and one in the community run by CROs. It is not acceptable to exclude any of

the central players, including the private CROs, from discussions pertaining to the clinical trial infrastructure in this country. If Canada is to succeed in achieving a streamlined approach to clinical trials, then the same standard must be applied to all trials for unapproved drugs regardless of whether they are conducted in an academic setting or within the community at CROs.

The committee is discouraged that the CGSB standard for research ethics review, which had been presented by CIHR as an important advance, was described by several witnesses as problematic as it would add complexity to the system, would fail to satisfy the requirements of existing regulations and policies and would be voluntary and therefore would not necessarily result in a uniform ethics review infrastructure in Canada. In addition, the process used to design the CGSB standard was not





discussed; it is unclear whether the interests of all affected parties were taken into consideration. The committee was told that a barrier to developing a national standard for ethics review relates to differences between provincial privacy statutes. The March 2012 document *International and Canadian Activities Related to the Ethical Review of Clinical Trials* prepared for Health Canada provides a discussion of the research ethics review activity within all of the provinces including a summary of the legal impact each jurisdiction's privacy legislation has on this review.<sup>15</sup>

There are clearly significant barriers to establishing national standards for ethics review. Nevertheless, in the interest of streamlining the process in order that clinical trials are run more efficiently and of

ensuring consistent protection for participants, there must be a national standard for all aspects of trial review including, but not limited to, the contracts (or clinical trial agreements) between the sponsor and an institution or investigator with parameters on compensation and fees, informed consent, placebo versus head-to-head trials, and review of adverse reaction reports. In order to ensure that all clinical trials of unapproved drugs are reviewed in a consistent and efficient manner, adoption of a national standard can be ensured through an accreditation program, as has previously been recommended in the *Moving Ahead* report of 2008. Achieving a truly national standard of ethics review will involve building upon the diligent and well-intended work that has already been undertaken.

The committee therefore recommends that the Minister of Health direct Health Canada to immediately undertake to develop an accreditation program for Research Ethics Boards. To this end, Health Canada will, as soon as possible:

- Launch discussions, in consultation with the provinces and territories, for a national standard for Research Ethics Boards which:
  - Includes all aspects of trial review including but not limited to; contracts or clinical trial agreements with parameters on compensation and fees, informed consent, placebo versus comparative effectiveness and, review of adverse reaction reports;
  - can be applied to the review of all clinical trials of unapproved drugs in Canada;
  - can serve as the basis for accreditation of research ethics boards, both institutionally-based and privately run; and
- Oversee the implementation of an accreditation program for research ethics review which:
  - Assesses and awards accreditation to research ethics boards that review, approve and oversee clinical trials of unapproved drugs; and,
  - Provides guidance on the training of those involved in research ethics boards. [Recommendation 3]

<sup>15</sup> Marianne Vanderwel, "International and Canadian Activities Related to the Ethical Review of Clinical Trials," March 2012.



The committee further recommends that the Minister of Health amend the clinical trial regulations contained in Part C, Division 5 of the *Food and Drug Regulations*, to stipulate that any reference to a research ethics board means an accredited research ethics board. [Recommendation 4]

#### 4. FACILITATE PARTICIPANT RECRUITMENT INCLUDING VULNERABLE SUB-GROUPS THROUGH THE DEVELOPMENT OF NETWORKS

The committee was frequently told that collaboration and the establishment of networks between academic institutions, research networks and patient groups were helping to streamline clinical trials and improve patient recruitment from the sponsor's perspective while also improving access to investigational drugs from the perspective of the patient. Networks were presented as a means of getting clinical trials up and running quickly at multiple sites across the country. They allow resources, such as research ethics review, to be pooled and increase the ability to recruit patients.



A network also provides a single point of contact for sponsors, can offer clinical trial design experts and can provide a portal to ongoing clinical trials.

Throughout this study evidence was presented that demonstrated the hesitation to recruit certain vulnerable sub-groups of the population into clinical trials. While certain groups have not traditionally been recruited due to ethical considerations, witnesses argued that since these populations will be exposed to the product once it is on the market anyway, it is also unethical to exclude them from clinical trials. The committee was told that these sub-groups, which include children, the elderly, and pregnant and nursing women, are frequently excluded automatically without giving any consideration to the possibility of including them. In other cases, members were told, these groups are excluded as they may not respond as well as the traditionally chosen trial group and therefore may reduce the measure of a drug's effectiveness.

While the committee is encouraged by Health Canada's draft guidance document on including women in clinical trials, *Considerations for inclusion of women in clinical trials and analysis of data by sex*, it trusts that the department will thoroughly review and address all submitted comments and issue a final document as soon as possible. Members also commend the work of Health Canada's Paediatric Expert Advisory Committee and urge it to provide guidance on the inclusion of children in clinical trials. In addition, it appears that networks, such as the Maternal Infant Child and Youth Research Network (MICYRN), can help to design appropriate trials that include these groups. Despite these ongoing efforts, the committee feels it is necessary to require that drug developers test their drugs in a population that is reflective of who could reasonably be expected to consume that product, should it obtain market approval. Implementation of this recommendation would provide assurance to stakeholders that market approval was based on satisfactory clinical trial data from all relevant population sub-groups.



The committee therefore recommends that the National Framework for Coordinating Clinical Trials:

- Encourage the creation of research networks as part of its goal of promoting the importance of clinical trials; and
- Provide guidance to research networks on centralizing research ethics review and on creating databases of patients willing to be considered for clinical trials. [Recommendation 5]

The committee further recommends that the Minister of Health:

- Amend the clinical trial regulations contained in Part C, Division 5 of the *Food and Drug Regulations*, to stipulate that clinical trials must be designed to reflect the same population that can reasonably be expected to consume the drug once approved for sale in Canada; and
- Implement modifications to its drug approval process to stipulate that market approval will only be granted if clinical trial evidence of the product's safety and efficacy includes data on all population groups that can reasonably be expected to consume that drug once approved for sale in Canada. [Recommendation 6]

## 5. AN ORPHAN DRUG POLICY FOR CANADA

The committee is concerned that Canadians suffering from rare diseases have access in this country to only half of the pharmaceuticals available in the U.S. While obtaining market approval is not contingent on conducting clinical trials in Canada, increasing the clinical trial activity in this area has a number of benefits. For example, it offers patients early access to new drugs, it familiarizes the healthcare providers with new treatment options and it may influence the drug company's decision to seek market approval.

Canada, however, has a relatively small population when compared to most other countries, particularly those countries with which it is

competing for clinical trial investment. Patient recruitment is challenging enough for those conditions that affect a larger proportion of the population; since rare diseases affect less than 1 in 2000, patient recruitment is made that much more difficult. In order to stimulate clinical trial investment for rare diseases, Canada must nurture innovation by implementing an orphan drug policy so that Canada can compete with other developed countries in this area.

On 3 October 2012, Health Canada announced two initiatives to address the unique needs of Canadians affected by rare diseases; a framework to support the development and authorization of orphan drugs, and a Web portal to facilitate access to information. The committee is pleased that action has been taken on this important issue.



The committee therefore recommends that the Minister of Health direct Health Canada to include the following elements in its Orphan Drug Framework for Canada :

- creation of 'orphan drug status' for drugs in development for specified rare conditions;
- assistance in the design of clinical trials for investigational orphan drugs;
- elimination or reduction of user fees charged by Health Canada to review orphan drug submissions; and,
- extension of market exclusivity for orphan drugs. [Recommendation 7]

The committee further recommends that the National Framework for Coordinating Clinical Trials:

- Promote Canada as a preferred site for clinical trials of orphan drugs; and
- Include a requirement for consultations with stakeholders including the Canadian Organization for Rare Disorders to explore ways to improve and maximize patient recruitment to trials. [Recommendation 8]

## 6. EXAMINE PATENT PROTECTION PROVISIONS AND TAX INCENTIVES

Industry representatives raised the issues of tax incentives and patent life as deterrents to investment in clinical trials in Canada. With respect to tax incentives, they stated that changes to the Scientific Research and Experimental Development (SR&ED) Tax Incentive Program under the Federal Budget 2012 will not encourage, or help the advancement of, clinical trials in Canada. The SR&ED Program is a federal tax incentive program designed to encourage Canadian businesses in all sectors to conduct research and development (R&D) in Canada. This program provides cash refunds and/or tax credits to claimants for their eligible R&D expenditures incurred in Canada.<sup>16</sup> Entitlements under this program were decreased in the recent federal budget (for instance the general

tax credit rate was reduced to 15% from 20%).

With respect to patent life, industry representatives suggested that Canada has fallen behind other countries in patent protection and as a result is reducing the incentive for companies to pursue innovation in this country. The committee was told that Canada should implement patent restoration such that patent protection is restored, for some of the time a drug has spent in the clinical trial phase, as is the case in the U.S. In addition, it was recommended that Canada should increase data protection from 8 to 10 years which would be similar to provisions in the European Union. Examining these issues may become even more critical if this committee's recommendations, such as expanded clinical trials and mandatory registration of data, are implemented.

<sup>16</sup> Canada Revenue Agency, Scientific Research and Experimental Development (SR&ED) Tax Incentive Program, <http://www.cra-arc.gc.ca/txcrdt/sred-rsde/menu-eng.html>.



These issues were not extensively explored by the committee; however it is aware that the pharmaceutical industry has raised them in the past and in various contexts. The committee agrees that these issues may have an impact on the attractiveness of Canada as a site for clinical trials, and indeed as a preferred site for innovation through R&D.

The committee therefore recommends that the federal government create an expert advisory committee to undertake a thorough study of the intellectual property and tax incentive issues raised by stakeholders during this study with a view to exploring options and recommending changes that will help to improve Canada's global competitiveness in drug development. [Recommendation 9]

The clinical trial regulations do not restrict clinical trial design, and therefore should not be a significant barrier to personalized medicine innovation. Nevertheless, Health Canada has indicated that it is working with industry on how to optimize development of personalized drugs and the committee encourages this collaboration.

The committee heard some concerns about the oversight of clinical trials. While some witnesses voiced a preference for the creation of an independent body to provide this oversight, others commented that Health Canada's Health Products and Food Branch Inspectorate should improve its inspection strategy and efficiency. These latter concerns were raised by the Office of the Auditor General, and Health Canada responded by agreeing with the OAG's recommendations. The committee looks forward to seeing the progress made by the department in implementing the changes.

## 7. ADDITIONAL OBSERVATIONS

Once comprehensive standards for clinical trials and compulsory accreditation of research ethics boards are implemented, the committee is confident that the number of clinical trials conducted in Canada will increase. The committee also believes that increasing the number of comparative effectiveness trials will lead to benefits to health care, to the research community and ultimately to personalized medicine. Combined with mandatory registration of a comprehensive set of information for all clinical trials, including results, this will allow payers access to data on incremental benefit of new drugs, may discourage development of me-too drugs and will encourage innovation, including development of personalized medicine.





The committee therefore recommends that the Minister of Health direct Health Canada to immediately address the recommendations made in Chapter 4 of the November 2011 Report of the Auditor General of Canada namely to:

- Strengthen the risk-based approach for monitoring and assessing clinical trial adverse reaction reports;
- Establish timelines for officially notifying clinical trial sites of non-compliant ratings; and
- Enhance public access to information on authorized clinical trials, including the results of inspections.

The committee further recommends that the Minister of Health direct Health Canada to address additional issues highlighted in the report and take immediate steps to:

- Realize the target of inspecting two percent of clinical trial sites; and
- Eliminate manual data entry of adverse drug reaction reports through full implementation of electronic reporting.

[Recommendation 10]

While some of the changes needed to modernize and streamline clinical trials in Canada can be accomplished by updating the regulations, Canada's *Food and Drugs Act* was also presented as being a barrier to this process. Bill C-51, which was introduced in 2008 but never progressed beyond second reading in the House of Commons, was pointed to by some witnesses as containing provisions critical to modernizing drug regulation in Canada, such as the authority for the Minister to require and in some cases disclose, certain information, including personal and business information. Some witnesses commented that the lack of transparency at Health Canada went beyond the clinical trial parameters, and in fact shrouded the entire drug approval process. In this regard they suggested that updating the *Food and Drugs Act* to facilitate the disclosure of information is necessary. Finally, witnesses commented on the need to establish substantial penalties for contravening the clinical trial regulations. Currently, the *Food and Drugs Act* provides for a maximum fine of \$5000, or three years imprisonment. Witnesses urged an increase to these penalties.

The committee therefore recommends that the Minister of Health pursue the necessary changes to the *Food and Drugs Act* in order that the statute provide the authorities required for increased transparency, increased penalties, and other provisions critical to modernizing drug regulation in Canada. [Recommendation 11]



Implementation of the recommendations proposed in this report should help to improve the clinical trial infrastructure in Canada. However, it is important to monitor whether these efforts have produced the desired effects. To that end, the committee makes its final recommendation:

The committee recommends that Health Canada establish the means to monitor and regularly measure the impact that implementing these recommendations has had on clinical trial activity in Canada and that it report publicly on this progress. [Recommendation 12]

While the committee has recommended mandatory registration of clinical trials in order to address the lack of transparency in this regard, it notes that several witnesses spoke of an overall concern for a lack of transparency at Health Canada in terms of drug approval and monitoring. A related matter was the concern raised by some witnesses about the frequency with which Health Canada fails to meet its own timelines for drug approval. As such, the committee intends to pursue these matters during the subsequent phases of this study.



## 5. CONCLUSION

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In the first phase of its study on prescription pharmaceuticals, the committee has thoroughly reviewed the state of clinical trials of unapproved drugs in Canada. The declining clinical trial activity that has been noted in recent years has meant less investment in research and development in this country, has reduced early access to new drugs for patients and ultimately, has resulted in fewer drugs being submitted to Health Canada for approval due to an increasing perception that Canada is not a ‘friendly’ country to drug manufacturers.

Canada has been too passive and for too long has relied on its reputation of offering high quality research to attract clinical trials. Lack of clinical trial infrastructure has resulted in a slow and cumbersome process taking over any advantage this country had due to the high quality trials it can be counted on to produce. Additionally, over the years, other countries have improved the quality they can offer, and can now do so at much less cost. Canada must implement a standard of ethics

review in order to reduce the time required to get clinical trial going. It must establish accreditation of research ethics boards to ensure that the standard is adhered to, and it must require that the research ethics boards that review clinical trials of unapproved drugs have obtained accreditation.

In terms of transparency of clinical trials, Canada lags far behind the standards now imposed by the European Union and the United States. Clinical trial registration and public accessibility to a range of information about them has been required in these jurisdictions for at least five years. Despite repeated assertions that Canada will follow suit, little has been done.

The time for Canada to act is now. Implementing the recommendations contained in this report will result in an improved clinical trial infrastructure, an increase in Canada’s global competitiveness in the clinical trial sector and ultimately, improved access to innovative medicine for Canadians.





# APPENDIX A – LIST OF ACRONYMS

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<b>ACAHO</b>	Association of Canadian Academic Healthcare Organizations	<b>IFPMA</b>	International Federation of Pharmaceutical Manufacturers and Associations
<b>BGTD</b>	Biologics and Genetic Therapies Directorate	<b>NDS</b>	New Drug Submission
<b>CGSB</b>	Canadian General Standards Board	<b>NOC</b>	Notice of Compliance
<b>CIHR</b>	Canadian Institutes of Health Research	<b>OAG</b>	Office of the Auditor General
<b>CORD</b>	Canadian Organization for Rare Disorders	<b>OCREB</b>	Ontario Cancer Research Ethics Board
<b>CRO</b>	Contract Research Organization	<b>OCT</b>	Office of Clinical Trials
<b>CTA</b>	Clinical Trial Application	<b>REB</b>	Research Ethics Board
<b>DIN</b>	Drug Identification Number	<b>SAP</b>	Special Access Programme
<b>DSMB</b>	Data safety monitoring board	<b>SPOR</b>	Strategy for Patient-oriented Research
<b>EMA</b>	European Medicines Agency	<b>TCPS2</b>	Tri-Council Policy Statement: Ethical Conduct for Research involving Humans (2nd edition)
<b>EU</b>	European Union	<b>TPD</b>	Therapeutic Products Directorate
<b>HPFB</b>	Health Products and Food Branch	<b>U.S.</b>	United States
<b>ICMJE</b>	International Committee of Medical Journal Editors	<b>WHO</b>	World Health Organization
<b>ICTRP</b>	International Clinical Trial Registry Platform		



# APPENDIX B – LIST OF RECOMMENDATIONS

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## RECOMMENDATION 1

The committee therefore recommends that the federal government assume a leadership role in facilitating, coordinating and encouraging a comprehensive clinical trials infrastructure by:

- Establishing a National Framework for Coordinating Clinical Trials to; provide leadership, promote the importance of clinical trials and the benefits of being a participant, help to establish Canada as a preferred site for clinical trials, and provide a point of contact between industry and networks;
- Convening the Federal/Provincial/Territorial Conference of Health Ministers to discuss initiatives in their respective jurisdictions with a view to sharing best practices and reducing duplication of efforts; and
- Encouraging the inclusion of all relevant stakeholders in discussions, consultations and events held in respect of establishing that infrastructure.

## RECOMMENDATION 2

The committee therefore recommends that the Minister of Health:

- move to immediately require clinical trial registration to the greatest degree permitted under its existing legislative and regulatory authorities;
- determine and propose the necessary amendments to the *Food and Drugs Act* and/or the clinical trial regulations contained in Part C, Division 5 of the *Food and Drug Regulations*, to require that manufacturers register a comprehensive set of data for clinical trial phases II and III on a WHO recognized website prior to recruiting any participants. Registration must include, but not be limited to, all results, adverse

reactions, withdrawal of participants (non-identifying), and prematurely ended trials;

- require that all foreign clinical trials that are used to support applications for market authorizations in Canada have met equivalent registration standards; and,
- implement measures to strictly enforce this recommendation in order to ensure transparency of the clinical trial process and of the processes at Health Canada.

## RECOMMENDATION 3

The committee therefore recommends that the Minister of Health direct Health Canada to immediately undertake to develop an accreditation program for Research Ethics Boards. To this end, Health Canada will, as soon as possible:

- Launch discussions, in consultation with the provinces and territories, for a national standard for Research Ethics Boards which:
  - Includes all aspects of trial review including but not limited to; contracts or clinical trial agreements with parameters on compensation and fees, informed consent, placebo versus comparative effectiveness and, review of adverse reaction reports;
  - can be applied to the review of all clinical trials of unapproved drugs in Canada;
  - can serve as the basis for accreditation of research ethics boards, both institutionally-based and privately run; and
- Oversee the implementation of an accreditation program for research ethics review which:
  - Assesses and awards accreditation to research ethics boards that review, approve and oversee clinical trials of unapproved drugs; and,
  - Provides guidance on the training of those involved in research ethics boards.



## RECOMMENDATION 4

The committee further recommends that the Minister of Health amend the clinical trial regulations contained in Part C, Division 5 of the *Food and Drug Regulations*, to stipulate that any reference to a research ethics board means an accredited research ethics board..

## RECOMMENDATION 5

The committee therefore recommends that the National Framework for Coordinating Clinical Trials:

- Encourage the creation of research networks as part of its goal of promoting the importance of clinical trials; and
- Provide guidance to research networks on centralizing research ethics review and on creating databases of patients willing to be considered for clinical trials.

## RECOMMENDATION 6

The committee further recommends that the Minister of Health:

- Amend the clinical trial regulations contained in Part C, Division 5 of the *Food and Drug Regulations*, to stipulate that clinical trials must be designed to reflect the same population that can reasonably be expected to consume the drug once approved for sale in Canada; and
- Implement modifications to its drug approval process to stipulate that market approval will only be granted if clinical trial evidence of the product's safety and efficacy includes data on all population groups that can reasonably be expected to consume that drug once approved for sale in Canada.

## RECOMMENDATION 7

The committee therefore recommends that the Minister of Health direct Health Canada to include the following elements in its Orphan Drug Framework for Canada:

- creation of 'orphan drug status' for drugs in development for specified rare conditions;
- assistance in the design of clinical trials for investigational orphan drugs;
- elimination or reduction of user fees charged by Health Canada to review orphan drug submissions; and,
- extension of market exclusivity for orphan drugs.

## RECOMMENDATION 8

The committee further recommends that the National Framework for Coordinating Clinical Trials:

- Promote Canada as a preferred site for clinical trials of orphan drugs; and
- Include a requirement for consultations with stakeholders including the Canadian Organization for Rare Disorders to explore ways to improve and maximize patient recruitment to trials.

## RECOMMENDATION 9

The committee therefore recommends that the federal government create an expert advisory committee to undertake a thorough study of the intellectual property and tax incentive issues raised by stakeholders during this study with a view to exploring options and recommending changes that will help to improve Canada's global competitiveness in drug development.

## RECOMMENDATION 10

The committee therefore recommends that the Minister of Health direct Health Canada to immediately address the recommendations made in Chapter 4 of the November 2011 Report of the Auditor General of Canada namely to:

- Strengthen the risk-based approach for monitoring and assessing clinical trial adverse reaction reports;
- Establish timelines for officially notifying clinical trial sites of non-compliant ratings; and



- Enhance public access to information on authorized clinical trials, including the results of inspections.

The committee further recommends that the Minister of Health direct Health Canada to address additional issues highlighted in the report and take immediate steps to:

- Realize the target of inspecting two percent of clinical trial sites; and
- Eliminate manual data entry of adverse drug reaction reports through full implementation of electronic reporting

## RECOMMENDATION 11

The committee therefore recommends that the Minister of Health pursue the necessary changes to the *Food and Drugs Act* in order that the statute provide the authorities required for increased transparency, increased penalties, and other provisions critical to modernizing drug regulation in Canada.

## RECOMMENDATION 12

The committee recommends that Health Canada establish the means to monitor and regularly measure the impact that implementing these recommendations has had on clinical trial activity in Canada and that it report publicly on this progress.



## APPENDIX C – WITNESSES

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### Wednesday, March 28, 2012

Health Canada	Paul Glover, Assistant Deputy Minister, Health Products and Food Branch Barbara Sabourin, Director General, Therapeutic Products Directorate Dr. Robert Cushman, Director General, Biologics and Genetic Therapies Directorate
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### Thursday, March 29, 2012

Canadian Institutes of Health Research	Dr. Alain Beaudet, President
Drug Safety and Effectiveness Network	Dr. Robert Peterson, Executive Director
Health Canada	Kimby Barton, Director, Bureau of Cardiology, Allergy and neurological sciences Barbara Sabourin, Director General, Therapeutic Products Directorate Dr. John Patrick Stewart, A/Director General, Clinical Trials Office

### Wednesday, April 4, 2012

Health Canada	Paul Glover, Assistant Deputy Minister, Health Products and Food Branch Barbara Sabourin, Director General, Therapeutic Products Directorate Dr. John Patrick Stewart, A/Director General, Clinical Trials Office
Office of the Auditor General of Canada	Neil Maxwell, Assistant Auditor General Louise Dubé, Principal



### Wednesday, April 25, 2012

Amgen Canada Inc.	Dr. Clive Ward-Able, Executive Director, Research and Development
BIOTECanada	Peter Brenders, President and Chief Executive Officer Luc Mainville, Vice-Chair, Board of Directors
Hoffmann-La Roche Ltd.	Nita Arora, Regional Head Affiliate Management, North America
Rx&D	Ken Hughes, Vice-President, Scientific and Regulatory Affairs Russell Williams, President

### Thursday, April 26, 2012

Canadian Stroke Consortium	Dr. Mukul Sharma, Chairman of the Board
Institutional Review Board Services	Jack Corman, President
Reformulary Group	Helen Stevenson, President and Chief Executive Officer

### Thursday, May 3, 2012

Best Medicines Coalition	Kathy Kovacs-Burns, Operations Committee Member
Canadian Organization for Rare Disorders	Kelly Gorman, Board Member



### Wednesday, May 9, 2012

As individuals	Dr. Stuart MacLeod, Professor, Child and Family Institute, University of British Columbia Dr. Robin Walker, Integrated Vice-President, Medical Affairs and Education, London Health Sciences Centre and St Joseph's Health Care
Association of Canadian Academic Healthcare Organizations	Dr. David Hill, Co-chair, Vice-Presidents of Health Research Group Tina Saryeddine, Assistant Vice-President, Research and Policy Analysis
Canadian Medical Association	Dr. Maura Ricketts, Director, Health Policy and Research Millicent Toombs, Senior Policy Analyst, Health Policy and Research

### Thursday, May 10, 2012

As individuals	Françoise Baylis, Professor and Canada Research Chair, Faculty of Medicine, Dalhousie University Trudo Lemmens, Scholl Chair in Health Law and Policy, Faculty of Law, University of Toronto Ann Silversides, Independent journalist, Health Policy.
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### Wednesday, May 16, 2012

As individuals	Dr. Joel Lexchin, Professor, School of Health Policy and Management, York University Miriam Shuchman, Chair, Research Ethics Board, Women's College Hospital
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### Thursday, May 17, 2012

As individuals

Matthew Herder, Assistant Professor,  
Health Law Institute, Faculties of  
Medicine and Law, Dalhousie University  
Dr. David Moher, Senior Scientist, Clinical  
Epidemiology Program, Ottawa Hospital  
Research Institute

### Wednesday, May 30, 2012

Canadian Association of Research Ethics Board Sharon Freitag, Past President

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Clinical Trials Ontario Ronald Heslegrave, Executive Director

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Ontario Institute for Cancer Research Janet Manzo, Executive Director, Ontario  
Cancer Research Ethics Board  
Dr. Raphael Saginur, Chair, Ontario  
Cancer Research Ethics Board,  
Governance Committee





