



Health
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**OPTIONS FOR IMPROVING PUBLIC ACCESS TO INFORMATION ON
CLINICAL TRIALS OF HEALTH PRODUCTS IN CANADA**

Welcome!

Health Canada is interested in your opinions on policy options related to improving access to information on clinical trials of health products in Canada. Your feedback is important as it will inform us and help shape the final policy for the registration and disclosure of clinical trial information.

Background - Improving Access to Information on Clinical Trials of Health Products in Canada

Patients, prescribers, researchers and regulators have all expressed support for increased public disclosure of information pertaining to clinical trials. Registration of clinical trials in publicly accessible registries has been identified as a key means of enhancing transparency and would provide the opportunity for more informed decision-making among patients, physicians, researchers and other stakeholders with interests in clinical trials.

There is currently no requirement in Canada for public disclosure of clinical trial information or results. To read about international activities, see the Appendix, page 5.

As you may be aware, Health Canada has been working to develop a Canadian approach to the registration and disclosure of clinical trial information. In June 2005, Health Canada held consultations with a wide range of stakeholders in order to identify “end-user” needs and requirements for clinical trial registries. Consultations consisted of an [online questionnaire](#) and three one-day workshops which took place in Ottawa, Halifax and Vancouver. See the [Report of Three Workshops: Ottawa, Halifax, Vancouver](#), for an overview of the workshop findings.

These early consultations contributed to the initial stages of policy development. An [External Working Group](#) was established to develop and advise on options for improving public access to clinical trial information in Canada. The EWG has now developed a preliminary list of considerations, principles, and suggestions regarding the components and scope of a system for the registration and disclosure of clinical trial information, which forms the basis of this workbook. The final report will be posted on-line on the Health Canada website in the summer 2006.

This online workbook seeks public input into the preliminary suggestions of the EWG.

The EWG will consider the results of this workbook in the development of final recommendations, which will be presented to Health Canada by Fall 2006. Decision-making authority rests with Health Canada.

How to Use This Workbook

Before continuing, we would like to provide you with an overview and a few instructions.

It will take approximately 30 minutes to complete the workbook.

Important! You can leave the workbook open for as long as you need and return to finish it at any time. However, if you **close** the document or **shut down your computer** before completing all of your responses, you will have to **re-enter** your answers.

First, you will be asked to tell us about yourself.

Then, you'll be asked to provide responses to six sections related to different aspects of the registration of clinical trials and the disclosure of clinical trial results:

- 1 - Purpose of the Registration of Clinical Trial Information
- 2 - Scope of Clinical Trials to be Registered
- 3 - Content for Clinical Trial Registration
- 4 - Content for Disclosure of Results
- 5 - Timing of Registration and Disclosure of Data
- 6 - Administration and Implementation

Additional sources of information appear throughout the workbook in **red** font (the additional information can be found in the appendix). "Discussion points" are also highlighted throughout the workbook (also found in the appendix) and provide some context and summarize the debate that exists around certain issues.

Please note that all responses will be kept confidential and no personal identification will be forwarded or disclosed.

Tell us about Yourself

Knowing a little about you will help us to better understand the information we receive during this consultation.

1. Please indicate which group(s) and/or sector(s) you belong to:

- Patient
- Informal Caregiver (e.g., parent, guardian, relative, friend, etc.)
- General Public
- Patient Group/Association
- Consumer Group
- Patient Advocacy Organization
- Health Professional, Please indicate your designation and specialty/field:

- Researcher
- Academia (e.g., administrator in a university research setting, etc.)
- Health Research Funder
- Canadian provincial/territorial governments
- Foreign governments (including the U.S.)
- Pharmaceutical Industry
- Natural Health Products Industry
- Medical Devices Industry
- Industry Association
- International Organization
- Other (Please specify) _____
- Do Not wish to Disclose

2. I live in:

[Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Quebec, Saskatchewan, Yukon]

Background - About Clinical Trials

What is a clinical trial?

A clinical trial is a research study that looks to discover or verify the effects of a health product through the use of human subjects. Clinical trials are one of the most important sources of scientific evidence on the safety and effectiveness of health interventions.

When a sponsor (an individual, corporate body, institution or organization) applies to have a new drug product approved for sale in Canada, it is expected to show scientific evidence of the drug's safety, efficacy and quality. While the effects of a new drug on people can be measured in other ways, such as astute observation or anecdotal evidence, a clinical trial is the best scientific approach to provide clear and reliable data. Specifically, a clinical trial is used to determine whether a drug is safe and effective, what dosages are most effective, and what side effects a drug may cause.

In a clinical trial, comparable groups of people receive different forms of treatments. One group may receive the drug being tested, while another group may receive a treatment already known to be effective, or a placebo (an inactive substance that looks like the drug being tested).

Clinical trials are normally done in four phases, with each successive phase involving a larger number of people. For definitions of each of the clinical trial phases, see the Appendix.

Background - About Clinical Trials, continued

Two terms often used when discussing the registration of clinical trial information are: “trial” and “intervention.” These terms are important to define because they help to demonstrate the range of health research initiatives involving humans. Some of these fall under Health Canada’s authority, while others are outside Health Canada’s regulatory responsibility and control.

The definitions provided below for “**trial**” and “**intervention**” were developed as part of “The Ottawa Statement,” a document supported by a number of individuals and organizations throughout the research community that aims to guide the implementation of trial registration worldwide. See: <http://ottawagroup.ohri.ca/index.html>.

“**Trial**” refers to a prospective controlled or uncontrolled research study evaluating the effects of one or more health-related interventions assigned to human participants.

“**Intervention**” refers to a deliberate act applied to an individual or group of individuals. Health-related interventions include, but are not limited to, the use of pharmaceuticals, biological products, surgery, procedures, radiation, devices, education, counselling, behaviour change, complementary health modalities, and management or economic policies.

Another term often used when discussing clinical trials is “**Research Ethics Board**” (REB). A REB is a group of people who review a proposal for a clinical trial to determine if it adequately protects the rights, safety and well being of the trial participants. Members of a REB are drawn from medical (or dental), legal, ethical, scientific and other fields as appropriate, as well as a member of the community. The REB is an independent body, not affiliated with the sponsor of the research or with Health Canada.

Health Canada has regulatory authority for:

- The sale and importation of drugs (**pharmaceutical** and **biological** used in clinical trials involving human subjects. This includes both new drugs (i.e., products not yet approved for sale in Canada), and existing marketed products that are being tested for a use, dosage or other therapeutic application other than those for which it was approved.
- The sale and importation of **medical devices** used in clinical trials involving humans.
- Clinical trials of **natural health products** involving humans.

All clinical trials in Canada that are under Health Canada’s authority are subject to review by an REB.

When you’re ready, please click **NEXT PAGE** to begin the workbook.

PART 1 - Purpose of the Registration of Clinical Trial Information

Users

Many people have expressed support for increased public disclosure of information pertaining to clinical trials.

Users of information on clinical trials may include patients, caregivers (informal and formal), health professionals, researchers, academics, research funders, industry and regulators.

3. Do you agree with this potential list of end users for clinical trial information?

Please check all that apply.

- Patients
- Caregivers (informal and formal)
- Health Professionals
- Researchers
- Academics
- Research Funders
- Industry
- Regulators

3a. Please provide any additional users of clinical trial information.

PART 1- Purpose of the Registration of Clinical Trial Information, continued

Overall Purpose

Why register clinical trial information?

Registration of clinical trials would be an official means of making information about ongoing and concluded trials of health products publicly available in a registry.

Supporters of clinical trial registration suggest that registries can improve the transparency of research and facilitate more informed, evidence-based decision-making, bringing with it increased public confidence in evidence-based research and the safety of research participants.

On the other hand, concerns have been expressed that the registration of clinical trials and public disclosure of results could compromise Canada's commercially competitive position as well as participant privacy.

The suggested **purpose** of improving public access to information on clinical trials is: to protect the public; serve the public trust; promote the integrity of science; and make Canada an attractive place for innovation on the global scene.

Please indicate your agreement or disagreement with each element of the Overall Purpose:

4. To protect the public

- Agree
- Disagree
- Not Sure

4a. Please provide comments or suggestions:

5. To serve the public trust

- Agree
- Disagree
- Not Sure

5a. Please provide comments or suggestions:

6. To promote the integrity of science

- Agree
- Disagree
- Not Sure

6a. Please provide comments or suggestions:

7. To make Canada an attractive place for innovation on the global scene

- Agree
- Disagree
- Not Sure

7a. Please provide comments or suggestions:

8. Any suggestions for other elements of the purpose?

Specific Objectives

9. The following are more **specific objectives** for the registration and disclosure of clinical trial information and results.

For each objective, please indicate your agreement by checking the box next to it, or your disagreement by leaving the box empty. Space is provided at the bottom of the list for your comments.

For an explanation of each objective, see pages 6 – 7 of the Appendix.

- a) To facilitate enrolment of prospective research participants in clinical trials.
- b) To mitigate selective reporting of trials.
- c) To promote efficient advancement of science by helping to set the direction for future research and avoid duplication of studies.
- d) To facilitate systematic and rigorous review (meta-analysis) of information about clinical trials that have been undertaken.
- e) To meet ethical obligations to participants by making information about the trials they participate in publicly available so that the trial outcomes might inform future research or care.
- f) To help patients and health providers make informed health decisions.
- g) To encourage quality clinical trials and **good clinical practice**.
- h) To facilitate Canada's contribution to the global body of health-related knowledge.
- i) To support information exchange about clinical trials between Canada and other countries.
- j) To support the development of common standards (which may include standards for practices, registration and results reporting) for clinical trials globally.
- k) To facilitate ethics oversight and research on research ethics.
- l) To facilitate the sharing of information among clinical trial registries.
- m) To facilitate transparency around research and trials.

10. Please provide any additional specific objectives or comments.

PART 2- Scope of Trials to be Registered

There are different opinions regarding **what types and phases** of clinical trials should be required for registration.

There are many types of health products that use clinical trials to determine safety and effectiveness. While clinical trials of drugs (pharmaceuticals and biologics) are the most common type of trial, there is a growing range of clinical trial types that includes medical devices, natural health products, surgical procedures and clinical trials that focus on health prevention and health outcomes.

These clinical trial types are further separated into **trial phases**.

There is strong support that Phases II, III, and IV clinical trials should be required to register. There is less agreement regarding the registration of Phase I trials.

Discussions Around Phase I Trials

On the one hand, many people believe that by registering all trials, including Phase I trials, the knowledge pool will be strengthened. This applies in particular to those trials that may not proceed beyond Phase I, usually because of an adverse reaction. Inclusion of Phase I trials is considered by many to be an important aspect of ethical oversight. It is also seen as a valuable information source for potential participants.

On the other hand, some people believe the registration of information related to Phase I trials could jeopardize academic or commercial competitive advantage, particularly for trials of new drugs.

Another concern is that a requirement to register Phase I trials could “swamp” a registry system because of the large number of Phase I trials taking place.

Another consideration is that it may be difficult to clearly define clinical trial phases. Distinction between Phase I, II, III, and IV trials may be less defined when new study designs (e.g., open label extension studies, epidemiology studies) are being developed. This may be the case, in particular, for Phase 1 and Phase 2 trials, or particular disease areas, such as AIDS research.

Other groups have suggested that all clinical trial phases require registration. However, the nature of registration of Phase I trials could be different than other trial phases in order to protect academic and/or commercial competitive advantage.

Part 2 - Scope of Trials to be Registered, continued

Please indicate your agreement or disagreement with each of the following statements regarding the **scope of trials to be registered**. Space is provided for your comments.

11. The full spectrum of trial types should be registered. This includes all types of health products, such as biologics, pharmaceuticals, medical devices, and natural health products.

- Agree
- Disagree
- Not Sure

11a. Please provide comments or suggestions.

12. All clinical trials of Phases II, III and IV should be registered.

- Agree
- Disagree
- Not Sure

12a. Please provide comments or suggestions.

13. Phase I trials with healthy volunteers should be registered, but the nature of the registration may differ from other phases.

- Agree
- Disagree
- Not Sure

13a. Please provide comments or suggestions.

14. Although Phase I trial information is primarily useful to the regulator, it may also be of value for ethics oversight, the research community, and possibly the public.

- Agree
- Disagree
- Not Sure

14a. Please provide comments or suggestions.

PART 3- Content for Clinical Trial Registration

The World Health Organization (WHO) is developing a **platform** (see Appendix for more details) for the international registration of clinical trials information. It will include a search portal for searching all member registers worldwide and a registration portal providing background, information, and advice on trial registration and results reporting. A Universal Trial Reference Number (UTRN) will be assigned to each registering trial.

For more information on the WHO's initiative, see: <http://www.who.int/ictrp/en/>.

The WHO has created a data set for standardizing the information that is registered in order to facilitate reliable and meaningful data searches. It identifies the minimum amount of trial information that must be provided for a given trial to be considered "registered." This information includes, for example, the official study title, intervention, target sample size and expected primary and secondary outcomes. A total of 20 fields make up the data set.

Please review the [WHO Trial Registration Data Set](#) on the WHO website before proceeding to the next questions.

PART 3- Content for Clinical Trial Registration, continued

Now that you have reviewed the WHO data set, please indicate your agreement or disagreement with the following statements **about the appropriateness of the WHO data set to a Canadian system**. Space is provided for your comments.

15. The [World Health Organization Trial Registration Data Set](#) should be part of a Canadian system.

- Agree
- Disagree
- Not Sure

15a. Please provide comments or suggestions.

16. The completion of all fields of the [World Health Organization Trial Registration Data Set](#) should be mandatory.

- Agree
- Disagree
- Not Sure

16a. Please provide comments or suggestions.

PART 3- Content for Clinical Trial Registration, continued

Why a Canadian Registry?

Many stakeholders support a Canadian clinical trial registration and disclosure system that provides both internationally required information (i.e., the WHO data set) and which meets unique Canadian needs from a Canadian perspective. Proponents believe a Canadian system would help increase awareness of the Canadian health research enterprise, increase opportunities for Canadian researchers to collaborate, and raise Canada's research profile on the international scene. A Canadian system would better promote local clinical trials, and could lead to increased access and participation in trials. These benefits could translate into increased numbers of clinical trials taking place in Canada, thereby increasing access of Canadians to innovative health products. In addition, a Canadian system could foster increased public confidence in the clinical trial process.

On the other hand, some stakeholders feel existing international systems can sufficiently address Canadian needs. A Canadian system would be an unnecessary duplication, resulting in increased administrative burden for both industry and researchers. There is a potential for conflicting registration requirements amongst jurisdictions, which may lead to confusion, inconsistency, and incomplete information being registered. Duplicate registration may also lead to the impression that more trials of an intervention are taking place than actually exist. There are also concerns related to the release of intellectual property and competitive advantage should Canadian clinical trial registration requirements differ from those of other countries.

The External Working Group believes it is important to consider and balance unique Canadian needs with the direction taken by the international clinical trial community.

PART 3- Content for Clinical Trial Registration, continued

Please indicate whether you agree or disagree that the following items, **in addition to the [World Health Organization Trial Registration Data Set](#)**, should be part of a Canadian system.

17. An Informed Consent Form from the clinical trial (a document that provides a summary of the trial design, risk factors and other information in lay language).

- Agree
- Disagree
- Not Sure

17a. Please provide comments or suggestions.

18. Information on known **adverse reactions.**

- Agree
- Disagree
- Not Sure

18a. Please provide comments or suggestions.

19. Information of an educational nature about clinical trials, such as a glossary of terms, information on the clinical trial process, sources for more information, etc.

- Agree
- Disagree
- Not Sure

19a. Please provide comments or suggestions.

20. Information about at least one **Research Ethics Board (REB) approval of the trial.** (See the Appendix for more information)

- Agree
- Disagree
- Not Sure

20a. Please provide comments or suggestions.

21. Information about any REB denial and reason for denial.

- Agree
- Disagree
- Not Sure

21a. Please provide comments or suggestions.

PART 4- Content for Disclosure of Results

Disclosure of results refers to the public release of information about the outcome of a clinical trial. Currently, this may be done by providing information in a results database or through publication in a peer-reviewed medical journal. Often though, these databases are not publicly accessible.

Many people believe that open access to clinical trial results is extremely important to sound and informed health decisions. In order to support informed decision making, results should be provided in a context that is meaningful and easily understood. Outcomes should be reported for all registered trials, whether completed or not.

Some stakeholders have concerns that clinical trial results, especially of early phase trials, may be misinterpreted by or cause confusion amongst the public. There are also issues related to the validity of results, concerns that results will be presented in a manner that “promotes” an unapproved health product, and concern that early positive results may lead to public pressure on the regulator for early approval of the product.

Some stakeholders have expressed concern that the disclosure of results could compromise commercial competitiveness. In addition, should Canadian results disclosure requirements differ from those of other jurisdictions, there is a risk that Canadian sites may not be included as part of international trials.

Please indicate your agreement or disagreement with the following statements:

22. All completed studies of **health products should be reporting results.**

- Agree
- Disagree
- Not Sure

22a. Please provide comments or suggestions.

23. All interrupted, uncompleted and/or cancelled clinical trials should report the reason(s) for interruption, stoppage, or cancellation.

- Agree
- Disagree
- Not Sure

23a. Please provide comments or suggestions.

24. All **adverse events, including **severe adverse events**, should be reported.**

- Agree
- Disagree
- Not Sure

24a. Please provide comments or suggestions.

25. The context of the results, links to more information, a disclaimer or other similar explanatory information should be included.

- Agree
- Disagree
- Not Sure

25a. Please provide comments or suggestions.

26. Raw data should be included with restricted/limited access. (See the Appendix for more information)

- Agree
- Disagree
- Not Sure

26a. Please provide comments or suggestions.

27. Lay summaries of results should be provided. (See the Appendix for more information)

- Agree
- Disagree
- Not Sure

27a. Please provide comments or suggestions.

PART 5- Timing of Registration and Disclosure of Data

Registration of Clinical Trial Information:

Growing support and pressure exists for the registration of clinical trials as early as possible. In July 2005, for example, the International Committee of Medical Journal Editors, a group representing 11 prestigious medical journals, instituted a policy whereby a scientific paper on clinical trial results cannot be published unless the trial had been recorded in a publicly accessible registry.

Disclosure of Results:

There are disagreements about when results of clinical trials should be disclosed. On one hand, many people believe that the disclosure of results from all registered trials should be required within a reasonable and established time of completion of the trial. On the other hand, some groups feel that the disclosure of results for trials should only be required after market approval of that indication in a major country, as providing information on results before market approval may give patients false hope based on incomplete conclusions.

The timing of disclosure of results is also related to issues of confidentiality (ie. to protect commercial or academic interests).

PART 5- Timing of Registration and Disclosure of Data, continued

Please indicate your agreement or disagreement with each of the following statements regarding the **timing of registration and disclosure of results**.

See the Appendix for additional explanations.

28. Registration of clinical trial information should take place before the first participant is enrolled.

- Agree
- Disagree
- Not Sure

28a. Please provide comments or suggestions.

29. Timeframes for reporting (for example, “within 6 months”) on results should be established for all completed and uncompleted trials.

- Agree
- Disagree
- Not Sure

29a. Please provide comments or suggestions.

30. Trials that were prematurely stopped for a clinical reason(s) (for example, a safety concern) should be disclosed in an expedited timeframe.

- Agree
- Disagree
- Not Sure

30a. Please provide comments or suggestions.

31. Established timeframes for disclosing results may be adjusted to accommodate peer review, publication constraints/restrictions and other circumstances.

- Agree
- Disagree
- Not Sure

31a. Please provide comments or suggestions.

PART 6- Administration and Implementation

The External Working Group has suggested that Health Canada should have responsibility for administration and oversight of the registration and disclosure of Canadian clinical trial information. This would include monitoring of compliance as well as ensuring the accuracy and completeness of information provided.

Health Canada, given its authority for regulation and marketing approval of drugs, medical devices and natural health products, could provide the required oversight for these products.

For products outside Health Canada's regulatory authority, it has been suggested that the governing body that oversees the particular area of focus of the clinical trial in question (e.g., the health professional association) should be responsible for ensuring compliance and accuracy of information registered.

In addition, agreements between funders and recipients could stipulate registration as a requirement of funding. For example, in Canada, the Canadian Institutes of Health Research (CIHR), the Government of Canada's agency for health research, requires that all CIHR-funded randomized controlled trials be registered with an International Standard Randomized Controlled Trial Number at the U.K.'s clinical trials registry (www.Controlled-Trials.com).

PART 6- Administration and Implementation, continued

Please indicate your agreement or disagreement with each of the following statements regarding the **administration of the system and Health Canada’s role and responsibility**.

Voluntary or Mandatory?

Governments and public health research agencies in several jurisdictions have leveraged their position as “funder” of clinical trials so that registration is a condition of research funding.

In Canada, the Canadian Institutes of Health Research (CIHR), the Government of Canada’s agency for health research, requires that all CIHR-funded randomized controlled trials be registered with an International Standard Randomized Controlled Trial Number at the U.K.’s clinical trials registry (www.Controlled-Trials.com).

In the United States, the Fair Access to Clinical Trials Act (FACT Act) proposed registration as a condition of approval by Institutional Review Boards (U.S. equivalent to Canada’s REBs).

The Australian Clinical Trials Registry (ACTR) is an online register of clinical trials undertaken in Australia, and is funded by Australia’s National Health and Medical Research Council (NHMRC). Registration is voluntary.

32. Health Canada should be directly responsible for ensuring the registration of clinical trials that fall under its regulatory authority.

- Agree
- Disagree
- Not Sure

32a. Please provide comments or suggestions.

33. Health Canada should work with partners and other authorities (provinces, funding agencies, research institutes, universities, etc.), so that registration is a mandatory criteria of funding, research, participation and other agreements.

- Agree
- Disagree
- Not Sure

33a. Please provide comments or suggestions.

34. Registration of clinical trial information should be required of all government-funded health research.

- Agree
- Disagree
- Not Sure

34a. Please provide comments or suggestions.

35. Registration of clinical trial information should be required of all health research funded by a council/agency.

- Agree
- Disagree
- Not Sure

35a. Please provide comments or suggestions.

36. Registration of clinical trial information should be required of all health research conducted in academic centres.

- Agree
- Disagree
- Not Sure

36a. Please provide comments or suggestions.

37. There should be no user fees associated with the registry system.

- Agree
- Disagree
- Not Sure

37a. Please provide comments or suggestions.

PART 6- Administration and Implementation, continued

Implementation of a Canadian System for the Registration and Disclosure of Clinical Trial Information

The preferred model of the External Working Group is an affiliation with an existing registry (for example, the U.S.-based www.Clinical-Trials.com), with a separate Canadian area or portal. This would allow for components that have been identified by Canadian stakeholders as important, yet which may be beyond the usual scope of the existing registry.

This model would support unique Canadian needs while facilitating Canada's participation in the international clinical trial community. This may be less resource intensive for Health Canada than a separate registry, and provide for domestic and international information searches. However, there have been concerns raised related to independence, public trust and control.

Please indicate your agreement or disagreement with the proposed model.

38. The Canadian system for the registration of clinical trial information and disclosure of results could be an affiliation with an existing registry, with a separate and independent Canadian portal/section.

- Agree
- Disagree
- Not Sure

38a. Please provide comments or suggestions.

Evaluation Questions

Before you go, please take a moment to let us you know how you found the experience of completing this workbook.

39. Please indicate your level of agreement or disagreement with the following statements:

	Strongly Agree	Agree	Neither Agree Nor Disagree	Disagree	Strongly Disagree	Not Sure
Overall, the workbook helped me understand issues around the registration and disclosure of clinical trial information.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information contained in the workbook was easy to understand.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The workbook took too long to complete.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The workbook was too technical and therefore too hard to use.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The workbook provided an opportunity to share my comments and feedback on proposed options for registration and disclosure of clinical trial information.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Based on this experience, I would consider completing another workbook in the future.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

40. Please let us know if you have additional comments about this workbook.

Thank you

Thank you for completing the consultation workbook on the registration and disclosure of clinical trial information. Your input will help shape Health Canada's future work in this area. In the coming months, you will receive a more detailed report on the outcomes of this consultation based on the valuable input provided by our stakeholders.

Once again, thank you for your involvement and contribution.

Please click "Submit the Workbook" to submit your responses.

Appendix

DEFINITIONS

Adverse Reaction

Adverse reactions are undesirable effects to health products. Health products include drugs, medical devices and natural health products. Drugs include both prescription and nonprescription pharmaceuticals; biologically-derived products such as vaccines, serums, and blood derived products; cells, tissues and organs; disinfectants; and radiopharmaceuticals.

Reactions may occur under normal use conditions of the product. Reactions may be evident within minutes or years after exposure to the product and may range from minor reactions like a skin rash to serious and life-threatening events such as a heart attack or liver damage.

Adverse Event

Any adverse occurrence in the health of a clinical trial subject who is administered a drug, that may or may not be caused by the administration of the drug, and includes an adverse drug reaction.

Biologics

Encompass most drugs whose manufacture involves purification from biological sources such as human or animal tissue or body fluids, or micro-organisms, including those derived using biotechnology. Typical examples include blood and blood products, vaccines, biological response modifiers (growth factors, cytokines, etc.) protein hormones, gene therapy vectors, and cell-based products. Biologics make up one large category of drugs; the other major category of drugs is pharmaceuticals, or synthetic drugs made from chemicals.

Good Clinical Practices

Generally accepted clinical practices that are designed to ensure the protection of the right, safety and well-being of clinical trial subjects and other persons.

Health Products

Includes pharmaceuticals, biologics, medical devices and natural health products.

Medical Device

Any article, instrument, apparatus or contrivance, including any component, part or accessory thereof, manufactured, sold or represented for use in

- a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
- b) restoring, correcting or modifying a body function or the body structure of human beings or animals,
- c) the diagnosis of pregnancy in human beings or animals, or
- d) the care of human beings or animals during pregnancy and at and after birth of the offspring, including care of the offspring,
and includes a contraceptive device but does not include a drug.

Medical devices are categorized into four classes based on the level of risk association with their use. Class I devices present the lowest potential risk (i.e., thermometers) and Class IV devices present the greatest potential risk (i.e., pacemakers).

Natural Health Product

The *Natural Health Products Regulations* define natural health products (NHPs) as a substance set out in Schedule 1 or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1, a homeopathic medicine or a traditional medicine, that is manufactured, sold or represented for use in

- a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- b) restoring or correcting organic functions in humans; or
- c) modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

However, a natural health product does not include a substance set out in Schedule 2, any combination of substances that includes a substance set out in Schedule 2 or a homeopathic medicine or a traditional medicine that is or includes a substance set out in Schedule 2. NHPs include, but are not limited to, the following: homeopathic preparations; vitamins; minerals; enzymes; coenzymes; co-factors; herbs or botanicals; naturally-occurring animal, plant and microorganism substances; and, a variety of molecules extracted from natural sources, such as amino acids, polysaccharides, peptides, naturally occurring hormones and biochemical intermediates, as well as naturally occurring molecules synthesized by chemical or biological means.

Pharmaceutical

Includes mostly synthetic products made from chemicals for therapeutic use. This can be either a prescription or non-prescription product, and includes products used in the treatment, mitigation, diagnosis or prevention of a disease or abnormal physical condition. Pharmaceuticals make up one large category of drugs; the other major category is biologics, or drugs that are prepared using a biological starting or source material.

Phase I Clinical Trials

Initial safety studies on a new drug, including the first administration of the drug into humans, usually conducted in healthy volunteers. These trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical.

Phase I trials are designed mainly to determine the pharmacological actions of the drug and the side effects associated with increasing doses. Pharmacokinetic as well as drug-drug interaction studies are usually considered as Phase I trials regardless of when they are conducted during drug development as these are generally conducted in healthy volunteers. Phase I trials also include trials in which new drugs are used as research tools to explore biological phenomena or disease processes.

Phase II Clinical Trials

Clinical trials to evaluate the efficacy of the drug in patients with medical conditions to be treated, diagnosed or prevented and to determine the side effects and risks associated with the drug. If a new indication for a marketed drug is to be investigated, then those clinical trials may generally be considered Phase II trials.

Phase III Clinical Trials

Controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the drug has been demonstrated. These are intended to gather the additional information about efficacy and safety that is needed for further risk/benefit assessment of the drug. In this phase, clinical trials are also conducted in special patient populations (i.e., renal failure patients), or under special conditions dictated by the nature of the drug and disease.

Phase IV Clinical Trials

All studies performed after the drug has been approved by the regulator for the market, and related to the approved indication. These studies are often important for optimizing the drug's use. They may be of any type, but must have valid scientific objectives. Commonly conducted studies include safety studies and studies designed to support use under the approved indication such as mortality and morbidity studies, or epidemiological studies.

Research Ethics Board

A body that is not affiliated with the sponsor, and:

- a) the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being; and
- b) that has at least five members, that has a majority of members who are Canadian citizens or permanent residents under the Immigration Act, that is composed of both men and women and that includes at least:
 - i) two members whose primary experience and expertise are in scientific discipline, who have broad experience in the methods and areas of research to be approved and one of whom is from a medical discipline or, if the clinical trial is in respect of a drug to be used for dental purposes only, is from a medical or dental discipline;
 - ii) one member knowledgeable in ethics;
 - iii) one member knowledgeable in Canadian laws relevant to the biomedical research to be approved;
 - iv) one member whose primary experience and expertise are in a non-scientific discipline; and
 - v) one member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the sponsor or the site where the clinical trial is to be conducted.

Severe Adverse Event

An adverse event that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening, or that results in death; includes severe adverse drug reactions.

POP-UP BOXES AND MORE INFORMATION

What are other countries doing?

The most significant and widely used of all international registries are www.ClinicalTrials.gov in the United States and www.controlled-trials.com in the United Kingdom.

ClinicalTrials.gov was established as a result of section 113 of the 1997 Food and Drug Administration Modernization Act (FDAMA). Section 113 required registration of all clinical studies for serious or life-threatening diseases or conditions, within 21 days of study inception. The site was developed by the National Library of Medicine and is maintained by the National Institutes of Health (an agency under the US Department of Health and Human Services). The registry contains information about trials, both foreign and domestic, that are conducted under an Investigational New Drug application submitted to the FDA.

ControlledTrials.com was developed by Current Controlled Trials (CCT) Ltd., part of the Current Science Group of biomedical publishing companies. The CCT developed the International Standard Randomised Control Trial Number (ISRCTN) scheme, which assigns unique identification numbers to clinical trials worldwide. The CCT site provides free access to two registries; the ISRCTN registry, and the metaRegister of Controlled Trials, which combines contents of many existing registries. Trials are eligible for an ISRCTN if they are in clinical areas relevant to healthcare and the trials are randomized.

There are also many other clinical trial registries sponsored by patient organizations, pharmaceutical/ health products industry and industry associations, public funding agencies, and government regulators.

Some estimates place the number of trial registries at over 350 in the United States alone. As a result, the extent and type of information available varies widely amongst registries. It can be difficult to find information, search for specific information, or to compare “apples to apples.”

Question 9

OBJECTIVES

The External Working Group identified a number of specific objectives for a clinical trial registration system.

These are explained below:

- a) **“To facilitate enrolment of prospective research participants in clinical trials.”** One of the benefits of registration is said to be that patients (and their physicians) are able to identify trials in which they may want to participate. Participation in trials gives patients access to the newest types of treatment, and allows patients to contribute to advances in medicine.
- b) **“To mitigate selective reporting of trials.”** Researchers are more likely to report statistically significant outcomes and medical journals tend to report positive outcomes and “startling” outcomes. Registration and disclosure of clinical trial information may help reduce this “selective” reporting and publication bias by adding some measure of accountability and transparency.
- c) **“To promote efficient advancement of science.”**
Registration and disclosure of clinical trial information may help researchers to avoid duplicating research and may help researchers to identify priority areas where current research is lacking. Duplicate publication of results in various jurisdictions, which can give the impression of more evidence pertaining to an intervention than actually exists, may also decrease if registration of trials is required.
- d) **“To facilitate systematic reviews.”** Systematic reviews (also known as meta-analyses) are a significant source of information on which decisions about health care or medical practice decisions are made. Researchers conducting systematic reviews on particular therapies are dependent on knowledge of the existence of the full range of relevant clinical trials in order to ensure the accuracy of the conclusions. Reviews will more likely produce biased results if they are missing information about the existence of certain trials. Registration of trials at inception would ensure that all trials form part of the public record and are available for the many stakeholders in clinical research.
- e) **“To meet ethical obligations to clinical trial participants.”** People participate in clinical trials in part because they want to contribute to greater knowledge about a particular medical condition or therapy, so that others may benefit. It has been argued that participants in any trial assume potential risks in order to contribute to knowledge and that investigators and sponsors are therefore ethically bound to make information about the clinical trial publicly accessible: after all, the new medical knowledge derived from the clinical trial was made possible by the collective altruism or good will of those who participated, and therefore that new knowledge should be accessible to all. The registration and disclosure of clinical trial information will help to advance this goal.

- f) **“To help patients and health providers make informed health decisions.”** It has been suggested that the registration and disclosure of information about clinical trials will allow patients to have access to information that they can use to make informed decisions about their health. On the other hand, the information provided through the registry may be taken out of context or misinterpreted by those outside the immediate research community, thereby leading to poor health choices.
- g) **“To encourage good clinical trials practice.”** It has been suggested that trial protocols are sometimes changed through the course of a trial, in order to obtain desired results. In some cases, significant changes have been discovered in primary outcomes between the original protocol and publication. Registration of clinical trial information, including primary outcomes, may result in a general improvement in clinical practices
- h) **“To facilitate Canada’s contribution to the global body of health-related knowledge.”** Many people believe that the registration of clinical trial information and the disclosure of results will help to:
- build the health knowledge-base (in Canada and globally),
 - improve understanding of illness, disease, and prevention, and
 - improve health outcomes.
- i) **“To support information exchange about clinical trials between Canada and other countries.”** Improving the exchange of information about clinical trials may provide researchers with valuable guidance for their research, help to save limited research dollars by reducing duplication, and encourage collaboration amongst researchers.
- j) **“To support the development of common standards (which may include standards for practices, registration and results reporting) for clinical trials globally.”** For example, a standardized reporting format may allow for better understanding of information among various users.
- k) **“To facilitate ethics oversight and research on research ethics.”** “Ethics oversight” ensures that the safety of clinical trial participants is not compromised and that Canadian values and rights regarding research, privacy, dignity and other principles are respected. Ethical oversight tools include REB [hyperlink to definition] review of proposed and ongoing clinical trials and the use of “Informed Consent forms” (a document that provides a summary of the trial design, risk factors and other information in lay language).

“Research on research ethics” refers to the practice of research to monitor effectiveness and develop improved research ethics practices. An example of “research ethics research” would be a study on the use and effectiveness of Informed Consent forms.

- l) **“To facilitate the sharing of information among clinical trial registries.”** There are numerous registries collecting and publishing a wide range of information on clinical trials. Each one tends to be designed for a specific purpose, e.g., for patient recruitment, investor information, research funding, etc. The sharing of information amongst registries may promote increased knowledge and reduce duplication.

- m) **“To facilitate transparency around research and trials.”** Many people believe that the registration of clinical trials and disclosure of trial results are fundamental to ensuring transparency in medical research and fulfilling ethical responsibilities to patients and study participants. On the other hand, some groups believe that some confidentiality is required to protect commercial or academic interests.

Pop Up Box “Platform”

The World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP)

The ICTRP is a global project to facilitate access to information about clinical trials and their results. Its primary objectives are to ensure that all clinical trials are registered and thus publicly declared and identifiable, so as to ensure that for all trials, a minimum set of results will be reported and made publicly available. Specific goals of the Registry Platform include establishing standards on the scope and content of trial registration, establishing a network of Member Registers that satisfy criteria for internationally acceptable registers, establishing and assigning a Universal Trial Reference Number (UTRN) to globally unique trials, defining minimum standards for the reporting of trial results, and launching a one-stop Search Portal for searching registers worldwide.

Question 20

Discussion Point:

Concerns Regarding REBs

It has been suggested that researchers be required to submit a listing of all REBs to which a clinical trial has applied. Although listing all REBs could provide valuable location information for potential recruits, concern has been expressed regarding potential administrative burden for researchers. This could be addressed by requiring notification of one REB that accepted/approved the trial.

Question 21

Discussion Point:

Some groups believe that information about all REBs that denied acceptance must be provided in context. The reason for denial is an important factor, as it may be related to timing, competitive studies, or REB philosophy (e.g., age restrictions) or other reasons rather than a trial's protocol, safety issues or its scientific value. The opportunity to provide the reason for denial or withdrawal would also be considered.

Question 26

Discussion Point:

Access to “**raw data**” is useful for verification purposes and to support the work of other researchers. There are concerns, however, related to participant privacy and to the potential for misinterpretation of data and results.

Question 27

Discussion Point:

A “**lay summary**” provides information about the results of a clinical trial in “plain language.” As much as possible, it avoids the use of scientific and technical language, so that a person outside the health or research fields readily understands the results. There are concerns related to interpretation and the summation process (what is included, what is excluded).

Question 28

Discussion Point:

It has been suggested that timing of registration be tied to REB review (which takes place prior to the start of a trial). For example, registration prior to REB review would provide information in the event that a trial is withdrawn or denied by the REB. Registration at the time of REB approval would provide a common standard for registration.

However, it has been argued that attempting to tie registration timing to REB review may be problematic, as REB processes vary widely across the country. The requirements of registration (timing, content) may help facilitate improved standardization and harmonization of REBs.

Question 31

Discussion Point:

Timing of disclosure of results is also critical to the publication of results in medical research journals. Journals may be reluctant to publish what is already publicly available.