Health Canada Santé Canada

Draft Guidance Document Registration of Clinical Trials and Public Disclosure of Results

Transparency of Health Canada-authorized clinical trials

This guidance document is being distributed for comment purposes only

Draft date 2023-02-23

Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre :
Ébauche de la ligne directrice : Enregistrement des essais cliniques et divulgation publique des résultats / Transparence des essais cliniques autorisés par Santé Canada

To obtain additional information, please contact:

Health Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications-publications@hc-sc.gc.ca

Publication date: February 2023

Health Canada Santé Canada

Note on guidance documents in general

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As always, Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us assess the safety, efficacy, or quality of a health product. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

Canada

Table of contents

1. Introduction

1.1 Purpose

Health Canada is the federal regulator responsible for the regulation of clinical trials involving a wide range of products, including:

- drugs that are:
  - biologic
  - pharmaceutical
  - radiopharmaceutical
- medical devices
- natural health products (NHPs)

Clinical trials are an important step in health product development. They are essential for the development of new treatment options and support early and safe access to health innovations.

Increasing transparency around clinical trials facilitates public access to clinical trial information. It can also result in improved recruitment by informing interested persons about trials that are taking place. This includes those who identify with population groups that are often underrepresented in clinical trials, such as:

- women
- Indigenous Peoples
- ethnic and racialized groups

Increased transparency can also increase public trust and confidence in the safety and efficacy of health products, and inform where further research is needed.

1.2 Scope and application

Currently, Health Canada authorizes the sale and importation of drugs, medical devices and NHPs for the purpose of conducting clinical trials or investigational testing involving human participants.

In addition, Health Canada introduced regulations authorizing the:

- sale and importation of COVID-19 drugs and medical devices for the purposes of a clinical trial
- conduct of clinical trials for COVID-19 drugs and medical devices in response to the COVID-19 pandemic

A Letter of Authorization is issued for medical devices, and a Notice of Authorization is issued for NHPs if all regulatory requirements have been met in the trial application. No authorization is issued for clinical trials investigating drugs, as the regulations give Health Canada the authority to object to a trial that does not meet regulatory requirements, rather than authorizing one that does. Drug trial applications meeting regulatory requirements are issued a No Objection Letter (NOL).

For the purpose of this guidance, the term "authorized" will be used to describe trials that have received:

- a No Objection Letter
- a Letter or Notice of Authorization, or
- a clinical trial authorization for a COVID-19 related drug or medical device

The term "sponsors" will refer to:

- authorization holders for investigational testing under the *Medical Devices Regulations* (MDR)
- sponsors of a clinical trial under the *Food and Drug Regulations* (FDR) and *Natural Health Products Regulations* (NHPR)

This guidance document applies to all sponsors with authorization to sell or import a health product for the purpose of a clinical trial. It also applies to sponsors with authorization to conduct a COVID-19 drug or medical device clinical trial involving human participants in Canada, as specified below:

- Health Canada-authorized clinical trials investigating drugs (including pharmaceuticals, biologics and radiopharmaceuticals), medical devices, and NHPs, with the exception of trials involving a single individual
- Including:
    - Classes 2 to 4 medical device studies
    - and Phases 1 through 3 of NHP development
    - Phases 1 through 3 of drug development and comparative bioavailability studies
- For marketed products where the authorized trial involves use of a product outside the parameters of the Notice of Compliance (NOC) for drugs, Medical Device Licence for medical devices or Product Licence for NHPs
    - For example, part of a commitment made for an NOC issued under the Notice of Compliance with conditions (NOC/c) policy or mandated by terms and conditions

1.3 Policy objectives

To provide guidance to sponsors of Health Canada-authorized clinical trials to support the registration and public disclosure of results (reporting of results) using international registries.

Additionally, this document describes the clinical trial information that Health Canada is publishing on the Health Canada Clinical Trials Portal.

1.4 Policy statements

This policy aims to improve public access to information about clinical trials in Canada by addressing elements relating to:

1. registration
2. reporting of results
3. access

Canadian sponsors should register their Health Canada-authorized clinical trials before recruitment of the first participant. This should be done in accordance with requirements of a clinical trial registry that complies with World Health Organization (WHO) standards.

Sponsors should submit the summary results of their Health Canada-authorized clinical trials to a clinical trial registry that complies with WHO standards. This will be the same registry where the sponsor first registered the trial. The information included in the summary results is considered summary information and does not include individual patient data.

Sponsors should submit the results of their clinical trial within 12 months following primary study completion. Primary study completion means the final study visit for collection of data on the primary outcome for the last trial participant.

1.5 Background

Health Canada is advancing the modernization of its clinical trial regulations to better serve stakeholders, while continuing to protect the safety of clinical trial participants.

Health Canada conducted consultations on the proposed clinical trials modernization initiative. The feedback we received supports mandatory registration and reporting of results, with the strongest support for requirements that are aligned internationally.

Health Canada is positioned to move towards regulating clinical trial transparency with:

- this stakeholder support
- established international standards
- the clinical trial authorities which came into force under the *Food and Drugs Act* (FDA) on May 23, 2020[1]

As a preparatory step, this policy gives stakeholders the opportunity to develop or augment existing practices associated with registration and reporting of results before regulations are proposed in Canada.

2. Guidance for implementation

2.1 Registration

2.1.1 WHO international standards and criteria

Part of the WHO International Clinical Trials Registry Platform (WHO ICTRP) mission statement emphasizes: “The registration of all interventional trials is a scientific, ethical and moral responsibility”.

The WHO ICTRP aims to encourage prospective registration of specific information (the WHO Trial Registration Data Set[2]) for all clinical trials and assist with public access to that information.

The WHO ICTRP Registry Network allows information exchange and collaboration to establish best practices for clinical trial registration. This Network includes:

- data providers
- partner registries
- primary registries
- registries working with the ICTRP towards becoming primary registries under its network

All must meet or be consistent with standards supporting criteria that fall under 6 main categories:

1. Content
2. Quality and validity
3. Accessibility
4. Unambiguous identification
5. Technical capacity
6. Administration and governance

As an example, under the content category, one criterion for primary registries is that they must be able to collect and publicly display the WHO Trial Registration Data Set for a trial to be considered fully registered.

Primary registries must attain the minimum standards for all criteria as described in the WHO ICTRP document titled "International Standards for Clinical Trial Registries". They must also meet the requirements set by the International Committee of Medical Journal Editors (ICMJE), such as:

- public access at no charge
- being open to all prospective registrants.

The ICMJE policy[3] recommends that medical journal editors require registration of clinical trials in a public registry at or before the time of patient enrollment as a condition of consideration for publication.

2.1.2 When to register

Sponsors should register their Health Canada-authorized clinical trial before recruitment of the first participant (this means prospectively).

In alignment with existing international best practices, including standards of the WHO ICTRP, Health Canada recommends prospective registration. If a study authorized in Canada is already registered with trial sites in other countries, sponsors should add each Canadian site to their existing registration record before recruitment begins at that site. All Canadian trial sites should be listed clearly.

2.1.3 Where to register

Sponsors should register their Health Canada-authorized clinical trials with a clinical trial registry that complies with WHO international standards.

For the purpose of this guidance, this includes data providers accepted by the WHO ICTRP that create and manage trial records in a manner that is consistent with the WHO Registry Criteria[4]. ClinicalTrials.gov is an example. Visit the WHO ICRTP website for an up to date list of eligible registries and data providers[5].

2.1.4 Protocol numbers

Along with a clear listing of Canadian trial site locations, sponsors should include the protocol number in the registry record. This is the same number that is submitted to Health Canada as part of a clinical trial application. The protocol number is a variable length, alpha-numeric sequence used by sponsors to assign a reference number to their clinical trial or investigational testing protocol.

All registries that comply with WHO international standards include "secondary identifying numbers" as part of their data set. Health Canada recommends submitting the protocol number as one of the secondary identifying numbers to assist with tracking and publication to the Health Canada CT Portal.

2.1.5 Trial identification numbers

A trial identification number is assigned by the registry to a particular clinical trial during the registration process. For example, ClinicalTrials.gov uses the trial identification number format of NCT12345678.

Health Canada will determine the appropriate process for sponsors to provide the trial identification number related to their authorized trial (sometimes called the registration number) to Health Canada. With this number, Health Canada is able to:

- augment information for publishing on the Health Canada CT Portal
- eliminate the need for sponsors to duplicate efforts in providing additional information to Health Canada

2.1.6 Use of controlled vocabularies

Follow the requirements of the registry including use of a controlled vocabulary thesaurus. Health Canada recommends using the:

- Medical Dictionary for Regulatory Activities (MedDRA)
- Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT)

Health Canada uses MedDRA to publish information on the CT Portal including the:

- names of the diseases or conditions studied in the clinical trial
- intervention types and names, where possible

The use of controlled vocabularies on the CT Portal enables more robust search functions. This helps to ensure that trials can be found among search results and that the search functions work in both official languages. This allows users of the CT Portal to more quickly find clinical trials that are relevant to their needs and can better facilitate the analysis of data derived from the CT Portal. Sponsors should use the same controlled vocabularies for the registry and their CTA submission to Health Canada.

2.1.7 Registries accepting Canadian trials

Two widely used registries that are publicly accessible and part of the WHO ICTRP Network are:

- ISRCTN in the United Kingdom
- ClinicalTrials.gov in the United States

Both registries:

- can be searched free of charge
- collect and display the WHO Registration Data Set for clinical trials
- accept prospective registration of clinical trials taking place in all countries

They both accept clinical trials:

- conducted in Canada
- investigating all product lines within the scope of this policy (drugs, medical devices and NHPs)

Not all registries and data providers that comply with WHO international standards will accept clinical trials conducted in Canada.

2.1.8 How to register a clinical trial

Sponsors should comply with any standards or requirements of their chosen registry, including the information required to be submitted. Typical processes include a review of the clinical trial study record submitted by the sponsor by registry staff members before it is published. This helps to ensure that the information is clear, informative and conforms to the specifications of the registry. The sponsor may be asked by registry staff to clarify items or make corrections before publication. This review process could take a few days, depending on the preparedness of the sponsor and quality of the clinical trial record.

After the clinical trial record is submitted by the sponsor and accepted by review staff for publication, it would be made available on the registry for public viewing, generally within a few days.

2.2 Reporting of results

Declaration of Helsinki

The 2013 World Medical Association, Declaration of Helsinki states:

"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject…Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports....Negative and inconclusive as well as positive results must be published or otherwise made publicly available."[6]

2.2.1 When to report results

Sponsors should strive to submit the summary results of their clinical trial within 12 months following primary study completion.

Primary study completion is understood to be the final study visit for collection of data on the primary outcome for the last participant.

Health Canada recommends this timeframe as it aligns with international best practices, including WHO international standards for registries.

More than the 12-month timeframe may be needed under special circumstances, including:

- certain clinical trials investigating NHPs
- situations where a sponsor is working with registry staff to conform to specific registry requirements

For clinical trials investigating NHPs involving a new investigational product or a new indication, sponsors may submit their results within whichever timeframe comes first:

- 12 months following Product Licence Issuance or
- 24 months following primary study completion

This timeframe takes into account time for a company to bring a new product to market after completing a trial.

Signatories of the WHO Joint Statement on Public Disclosure of Results from Clinical Trials[7] (Joint Statement) also commit to implementing policies for timely public disclosure of results for all clinical trials that they fund. This includes a 12-month timeframe from primary study completion for posting results to a clinical trial registry.

The Canadian Institutes of Health Research (CIHR), Canada's federal funding agency for health research, is now aligned with the joint statement. The agency became a signatory and strengthened its open science and transparency requirements[8] for investigators who receive CIHR grant funds for clinical trials on or after January 1, 2022.

Investigators must have summary results publicly available within 12 months from primary study completion. Publications must be open access from the date of publication and include the registration number. Compliance with the policy requirements is necessary to remain eligible for any new CIHR funding.

2.2.2 Where to report results

Sponsors are expected to provide the summary results of their Health Canada-authorized clinical trials to the same registry where their clinical trial is registered. This is the sponsor's registry of choice that complies with WHO international standards.

2.2.3 What results information to report

Sponsors should update their registry information with the summary results of their clinical trials. Summary results information does not include individual patient data. In line with the content requirements under the WHO Trial Registration Data Set, this guidance describes summary results as including 4 areas.

Participant flow

Information that documents the numbers of research participants:

- enrolled
- screened
- dropped out of a study
- completing each stage of a study

This is for both the study arm and comparator arm.

Demographics and baseline characteristics

Data collected at the beginning of a clinical study for all participants, for each investigational arm and the comparator arm. These data include demographics, such as disaggregated data on:

- age
- sex
- gender
- race or ethnicity

Outcome measures

Data for each primary and secondary outcome measure for the investigational and comparator arms, including the summary result(s) of statistical analyses that were performed on the outcome measure data.

Adverse events

Information relating to an unfavorable change in the health of a participant, and all serious adverse events and deaths that happen:

- during a clinical study
- within a certain time period after the study has ended

This data should include demographic data, where possible.

2.2.4 Journal publications

Health Canada's policy expectations for prospective registration of clinical trials and summary results reporting align with guidance set out in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E8(R1), implemented by Health Canada[9], for drug trials, which states that:

Making objective and unbiased information publicly available can benefit public health in general, as well as the indicated patient populations, through:

- enhancing clinical research
- reducing unnecessary clinical studies
- informing decisions in clinical practice

This international standard is considered of critical scientific and ethical importance for research involving humans.

Sponsors are encouraged to:

- include the registration number or trial ID in the article summary or abstract
- use open access, peer-reviewed journals for publications associated with clinical trials

Use of open access peer-reviewed journals for publication is aligned with the Chief Science Advisor of Canada's Roadmap for Open Science. It promotes a science culture that is "open by design and by default," which means open science is an integral part of the scientific process.

Although the roadmap recommendations are intended for science and research funded by federal government departments and agencies, the imperative for making scientific information available to all is universal. In particular, sponsors are encouraged to apply the principles that research outputs are “FAIR”:

- Findable
- Accessible
- Interoperable
- Reusable

Although journal publication increases transparency of clinical trials, it should not replace the reporting of summary results with registries that comply with WHO international standards, where full study protocols and statistical analysis plans, along with the informed consent forms may also be found.

2.2.5 Providing results to participants

The inclusion of summary results in the registry provides an important resource for participants. However, sponsors, including researchers, are also encouraged to adhere to any guidelines that describe best practices for communicating results with clinical trial participants. For example, ICH E8(R1) states that:

“Consideration should be given to providing a factual summary of the overall study results to study participants in an objective, balanced and non-promotional manner, including relevant safety information and any limitations of the study…Participants should be informed about the information they will receive and when they will receive it at the time of providing informed consent.”

2.2.6 How to submit results to registries

Generally, summary results from registered and completed studies are submitted in a standard format without discussions or conclusions. Sponsors should comply with any standards or requirements of their chosen registry, including those relating to the type of information to be submitted.

Typical processes include a review of results submissions by registry staff members to help ensure that they are clear and informative before they are published. There may be different validation steps for different registries. Sponsors are responsible for ensuring that the submitted information is accurate and complete.

Sponsors are encouraged to work directly with the international registry they have chosen if they are experiencing any difficulty uploading their clinical trial information. A contact email and phone number are typically listed on a registry's webpage.

2.3 Health Canada Clinical Trials Portal

Health Canada's Clinical Trials Portal displays information about authorized Canadian drug trials, including:

- biologics
- pharmaceuticals
- radiopharmaceuticals

Subsequent releases of the CT Portal under a phased implementation strategy are planned. They will include information for all authorized Canadian clinical trials investigating:

- medical devices
- NHPs
- prescribed FSDPs, once they are permitted by regulation

Sponsors of trials for all product lines (this means drugs, medical devices and NHPs) are encouraged to follow the registration and reporting steps outlined in this guidance document in anticipation of subsequent releases of the portal.

2.3.1 Data sources and fields

The portal contains information about Health Canada-authorized trials from three data sources:

1. Information provided to Health Canada in support of a clinical trial application, after the application is authorized
2. Information Health Canada will extract from the WHO ICTRP
3. Information Health Canada will extract directly from registries that comply with WHO standards

Users of the portal will have access to information about authorized Canadian trials. Through evolution and subsequent phases of the portal, the information reflected may change over time. The information contained on the portal includes:

- details about the trial and product being investigated
- a link to the record for the trial in either the WHO ICTRP **or** the registry where the trial was registered by the sponsor

2.3.2 Missing registry information

At the time of initial publication of an authorized clinical trial on the portal, certain information may not be available until:

1. the sponsor has registered the trial with an international registry
2. Health Canada has extracted the trial record

Trials that opened before implementation of this policy may include more limited information.

If an authorized trial has opened and Health Canada has not been able to find a record of registration from the WHO ICTRP or a registry, the portal will state “Not currently listed in registry”, or a similar statement.

2.4 Resources

2.4.1 Search portals and inventories

- ISRCTN search portal (BioMed Central) (https://www.isrctn.com/)
- WHO ICTRP search portal (World Health Organization) (https://trialsearch.who.int/)
- ClinicalTrials.gov search portal (US National Library of Medicine, National Institutes of Health) (https://clinicaltrials.gov/)

2.4.2 International registration and results reporting

- Declaration of Helsinki (World Medical Association) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)
- Consolidated Standards of Reporting Trials (CONSORT) (https:\www.consort-statement.org\)
- International Clinical Trials Registry Platform (World Health Organization) (https://www.who.int/clinical-trials-registry-platform)
- Clinical Trials Registration (International Committee of Medical Journal Editors) (https://www.icmje.org/about-icmje/faqs/clinical-trials-registration/)

ClinicalTrials.gov

- Investigator's login page (https://register.clinicaltrials.gov/)
- Protocol registration quality control review criteria (https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf)
- Protocol Registration and Results System user guide (https://prsinfo.clinicaltrials.gov/prs-users-guide.html
- Study record manager’s training and support materials (https://www.clinicaltrials.gov/ct2/help/for-manager)

ISRCTN

- Registering a study (https://www.isrctn.com/page/definitions)
- Completing an application, updating study records and reporting results (https://www.isrctn.com/page/resources)

2.4.3 Guidelines for sharing results with participants

- Information for Patient Partners/Potential Trial Participants (Health Research BC) (https://www.bcahsn.ca/our-network/clinical-trials-bc/participant-experience/study-results-best-practices)

- General Considerations for Clinical Studies, ICH E8(R1), Chapter 6.3, October 2021 (https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2022_0204%20%281%29.pdf)
- TCPS 2 (2018) – Chapter 9: Research Involving the First Nations, Inuit and Métis Peoples of Canada (https://ethics.gc.ca/eng/tcps2-eptc2_2018_chapter9-chapitre9.html)

Appendix A: Regulatory authorities

Pursuant to the FDA and its Regulations, Health Canada has regulatory authority over the sale and importation of drugs (pharmaceuticals, biologics and radiopharmaceuticals), medical devices and NHPs used in clinical trials.

For COVID-19 clinical trials, Health Canada also has authority over the:

- conduct of the trial
- sale and importation of the drugs or medical devices used in the trial

Health Canada has proposed that modernized clinical trial regulations would include prescribed foods for a special dietary purpose (FSDPs), for which there is currently no regulatory framework that allows clinical trials.

Drug and NHP trials are grouped according to 'phases':

1. **Phase 1 trials** test an experimental drug (or NHP) on a small group of people for the first time. The purpose is to:
    a. look at the drug's safety
    b. find out the safe dosage range
    c. see if there are any side effects
2. In **Phase 2 trials**, the drug is given to a larger group of people (usually 100 or more) to:
    a. gather data on how well the drug works to treat a disease or condition
    b. obtain information on the drug's safety on a wider range of people
    c. determine the best dose going forward
3. In **Phase 3 trials** the drug is given to even larger groups of people (usually 1,000 or more) to determine if it is effective in the treatment of the condition under study and further define its safety profile.
4. Finally, **Phase 4 trials** take place after the drug is approved and is on the market. These trials often include safety studies and studies designed to support optimum use of the drug under its approved indication.

Drugs

Part C, Division 5 of the FDR requires the filing of a Clinical Trial Application (CTA) for:

- drugs not yet marketed in Canada, including Phase 1, 2, and 3 of drug development
- marketed drugs used outside their Canadian market authorized conditions of use, such as different:
    - indication
    - population
    - dosage regimen
- comparative bioavailability studies (used in generic drug development)

Phase 4 clinical trials involve drugs used in clinical trials according to their Canadian market authorized conditions of use and do not require the filing of a CTA.

Health Canada reviews the CTA to determine if:

- There is sufficient information to enable an assessment that the:
    - objectives of the clinical trial are achievable

    - use of the drug is not contrary to the best interests of the participant
    - use of the drug in the clinical trial will not endanger the health of the clinical trial participant or other person
- The information and documents were provided in accordance with the FDR

A clinical trial site is the location where trial-related activities are actually conducted. Under Part C, Division 5 of the FDR, the sponsor must obtain approval of a properly constituted Research Ethics Board (REB) before the trial may begin at each clinical trial site.

All trials (including Phase 4) must be conducted in accordance with good clinical practice principles.

Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html)

Medical devices

Part 3 (Sections 79 to 88) of the MDR governs the sale and importation of a medical device for investigational testing involving human participants. As per Section 6 of the MDR, medical devices are classified into one of four classes where Class I represents the lowest risk and Class IV the highest.

Manufacturers and importers must meet the regulatory requirements therein, including requirements outlined in Subsection 80(2) and 83(1) of the MDR. They can then receive authorization from Health Canada to sell a device to a qualified investigator for the purpose of conducting investigational testing.

Under Section 80 of the MDR, the manufacturer or importer must possess the records specified in Section 81 prior to the sale of the medical device for investigational testing, including:

- device label
- patient consent form
- investigational testing protocol
- information on the investigators involved
- written approval from the institution indicating that investigational testing may be carried out there
- risk assessment comprising an analysis and evaluation of the risks associated with the use of the device being tested

The MDR requires the submission of an Investigational Testing Authorization (ITA) application in order to sell or import a Class 2, 3 or 4 medical device for conducting investigational testing. In addition, the MDR set out requirements to be followed post-authorization including:

- recalls
- labelling
- advertising
- implant registration

- foreign risk notification
- incident reporting procedures
- complaint handling procedures
- maintaining distribution records

Applications for Medical Device Investigational Testing Authorizations Guidance Document (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/investigational-testing-authorizations-guidance/guidance-document.html#2.4)

Natural health products

Clinical trials investigating NHPs are currently regulated under Part 4 of the NHPR. These trials may be conducted to provide further information about a product including its safety and efficacy. More precisely, Part 4 of the NHPR is to ensure:

- the safety, efficacy and quality of the study's:
  - clinical trial protocol
  - investigational product(s)
  - placebo or comparator
- the safety of clinical trial participants and other people
- compliance with good clinical practices (Section 74 of the NHPR)
- that people with suitable expertise conduct properly designed clinical trials

In general, the requirements for clinical trials under the NHPR are similar to the clinical trial requirements for drugs; however, the NHPR recognize that NHPs may differ from single chemical entities in both manufacturing and evaluating processes.

Guidance for Clinical Trials for Natural Health Products (https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/clinical-trials.html)

Food for a special dietary purpose: future planned scope

Foods that are not compliant with the FDR cannot be sold in Canada, including for the purpose of a clinical trial. The proposed modernized clinical trial regulations would prescribe certain foods for a special dietary purpose ("prescribed FSDPs") and enable Health Canada to authorize clinical trials on prescribed FSDPs that are not in compliance with certain compositional or premarket notification and authorization requirements set out in the FDR. Once the proposed regulations are in place, prescribed FSDPs would fall under the scope of this guidance.

As defined in the FDA, an FSDP is "a food that has been specially processed or formulated to meet the particular requirements of an individual in whom a physical or physiological condition exists as a result of a disease, disorder or abnormal physical state, or, to be the sole or primary source of nutrition for an individual."

For example, this category could include foods intended for vulnerable populations such as:

- infants (such as infant formula and human milk fortifiers, defined under Division 25 of Part B of the FDR)

- people with metabolic disorders or other health conditions (such as specially formulated liquid diets and other foods for special dietary uses defined under Division 24 of Part B of the FDR)

The proposed modernized clinical trial regulations would have a common approach for all of the above health products, as well as for prescribed FSDPs. There would be a few differences necessitated by the nature of the investigational products. Clinical trials investigating FDR-compliant foods, including compliant FSDPs, would be out of the scope of these regulations. Trials on these foods can currently be conducted in Canada, without authorization from Health Canada.

Appendix B: Glossary

Clinical Trial: A study, involving human subjects, for the purpose of discovering or verifying the effects of a drug, a device or a food for a special dietary purpose. (*Food and Drugs Act*) Note: the definition of "drug" in the Act includes a natural health product.

Clinical trial application: the information required by Health Canada from sponsors seeking authorization to sell or import a drug or NHP for the purpose of a clinical trial or a medical device for the purpose of investigational testing, involving human participants.

Device: An instrument, apparatus, contrivance or other similar article, or an *in vitro* reagent, including a component, part or accessory of any of them, that is manufactured, sold or represented for use in

a) diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physical state, or any of their symptoms, in human beings or animals,
b) restoring, modifying or correcting the body structure of human beings or animals or the functioning of any part of the bodies of human beings or animals,
c) diagnosing pregnancy in human beings or animals,
d) caring for human beings or animals during pregnancy or at or after the birth of the offspring, including caring for the offspring, or
e) preventing conception in human beings or animals;

however, it does not include such an instrument, apparatus, contrivance or article, or a component, part or accessory of any of them, that does any of the actions referred to in paragraphs (a) to (e) solely by pharmacological, immunological or metabolic means or solely by chemical means in or on the body of a human being or animal. (*Food and Drugs Act*).

Note: "**medical device**": means a device within the meaning of the Act, but does not include any device that is intended for use in relation to animals (*Medical Devices Regulations*)

Drug: Includes any substance or mixture of substances 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 organic functions in human beings or animals, or
c) disinfection in premises in which food is manufactured, prepared or kept. (*Food and Drugs Act*)

Food for a special dietary purpose: means a food that has been specially processed or formulated

a) to meet the particular requirements of an individual in whom a physical or physiological condition exists as a result of a disease, disorder or abnormal physical state, or
b) to be the sole or primary source of nutrition for an individual (*Food and Drugs Act*)

Good Clinical Practices: Generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial participants and other persons, and the good clinical practices for drug trials referred to in Section C.05.010 of the *Food and Drug Regulations* and NHP trials referred to in Part 4, section 74 of the *Natural Health Products Regulations*. There is no applicable reference in the *Medical Devices Regulations*. Certain general practices are set out in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-E6 Guideline.

Natural Health Product: 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

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.

A substance or combination of substances or a traditional medicine is not considered to be a natural health product if its sale, under the *Food and Drug Regulations*, is required to be pursuant to a prescription when it is sold other than in accordance with section C.01.043 of those Regulations. (*Natural Health Products Regulations*)

Manufacturer: has the same meaning for drugs as in Section A.01.010 of the *Food and Drug Regulations*; for medical devices as in Section 1 of the *Medical Devices Regulations*; for NHPs as in Section 1(1) of the *Natural Health Products Regulations*.

Register and **registration:** the act of placing information about a clinical trial into an electronic repository.

Registry: an electronic repository of information about clinical trials, whether the information is about ongoing or completed trials. Includes results of clinical trials.

Research Ethics Board: While there is no regulatory definition under the *Medical Devices Regulations*, both the *Food and Drug Regulations* and *Natural Health Product Regulations* share similar definitions. The *Food and Drug Regulations* definition is as follows:

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 a 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 natural health product 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 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 (*Food and Drug Regulations*)

Sell: Includes

a) offer for sale, expose for sale or have in possession for sale — or distribute to one or more persons, whether or not the distribution is made for consideration, and
b) lease, offer for lease, expose for lease or have in possession for lease. (*Food and Drugs Act*)

Sponsor: An individual, corporate body, institution or organization that conducts a clinical trial. (*Food and Drug Regulations*), (*Natural Health Product Regulations*)

[1] https://laws-lois.justice.gc.ca/eng/acts/f-27/fulltext.html#1156051-1249399
[2] https://www.who.int/clinical-trials-registry-platform/network/who-data-set
[3] https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html
[4] https://www.who.int/clinical-trials-registry-platform/network/registry-criteria
[5] https://www.who.int/clinical-trials-registry-platform/network/who-data-set/data-providers
[6] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
[7] https://www.who.int/news/item/18-05-2017-joint-statement-on-registration
[8] https://cihr-irsc.gc.ca/e/52820.html

[9] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-council-harmonisation/guidelines.html