Health Canada Santé Canada

Draft Guidance Document

Expanded access clinical trials

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Draft date	2024-08-02
Effective date	2024-08-02

Canada

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Publication date: August 2024

Foreword

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 adequately assess the safety, efficacy or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read along with the relevant sections of the regulations and other applicable guidance documents.

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1. Introduction

1.1 Purpose

The Food and Drugs Act (act) and the Food and Drug Regulations (regulations) govern the sale and importation of drugs for use in human clinical trials in Canada, including expanded access clinical trials. This draft guidance document explains the regulatory requirements for expanded access clinical trials. These requirements are supported by Part C, Division 5 of the regulations, entitled "Drugs for Clinical Trials Involving Human Subjects".

1.2 Scope and application

This draft guidance document is for sponsors, health care providers and potential participants who are interested in, involved in or participating in expanded access clinical trials involving sites in Canada.

Health Canada has authorized a number of expanded access clinical trials, including trials that are part of international, multi-site expanded access programs. However, the number of clinical trial sites opened and participants enrolled in Canada has been limited. This document provides additional information about how expanded access clinical trials are managed in Canada.

Expanded access clinical trials are clinical trials, and therefore require the completion of a clinical trial application (CTA), for review by Health Canada.

A clinical trial is an investigation of a drug for use in humans that involves human subjects. The trial is intended to:

- discover or verify the drug's clinical, pharmacological or pharmacodynamic effects
- identify any adverse events resulting from the drug
- study the drug's absorption, distribution, metabolism and excretion properties or
- assess the drug's safety or efficacy

Our scientists review applications to assess whether:

- any risks in using the drug and in conducting the trial are mitigated
- the best interests of those taking part in the trial have been considered, including that drugs are used in the right way for the participants being studied
- the goals of the trial can be met

Sponsors may request a pre-CTA consultation meeting. Such consultations may be particularly useful for new active substances or applications that will include complex issues that may be new to Health Canada.

In this guidance document, "investigational drugs" (pharmaceutical, biologic and radiopharmaceutical) are those that are tested or studied in a clinical trial and have never

been authorized for sale in Canada for any indication. Natural health products, veterinary drugs and medical devices are excluded from the scope in this guidance document.

Learn more about the CTA process in the section below, "Information for Sponsors".

1.3 Policy objectives

Clinical trials, including expanded access clinical trials, are investigations that can sometimes help to facilitate access to novel therapies before they have been authorized for sale by Health Canada. This could include therapies for serious or life-threatening conditions where authorized alternatives may be limited for certain patients (for example, related to oncology, rare diseases and some mental health disorders).

- **For potential participants and health care providers:**
  - provide information to support access to investigational drugs through an expanded access clinical trial when appropriate
- **For sponsors:**
  - provide supplemental information on the requirements to conduct an expanded access clinical trial in Canada
  - clarify the application and post-authorization requirements
  - outline procedures for obtaining authorization for expanded access clinical trials in Canada

Sponsors should also consult other relevant guidance documents, including:

- Guidance document for clinical trial sponsors: Clinical trial applications

1.4 Policy statements

An expanded access clinical trial is a type of clinical trial that provides access to investigational drugs that have the potential to treat people living with medical conditions who do not qualify for other clinical trials or are not able to participate in one. This type of trial can be designed to facilitate access for a larger, potentially more diverse population of participants, in more accessible settings.

As stated in C.05.010 of the regulations, sponsors must ensure that an expanded access clinical trial, like all clinical trials, is conducted in accordance with good clinical practices (GCP). The rights, safety and well-being of clinical trial participants are to be protected in accordance with these principles. This includes obtaining the approval of a research ethics board for each Canadian clinical trial site.

Sponsors must provide substantial evidence from previous studies to demonstrate that the proposed use of the investigational drug in an expanded population does not endanger the health and safety of participants. All CTAs are assessed on a case-by-case basis.

Many types of clinical trials can adopt a decentralized model, as a business decision. Expanded access clinical trial sponsors may consider following a decentralized clinical trial model to facilitate trial participation and to recruit and enrol a diverse population of participants.

This decentralization can involve a qualified investigator at a clinical trial site delegating tasks to a qualified third party in a different physical location. This can include, where appropriate and justified, the delegation of tasks related to administering the drug and associated follow-up and safety monitoring of participants.

The clinical trial site where the qualified investigator is located must be reflected in a clinical trial site information (CTSI) form submitted to Health Canada. Delegated health care providers may be located at other physical locations, which do not require separate CTSI forms or additional research ethics board approvals.

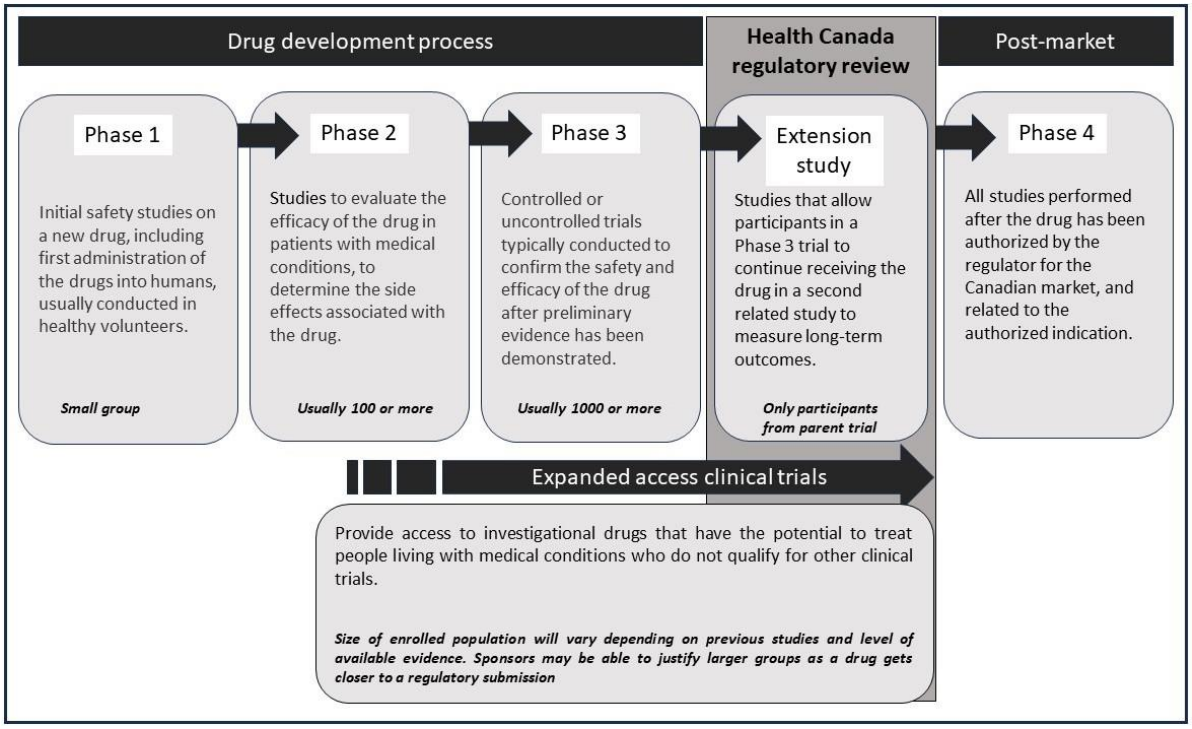
All locations where clinical trial activities occur are considered to be part of the main clinical trial site and may be inspected as part of a clinical trial site inspection. All activities related to the practice of medicine are under provincial or territorial jurisdiction.

Learn more about the ICH E6 guideline for good clinical practice.

1.5 Background

As development of the drug progresses, the goal of late-phase (phases 2 and 3) confirmatory trials is usually to gather evidence that meets the standards required by drug regulators (Figure 1).

Figure 1: Types of clinical trials



Late-phase clinical trials aim to show a statistically conclusive effect on a specific outcome of interest, by setting specific criteria for who can and cannot participate.

These controls make it more likely that the results will lead to reliable and useful findings. But this also means that not everyone can participate in these clinical trials for the following reasons:

- they do not meet the eligibility criteria
- their disease has progressed too far
- they live too far from study sites **or**
- there are no available clinical trials or ongoing trials are not recruiting

In such cases, patients might be able to receive investigational drugs, when appropriate, through an expanded access clinical trial. Expanded access clinical trials provide access to investigational drugs that have the potential to treat people living with medical conditions who do not qualify for other clinical trials or are not able to participate in one. They can be designed to facilitate access for a larger, potentially more diverse population of participants, in more accessible settings.

As with other clinical trials, the sale or importation of a drug for an expanded access clinical trial is authorized under Part C, Division 5 of the regulations. Sponsors of expanded access clinical trials must protect participants in accordance with ethical, medical and quality standards of the clinical trials framework.

Sponsors may propose an expanded access clinical trial at any point in the drug development process, even if a clinical trial studying that drug has not been previously conducted in Canada. However, an expanded access clinical trial should only be conducted for drugs that are being actively developed. An example would be a drug under investigation in a study intended to form the primary basis of safety and efficacy, leading to a planned submission for regulatory authorization.

There must be a strong rationale for initiating an expanded access clinical trial that provides access to a drug before it has been authorized for sale by Health Canada. For example, an expanded access clinical trial could enable access to a new drug for a specified population while a regulatory submission is under review by Health Canada. As part of their rationale, sponsors may refer, for example, to the severity of the condition, lack of available therapeutic alternatives, or possible increased benefits or decreased risks compared to existing authorized products.

To conduct an expanded access clinical trial, sponsors must provide substantial evidence from previous clinical trials or other studies in a CTA. They must demonstrate that the investigational drug will not endanger the health and safety of participants, and may be beneficial in treating the specific disorder in the population being studied.

Expanded access clinical trials also require an investigator's brochure specific to the investigational product proposed for this type of trial.

Learn more about the type of information that should be submitted in a CTA.

1.5.1 Expanded access clinical trials compared to other types of clinical trials

Expanded access clinical trials are different from extension studies because they allow for the recruitment of new participants who may not have participated in any prior clinical trials.

Extension studies (also known as extended trials) are associated with a particular prior trial. They are designed to allow access, but only for those participants of the prior trial, so that those participants can continue receiving the drug in a second related study and the sponsor can investigate long-term outcomes. Extension studies can allow participants to continue accessing an investigational drug after a prior trial is completed and closed. This can be important in situations where discontinuing access to the investigational drug may adversely affect participants.

Expanded access clinical trials are also different from open label individual patient (OLIP) clinical trials, which are for individual participants only. Expanded access clinical trials, which can be designed for a broader, expanded population of participants, may be a better option for managing exceptional access for large groups of participants and may generate more useful evidence.

Expanded access clinical trials may be designed to collect long-term safety or tolerability data and real-world evidence that can be used to supplement results from confirmatory clinical trials in a regulatory submission. While the evidence generated is often not as reliable as evidence from traditional confirmatory trials, it can characterize effects such as rare adverse reactions or longer-term outcomes that may only appear in larger populations over time. Depending on the research protocol proposed by the sponsor, expanded access clinical trials may be able to generate real-world evidence on treatment use of the investigational drug in a setting that's closer to real-world conditions.

1.5.2 Expanded access clinical trials: special considerations

A drug must receive market authorization before it can be sold in Canada. The purpose of the act and its regulations is to:

- ensure that therapeutic products brought to market are safe, effective and of high quality
- prevent deceptive marketing practices and protect the public from risks and injury from unsafe products

Thus, to meet the threshold for authorization by Health Canada when applying for market authorization, a trial sponsor must demonstrate the safety, efficacy and quality of its therapeutic product. Evidence of this is generally supported by information and data generated through extensive clinical trials and non-clinical research.

It's in the best interest of patients that Health Canada reviews and regulates the drug products they use. We have put in place a framework to enable sponsors to manage a drug's risks over the entire lifecycle of the drug, which includes post-market surveillance activities.

In addition to helping safeguard health and safety, the need to receive authorization, as framed by the act and regulations, is a basic cornerstone of the drug development, commercialization and regulatory process.

As expanded access clinical trials provide access to unauthorized drugs to a broader group of potential participants, they carry unique risks compared to other types of clinical trials.

There is a risk that expanded access clinical trials may:

- **expose a broader participant population to risks associated with investigational drugs**
    - These investigational drugs have not yet undergone regulatory review for market authorization by Health Canada. For this reason, their efficacy and safety have not been fully evaluated. Sponsors must provide evidence from completed or ongoing clinical trials or other studies to demonstrate that the investigational drug in a proposed expanded population does not endanger the health and safety of patients.
- **impede the clinical development of the drug**
    - There is a risk that these types of trials could divert participants or supply from a confirmatory clinical trial. Sponsors should be able to demonstrate that providing the drug in an expanded access clinical trial will not interfere with clinical development.
- **bypass regulatory review before market access**
    - Broad market access to a drug should only occur after Health Canada has reviewed the drug's safety, efficacy and quality evidence and authorized its sale in Canada. Sponsor protocols should define the Canadian participant population and how access will be limited to those in exceptional need.

Sponsors of expanded access clinical trials must meet all applicable regulatory requirements in their CTA and provide specific information in their protocol on the potential risks.

2. Information for potential participants and health care providers

2.1 General considerations

Clinical trials are investigations that help advance medical knowledge, to try and find out whether a drug is safe and effective in humans for a specific disease or condition. They are essential to develop scientific evidence about a therapeutic product that can potentially improve the quality of life for people living with a disease or condition.

Clinical trials are conducted in phases and progress from exploratory trials to confirmatory trials. Exploratory clinical trials (phases 1 and 2) test the initial effects of a drug in a small number of participants. Confirmatory (phase 3) trials generate statistically conclusive evidence of the drug's efficacy and safety by testing it in larger groups. Evidence from

clinical trials is then used to seek authorization from Health Canada to market the drug in Canada.

People living with a medical condition or disease who participate in a clinical trial may benefit from having access to a drug that may cure or control their condition or improve their quality of life.

While clinical trials may provide access to an investigational drug for some participants, their main purpose is to answer a specific research question. To achieve this objective, clinical trials must be rigorously designed with appropriate measures (for example, by setting criteria for who can participate or by giving some participants a placebo). This may result in certain potential participants living with medical conditions being excluded from a clinical trial or from receiving the drug as part of a trial. Therefore, participation in a clinical trial does not always result in a participant gaining access to the investigational drug.

Expanded access clinical trials are a type of clinical trial designed to facilitate access to investigational drugs to people living with medical conditions who may be expected to benefit from the drug and cannot participate in other clinical trials. Although one of the objectives is to facilitate access for treatment use, like all clinical trials, access to the investigational drug in expanded access clinical trials:

- is part of the overall investigational plan, which is intended to achieve the following:
    - discover or verify the drug's clinical, pharmacological or pharmacodynamic effects
    - identify any adverse events from the drug
    - study the drug's absorption, distribution, metabolism and excretion properties or
    - assess its safety or efficacy
- includes the monitoring of outcomes and the collection of related data

In general, expanded access clinical trials have broader research objectives, such as long-term safety and effectiveness. They can aim to gather information about rare side effects that may only become evident in an expanded participant population.

Despite the expanded inclusion criteria, it's possible that some people may still not be able to gain access to an investigational drug through an expanded access clinical trial.

2.2 Benefits and risks

Like all drugs, drugs used in clinical trials come with possible benefits and risks. In general, there is less information about the efficacy and safety of an investigational drug being studied in a clinical trial compared to a drug that Health Canada has reviewed and authorized for sale.

Evidence to demonstrate a drug's safety and efficacy can vary depending on whether it's in the early or later phase of development. The drug may ultimately prove to be of no benefit

to a particular participant or may be associated with unexpected and serious adverse effects. Only some drugs that begin clinical trials eventually seek market authorization.

After considering treatment options that are available on the market, people with medical conditions may choose to explore investigational drugs as potential treatments for their condition.

Potential participants who wish to enrol in an expanded access clinical trial to gain access to an investigational drug should discuss the risks and potential benefits with their health care provider. For all clinical trials, including expanded access clinical trials, the Food and Drug Regulations (regulations) require that the health and safety risks and potential but unconfirmed benefits be clearly communicated to potential participants. Potential participants must give their informed consent before they can be enrolled in a trial.

Learn more:

- Informed consent
- Clinical trials and drug safety

2.3 How sponsors initiate expanded access clinical trials

There is no requirement for a drug manufacturer to provide access to their investigational drug through an expanded access clinical trial. Health Canada cannot compel a drug manufacturer to do so.

Sponsors (usually the drug manufacturer) may initiate expanded access clinical trials when there's an identified need for people living with medical conditions who are unable to participate in ongoing clinical trials. Sponsors develop a protocol that outlines the investigational plan. This plan includes criteria for patient eligibility, treatment administration, monitoring outcomes and participant safety, and collecting data. The sponsor then submits this protocol to Health Canada for review by filing a clinical trial application (CTA).

Health Canada reviews CTAs for expanded access clinical trials like any other clinical trial. We review the information to make sure that:

- the investigational drug will be used in a safe way for the proposed participants **and**
- any health and safety risks associated with the drug will be addressed appropriately

For expanded access clinical trials, we review evidence provided by the sponsor from previous clinical trials or other studies. The sponsor must demonstrate that the proposed use of the investigational drug, in the proposed expanded population, is evidence-based and adequately identifies, addresses and discloses risks to prospective participants.

Sponsors of expanded access clinical trials must also provide specific information in their CTA that will allow us to thoroughly assess the risks of the trial. Some of these requirements and their impact on potential participants are listed in Table 1.

Table 1: Requirements for expanded access clinical trials and impact on potential participants

Specific requirements	Impact on potential participants
Sponsors must provide information on why providing access to an investigational drug for an expanded population outweighs any possible risks. For example, sponsors can provide information on the: • severity of the condition • lack of available therapeutic alternatives • possible increase in benefits or decrease in risks compared to existing authorized products	Potential participants may be: • required to be diagnosed with a certain condition to be included • required to have tried other available alternatives or • excluded based on safety reasons (for example, potentially dangerous interactions with other drugs) Expanded access clinical trials may not be appropriate for certain drugs.
Sponsors must provide information on whether the expanded access clinical trial will affect participation in a confirmatory trial. For example, a sponsor may: • delay enrolment in an expanded access clinical trial until phases 1 to 3 trials have completed enrolment • define inclusion criteria for the expanded access clinical trial based on exclusion criteria from other ongoing confirmatory trials	Potential participants who qualify for an ongoing clinical trial may: • not be permitted to enrol in an expanded access clinical trial • be invited to enrol in an ongoing clinical trial instead Participation in clinical trials is always voluntary.

If the CTA meets the regulatory requirements, Health Canada issues a 'no objection' letter to the sponsor within the review period of 30 days. The clinical trial site must also be approved by a research ethics board, and the approval filed with Health Canada, before the sponsor can begin enrolling participants at the site.

2.4 Finding, joining and participating in a clinical trial

2.4.1 How to find a trial

People living with medical conditions can search Health Canada's Clinical Trials Database for information about all clinical trials that have met regulatory requirements. This includes the status of any expanded access clinical trial for a certain medical condition or a specific drug product.

Potential participants may find a potential expanded access clinical trial for their condition by, for example, searching for their medical condition. They may contact the sponsor directly to start the screening and enrolment process. The sponsor of the clinical trial should also be contacted for more information about a trial's objectives, patient enrolment criteria, potential clinical trial sites and to confirm the status of the trial.

Health Canada does not sponsor or design clinical trials, and the database is not a patient recruitment tool. Individuals who want more information on clinical trials found in the database should speak with their health care provider and contact the clinical trial sponsor.

Information made public by sponsors (for example, through a website) should make it possible for potential participants or their health care provider to contact the trial sponsor about enrolment.

If there isn't an expanded access clinical trial for a specific drug or condition, potential participants or their health care provider could contact a drug manufacturer to ask them to consider initiating one.

Find information on clinical trials in the Clinical Trials Database.

2.4.2 Joining a trial

A sponsor sets out the eligibility criteria for enrolling in an expanded access clinical trial. Potential participants may be excluded due to potential safety risks posed by existing conditions or dangerous interactions with other drugs, or if they have not tried other available treatments. Sponsors establish these criteria to mitigate the risks posed by the investigational drug.

After the sponsor of the expanded access clinical trial has been contacted, potential participants are screened for enrolment. The sponsor makes the final determination on who is enrolled in an expanded access clinical trial, based on the eligibility criteria.

In some cases, the investigator responsible for the trial may be required to invite potential participants to enrol in ongoing confirmatory clinical trials first, before they can be considered for enrolment in the expanded access clinical trial. Enrolment in a different clinical trial instead of the expanded access clinical trial could potentially also give participants access to the investigational drug.

2.4.3 Giving informed consent

To participate, sponsors must ask potential participants who are deemed eligible for an expanded access clinical trial to provide their informed consent. The trial's qualified investigator must obtain and keep a record of this consent.

Informed consent means that a potential participant is willing to participate in a specific trial, after having been fully informed about the trial and given the opportunity to ask questions. The process of obtaining consent usually involves a face-to-face meeting or communication between the qualified investigator or delegated third party and the potential participant.

In some cases, the sponsor may be able to justify conducting the process through a virtual meeting platform. This should take place in real-time and face-to-face, using both audio and video.

Before agreeing to participate in any clinical trial, potential participants should consider if they:

- are fully informed of all aspects of the trial that are relevant to their ongoing decision to participate, including potential indemnity coverage if they are harmed during the trial
    - this is documented in an informed consent form (ICF) (developed by the sponsor and reviewed and authorized by a research ethics board)
- know who to contact if they have questions about the research or how to end their participation in the clinical trial
- have a 24-hour contact number or know who to contact if they experience a research-related injury (for example, local health care provider, qualified investigator, research personnel)
- know who will have access to their personal health information collected during the study and how it will be stored
- have a written record of their informed consent, which the qualified investigator should also retain

People with medical conditions, in consultation with their health care provider, should carefully consider and weigh the:

- potential benefits and risks of an unapproved investigational drug **and**
- possible harms and inconveniences of participating in a clinical trial

2.4.4 Health care provider participation

Health care providers who agree to undertake activities delegated by the expanded access clinical trial's qualified investigator (such as administering the investigational drug, monitoring participants and collecting data) are conducting clinical trial activities.

Health care providers who participate in an expanded access clinical trial should verify that:

- their roles, responsibilities and liabilities are specified in an agreement (such as the clinical trial protocol or through additional contracts)
- the clinical trial site where the qualified investigator runs the trial has received approval by a Canadian research ethics board

Additional clinical trial site information (CTSI) forms and additional research ethics board approval are not required for physical locations that are added to an existing clinical trial site. An example would be adding a health care provider's office where activities that are delegated by the qualified investigator are to be conducted.

These activities must be clearly defined in the trial protocol and appropriately recorded in the trial's delegation log. Ultimately, the qualified investigator is responsible for medical decisions taken in relation to trial activities, wherever those activities (delegated or not) have occurred.

Health care providers connected to a different institution than the qualified investigator should be aware of local and institutional policies and requirements that may apply to their activities at their institution. In other words, third parties may have additional responsibilities under a local or institutional research ethics board.

Health care providers who have the legal ability to sponsor a clinical trial in Canada could offer to sponsor an expanded access clinical trial or to open a new clinical trial site as part of an existing expanded access clinical trial. The manufacturer may consider requests to provide a supply of the investigational drug for an expanded access clinical trial or an additional clinical trial site, but there's no legal requirement for the manufacturer to do so.

3. Information for sponsors

3.1 General considerations

Drug manufacturers who want to market their drug in Canada must first file an appropriate drug submission for their product. It's in everyone's best interest that Health Canada reviews and regulates the drugs that people use, to enable sponsors to manage a drug's risks over its lifecycle, including appropriate post-market safety monitoring and reporting.

The decision to provide, or not, potential access to investigational drugs before making a drug submission is made by the manufacturer.

There can be benefits to the sponsor in running an expanded access clinical trial. For example, these trials may:

- develop a better understanding of long-term safety, tolerability and rare adverse events, to support proactive safety labelling
- generate data and evidence on real-world use, which may help support:
    - a regulatory submission

- health technology assessment agencies in making reimbursement recommendations

Many health system stakeholders are integrating real-world evidence into their decision-making. This includes Health Canada, Canada's Drug Agency (CDA) and the Institut national d'excellence en santé et en services sociaux (in Quebec).

The following guidance by Health Canada and CDA lays the foundation for using real-world evidence in regulatory approval and health technology assessment:

- Guidance for reporting real-world evidence (PDF)

Expanded access clinical trials should not displace, affect or discourage confirmatory clinical trials from taking place, as confirmatory trials generally aim to generate evidence required for market authorization. For example, sponsors should not:

- divert the supply of investigational drugs to an expanded access clinical trial to the detriment of a confirmatory clinical trial **or**
- make it difficult to recruit participants in a confirmatory trial (participants may prefer expanded access)

For these reasons, sponsors must account for how they plan to continue any planned or ongoing confirmatory trials as part of their clinical trial application (CTA). This is described in the What to include in an annex to the protocol section.

3.2 Who can sponsor

The Food and Drug Regulations (regulations) define a sponsor as "an individual, corporate body, institution or organization that conducts a clinical trial". A manufacturer would always be involved in an expanded access clinical trial, at the very least as the supplier of the investigational drug.

As stated in C.05.006 of the regulations, sponsors of expanded access clinical trials are expected to provide information and documents as part of their CTA. This information must be sufficient for Health Canada to assess the drug's risks and those of the trial.

Sponsors are not required to conduct a prior clinical trial specifically in Canada. However, sponsors of expanded access clinical trials must provide in their CTA substantial evidence from previous clinical trials or other studies to demonstrate that use of the investigational drug is justified:

- for expanded access
- in an expanded study population

Sponsors of an existing clinical trial may add an expanded access arm to an existing clinical trial by submitting an amendment (CTA-A) to the original trial application.

They must:

- meet the same information requirements that are applied to all expanded access clinical trials

- for example, the requirements laid out in the following section about an annex to the protocol

- demonstrate that the expanded access clinical trial will not jeopardize the original clinical trial, as well as the validity of the data collected as part of that trial

Health Canada may find that the requirements or scope for a proposed expanded access arm are very different than those of the original trial. In some cases, we may suggest that the sponsor re-submit the application as a new CTA (not as an amendment to an existing trial).

3.3 Quality requirements

Chemistry and manufacturing requirements for expanded access clinical trials are the same as for all clinical trials. The scope and detail of information submitted to support the quality portion of a CTA should be sufficient to adequately assess the drug's characteristics.

For information on quality requirements, consult the following guidance document and notice:

- Quality (chemistry and manufacturing) guidance: Clinical trial applications (CTAs) for pharmaceuticals
- Quality requirements for investigational biologic drugs used in clinical trials: Notice to clinical trial sponsors

The information contained in the investigator's brochure must be specific to the investigational product used in the expanded access clinical trial. A literature-based investigator's brochure would likely not be appropriate for an expanded access clinical trial, given the need to characterize the investigational product being provided to an expanded population of participants.

In addition, quality requirements should generally meet the standard for a phase 3 clinical trial, given the broad participant population that may receive the investigational drug.

3.4 Filing a clinical trial application

Like all clinical trials, expanded access clinical trials can be initiated when a sponsor submits a CTA or CTA-A and receives a no objection letter, pursuant to section C.05.005 or C.05.008 of the regulations, respectively.

Find more information on clinical trial applications (CTAs).

Sponsors should clearly identify expanded access clinical trials by naming their trial protocol accordingly, by including the words "expanded access" in the title. For example: "An expanded access protocol for the treatment of … with …"

Sponsors proposing an expanded access arm to an existing trial (as an amendment, via a CTA-A) should consider adding "… with an expanded access arm" to the end of the existing trial title.

Sponsors of expanded access clinical trials (or arms of existing trials) should identify that they are offering expanded access in their cover letter.

In some cases, Health Canada may conclude that a clinical trial not identified in the CTA as an expanded access clinical trial does indeed fit the definition of an expanded access clinical trial. We will then suggest to the sponsor that the trial should be identified as such, for transparency and consistency.

In all cases (whether or not the sponsor has agreed to identify the trial as expanded access), Health Canada will assess the trial's risks and the manner they are proposed to be addressed. If applicable, our assessment will include the risk of the trial impeding clinical development and bypassing regulatory review before the drug is allowed to be used broadly in Canada.

If Health Canada is unable to assess the risks of the drug or the clinical trial from the information submitted as part of the CTA or CTA-A, we may notify the sponsor that they may not sell or import the drug. The notice is sent within 30 days after the application has been received.

Expanded access clinical trials may be associated with specific risks, which Health Canada evaluates during a review of a CTA or CTA-A. As described in the Overview section, there's a risk that expanded access clinical trials may:

- **expose a broader participant population to risks associated with investigational drugs**
- **impede clinical development of the drug**
- **bypass regulatory review before market access**

Sponsors should include information about how their protocol proposes to address these 3 risks, as relevant, throughout their protocol and specifically in an annex to the protocol submitted as part of their CTA. Submitted protocols should be consistent with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline:

- M11 guideline, clinical study protocol template and technical specifications - Scientific guideline

3.4.1 What to include in an annex to the protocol

The annex to the protocol submitted as part of the CTA or CTA-A for an expanded access clinical trial should contain sufficient information and evidence for Health Canada to assess the risks of the drug and the clinical trial. This information may also appear throughout the protocol.

Table 2 gives examples of information a sponsor may consider submitting as part of the annex to the protocol. The examples demonstrate that their protocol incorporates proposed risk mitigation measures into the trial design.

Every CTA or CTA-A is assessed on a case-by-case basis.

565 **Table 2: Examples of information and evidence to include in the annex**

Risk to be addressed	Potential information and evidence to include
Expose a broader participant population to risks associated with investigational drugs	For example, that: • a defined population of participants is expected to significantly benefit from treatment with the investigational drug because … • the condition is serious, life-threatening or debilitating • there is unmet medical need • the drug presents a significant increase in efficacy or a significant decrease in risk in relation to an existing drug marketed in Canada • participation is restricted to eligibility criteria commensurate with identified risks from previous clinical trials with the investigational drug
Risk of impeding clinical development of the drug	For example: • information on any confirmatory clinical trials ongoing or planned to support an eventual drug submission • plans, for example as defined in the trial protocol, to complete enrolment in ongoing phase 1 to 3 clinical trials before the launch of an expanded access clinical trial (may include potential participant screening and triaging by the qualified investigator) • defined inclusion criteria for expanded access clinical trials based on participant exclusion from other ongoing trials, as supported by evidence

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Risk of bypassing regulatory review before marketing of the drug	For example: • tentative projected timeline to bring the proposed drug to market • proposed sunset date for the expanded access clinical trial • proposed size of Canadian participant population, and how access to the drug will be limited to those in medical need who will likely benefit from access • information on how the drug is potentially transitioning from access under the Special Access Program to access under an expanded access clinical trial

3.5 Transparency, equity and fairness

Sponsors should register their clinical trials with an international registry that's acceptable by the World Health Organization, to:

- be transparent about clinical trial information **and**
- show equity and fairness of access for participants

An example of an acceptable registry is the clinical trial registry operated by the National Institutes of Health in the United States.

Sponsors should register their trial once they have received the no objection letter from Health Canada.

Learn more:

- Clinical Trials Database
- Draft guidance on the registration of clinical trials and public disclosure of results

Information made public by sponsors (for example, through a website) should be sufficient to enable potential participants or their health care providers to contact the trial sponsor to enquire about enrolment.

Sponsors should consider how they convey information about expanded access clinical trials with investigational drugs that have not been authorized for sale by Health Canada. Sections 9(1) and 20(1) of the Food and Drugs Act (act) prohibit advertising any drug or device in a manner that's:

- false, misleading or deceptive **or**
- likely to create an erroneous impression regarding its character, value, quantity, composition, merit, design, construction, performance, intended use or safety

The act defines "advertisement" as "including any representation by any means whatever for the purpose of promoting directly or indirectly the sale or disposal of any food, drug, cosmetic or device." Health Canada will rely, as a general principle, on the ordinary meaning of "promote," which is to encourage or incite the sale of a health product.

For more information, consult:

- Guidance on distinction between advertising and other activities for health products

3.6 Delegating activities outside of the clinical trial site

There is growing recognition for the need for flexible clinical trial models that facilitate easier and more diverse participation. In Canada, many people live outside urban areas and away from major clinical research networks. This can make it difficult to recruit people from rural or remote areas who face logistical or financial challenges, impacting the ability of potential participants to access investigational drugs that may provide benefits.

All types of clinical trials can adopt a decentralized model. However, in confirmatory clinical trials, not being able to go to a clinical trial site may pose challenges with standardized evaluation of the patient and reliability of the collected data.

In expanded access clinical trials, the emphasis is on providing promising drugs to participants in need and recruiting as diverse a participant population as possible. For this reason, sponsors could consider adopting decentralized clinical trial models to facilitate conducting trial activities outside of the main location of the clinical trial site.

Additional locations where clinical trial activities occur (outside of the main location of the clinical trial site, as delegated and overseen by the qualified investigator) are not considered additional clinical trial sites. As such, additional locations do not require separate clinical trial site information (CTSI) forms.

However, all locations where clinical trial activities occur, including distant locations, are considered to be part of the clinical trial site. They may be inspected as part of a clinical trial site inspection.

With appropriate risk-based safeguards for participants, sponsors may justify delegating drug administration and safety monitoring activities to qualified local health care providers, who may be located in a variety of locations. An example of an appropriate safeguard would be a risk-based monitoring plan that takes into account treatment complexity, participant safety and individual competencies. Local providers could, for example, already be providing health care to the participant (such as their family doctor).

Sponsors could also consider delegating activities to contract research organizations or other service providers through recorded agreements.

Regardless of the model proposed, delegated activities remain under the supervision of the qualified investigator. The qualified investigator is ultimately responsible for medical decisions taken as part of the trial at all locations associated with their clinical trial site.

A decentralized model can support equitable access to all potential participants in need, regardless of where they live. The concept of delegation is:

- broad enough to allow for various scenarios and situations
- governed by regulations as well as the requirements listed in the current ICH Guideline for Good Clinical Practice (ICH E6), as implemented by Health Canada

3.6.1 One or multiple clinical trial sites

To comply with regulatory requirements, a clinical trial must always have at least 1 clinical trial site, which must be listed on a CTSI form.

In addition to complying with the regulations, sponsors must have a qualified investigator (no more than 1) for each clinical trial site. The site must:

- have research ethics board approval before the trial can start at the site and follow all good clinical practice (GCP) requirements
- be able to provide sufficient evidence to Health Canada that all locations where trial activities are taking place comply with the clinical trial requirements
    - include a detailed account of these activities in the delegation log

Sponsors could consider opening multiple clinical trial sites and delegate activities from each site. This would help overcome issues related to local legislation, which may have an impact on sharing participant data or on the ability to conduct trial activities approved by a research ethics board based in another jurisdiction. For example, to comply with provincial and territorial requirements, sites could be established in each province and territory, from which activities could be delegated to third parties located in the same province or territory.

Learn more in the Delegation and data management and privacy section.

3.6.2 Delegation principles

The regulations and ICH guidelines contain important sponsor considerations related to delegation. Health Canada takes these into account when we review a CTA or conduct an inspection.

Generally, as per C.05.010, each individual involved in conducting the clinical trial must be qualified by education, training and experience to perform their respective tasks. This includes third parties who are delegated tasks in additional locations associated with the clinical trial site.

ICH guidelines are as follows:

- Each individual involved in conducting a trial should have the appropriate education, training and experience to perform their respective task(s) (ICH E6, 2.8)
- The investigator should maintain a list (the delegation log) of appropriately qualified persons to whom they have delegated significant trial-related duties (ICH E6, 4.1.5)

- The investigator is responsible for supervising any individual or party to whom they have delegated trial-related duties and functions (ICH E6, 4.2.5)

All locations where delegated activities occur are considered to be part of the investigator's clinical trial site. As previously mentioned, these additional locations do not require separate CTSI forms, but their addresses should be readily available as part of the delegation log. For the purposes of an inspection, all locations associated with a site may be inspected and are expected to comply with good clinical practices and regulatory requirements.

As part of their CTA, sponsors should describe the following in their trial protocol:

- if duties are expected to be delegated
- what participant intervention, monitoring and follow-up activities are expected to occur at decentralized locations **and**
- how this will be achieved in accordance with good clinical practices and while maintaining patient safety

This also allows sponsors and qualified investigators to appropriately consider and manage risk involved in delegating activities. The protocol should:

- indicate how the sponsor will address the involvement of third parties, potentially required training, equipment, data sharing and facility requirements
- include existing or planned contracts or agreements between the sponsor and other third parties, institutions or locations (and outline specific roles, responsibilities, liabilities and indemnities)
    - these agreements should be available at the clinical trial site

A protocol may not necessarily list, in advance of the trial launching, all specific locations where trial activities will occur. In some cases, sponsors may be able to justify delegating activities to a certain type of location or setting, institution or type of health care or service provider. They do not have to know in advance who will ask to participate in a trial or be involved in trial activities.

In their protocol requirements for training, qualification and experience of additional trial personnel, sponsors should address:

- how agreements to manage delegated activities will be established **and**
- how this will be recorded in a delegation log

3.6.3 Delegation log

Within the delegation log, a qualified investigator may designate other physicians or in some instances other appropriate third parties qualified to perform trial-related procedures or make important trial-related decisions. However, the qualified investigator is always accountable for the actions and decisions taken as part of a clinical trial at a clinical trial site, including at all its associated additional locations.

A delegation log has to be legible, adequately completed and clearly identify the names and signatures of key personnel and delegated third parties, their key duties, and the start and end dates of those duties. This log can be used as a reference (for example, by monitors and inspectors), to verify that all third parties who are delegated trial tasks are appropriately qualified for the tasks they have been delegated.

Sponsors may use electronic formats and e-signatures to facilitate the involvement of participants and third-parties in various physical locations.

The delegation log should be developed before commencement of the study and updated as necessary. The qualified investigator should sign and date the log prior to a task being delegated. Site personnel and delegated third parties should not conduct study-specific tasks until the qualified investigator has documented the delegation, and any required training has been completed.

Learn more about delegation logs in the guidance document on drugs for clinical trials involving human participants (GUI-0100).

3.6.4 Delegation and agreements

ICH guidelines recommend that delegation or distribution of tasks be managed through agreements. The protocol may serve as the basis of agreements.

Decentralized clinical trial models, involving the delegation of trial activities, can involve risk for participants, sponsors and qualified investigators. Agreements can support all parties involved in conducting trial activities in knowing their roles, responsibilities and liabilities, and this helps to support participant safety.

Agreements may set out such considerations as:

- individual roles and responsibilities
- how specific trial activities should be conducted, and their setting
- professional liability among investigators, sub-investigators, delegated third parties, health care providers, insurers and sponsors
- safety monitoring and reporting of adverse events
- indemnity coverage for participants

Clearly written agreements can help support health care providers in complying with all applicable laws, regulations and professional standards.

3.6.5 Delegation and participant screening

Medical care and medical decisions are supervised by the qualified investigator.

To address the risk of impeding clinical development of the drug, the qualified investigator is responsible for ensuring that potential participants are screened at the time they enrol in an expanded access clinical trial. Screening is done to determine that potential participants are not able to enrol in ongoing confirmatory trials.

A protocol that proposes to delegate duties related to participant screening and enrolment from the qualified investigator to other personnel or delegated third parties should adequately address this risk.

3.6.6 Delegation and informed consent

As per C.05.010, written informed consent needs to be given in accordance with the applicable laws governing consent. This includes applicable provincial and territorial rules.

In some cases, the informed consent process may need to be carried out in a decentralized context involving several different physical locations. Sponsors and qualified investigators should mitigate any risks to participants when obtaining informed consent in a decentralized context. The trial protocol should include rationale to support:

- delegating duties related to the informed consent process to other personnel or third party **or**
- obtaining informed consent through a virtual meeting (for example, at a health care provider's office or potential participant's home)
    - such meetings should take place in real-time and face-to-face, using both audio and video

Sponsors must provide a trial-specific informed consent form (ICF). This form must clearly and concisely outline:

- the risks and anticipated benefits **and**
- other information that potential participants require in order to decide if they will participate in the trial

Sponsors must ensure that research ethics board approval has been obtained for the trial protocol and the ICF. Sponsors should ensure that the informed consent process:

- fully informs potential participants of all aspects of the trial that are relevant to their decision to participate, including potential indemnity coverage
    - this is documented in an ICF (developed by the sponsor and reviewed and authorized by a research ethics board)
- informs potential participants so they know who to contact if there are questions about the research
- provides a 24-hour number or tell participants who to contact if they experience a research-related injury (for example, local health care provider, emergency services, qualified investigator)
- informs potential participants on who will have access to their personal health information collected during the study and how it will be stored
- retains a retrievable record of the participant's informed consent

New information that might affect a participant's willingness to continue should be evaluated to decide if their re-consent is necessary. If re-consent is required, such as due to emerging safety concerns or signals from other clinical trials, the new information must be clearly highlighted in the updated informed consent materials. These updated materials should be approved by a research ethics board before they are used.

A written, signed and dated ICF is required as documentation of consent in paper or electronic format. A valid record of the participant's signature must be kept. Documentation should also confirm that the participant received the information, a discussion took place with the qualified investigator or delegated third party and the participant gave consent. The informed consent process must comply with all applicable regulatory requirements and adhere to GCP requirements.

Virtual meeting platforms and electronic signatures may make the informed consent process more efficient for those who live in remote areas. However, sponsors should be careful not to unintentionally discriminate against those who do not have access to, or prefer not to use, virtual platforms. Alternative methods, including in-person consent meetings and physical copies of the ICF, should be available to those who request it.

3.6.7 Delegation and institutional research ethics boards

As with all clinical trials, clinical trial sites of expanded access clinical trials must be authorized by a research ethics board. This approval must be provided to Health Canada as part of the CTSI form before trial activities can begin at a clinical trial site or at its other associated locations.

Some research ethics boards may accept alternate review models, or accept prior ethics reviews and decisions from another board, especially if the institutional board is part of a consolidated or streamlined ethics review network. Indeed, some clinical trial organizations in Canada have facilitated more streamlined approval processes that can now include simultaneous participation and representation from many institutional research ethics boards. Approval from one of these networked research ethics boards may help to streamline required approvals for opening multiple clinical trial sites.

3.6.8 Delegation, data management and privacy

Delegating clinical trial activities to a different physical location than the clinical trial site may require that information and data be shared between those involved in conducting various activities and the qualified investigator. Often, this data will contain participants' sensitive and private medical information.

The collection, transfer, storage and handling of clinical trial data are regulated by federal and provincial personal information and privacy laws. Sponsors should be aware of any local laws and regulations that might have an impact on their trial activities, especially across borders.

Learn more:

- Privacy legislation (Health Data Research Network Canada)

3.6.9 Delegation and safety monitoring plans

Trial activities, including those that have been delegated, should be monitored properly and comply with good clinical practices and regulatory requirements.

Protocols should include a risk-based safety monitoring plan that takes into account treatment complexity, participant safety, individual competencies and intended research outcomes of the expanded access clinical trial. This plan should indicate how the trial will be monitored, compliance assessed, and records collected, reviewed and analyzed for safety outcomes.

3.6.10 Delegation and reporting adverse drug reactions

The regulations state:

"During the course of a clinical trial, the sponsor shall inform the Minister of any serious unexpected adverse drug reaction in respect of the drug that has occurred inside or outside Canada as follows:

a. if it is neither fatal nor life threatening, within 15 days after becoming aware of the information and

b. if it is fatal or life threatening, within seven days after becoming aware of the information

The sponsor shall, within 8 days after having informed the Minister under paragraph (b), submit to the Minister a complete report in respect of that information that includes an assessment of the importance and implication of any findings made."

Agreements can support all parties involved in conducting trial activities in being aware of their roles and responsibilities for reporting adverse drug reactions to the sponsor. In this way, all individuals involved in expanded access clinical trial activities can effectively play their part in supporting participant safety.

3.7 Annual reports

The risks of impeding the clinical development of the drug or of bypassing regulatory review before broad marketing of the drug are not static. The risks depend on context and will evolve depending on such things as progress of the drug development program and other factors.

To be able to assess the safety and evolving risks of an ongoing expanded access clinical trial, Health Canada may request that sponsors of such trials submit a report every year. Assessment would start 1 calendar year after trial activities begin, until study completion.

For Health Canada to undertake this assessment, sponsors could be instructed to include the following information in their annual report:

- number of participants enrolled since the last report and total number since the expanded access clinical trial began
- number of third-party individuals involved in administering the drug, if applicable, since the last report and total number since the expanded access clinical trial began
- status of any planned, ongoing or completed confirmatory trials since the last report, or other commitments related to clinical development of the drug made in the CTA
- updates on any other commitments made in the CTA, including proposed milestones for bringing the drug to market

Health Canada may suspend the authorization to sell a drug for the purposes of a clinical trial if there are reasonable grounds to believe that information submitted about the trial is false or misleading (there may be other grounds to suspend). The ability to suspend is outlined in section C.05.016(1) of the regulations.

3.8 Expanded access clinical trials with controlled substances

Clinical trials are regulated under Part C, Division 5 of the regulations. However, sponsors who wish to conduct a trial with a controlled substance listed in Schedules I to V of the Controlled Drugs and Substances Act (CDSA) must also comply with this act's requirements.

Under the CDSA, all activities with controlled substances, including the sale, import, export, production, transportation and possession of controlled substances, are prohibited unless authorized under its regulations or by exemption. (Possession is only prohibited for controlled substances listed in Schedules I, II and III to the CDSA).

A qualified investigator requiring a controlled substance for research purposes, which includes administration to humans in a clinical trial, must receive an authorization from Health Canada. This is done by submitting a separate application to the Office of Controlled Substances, after a no objection letter for the clinical trial has been issued by Health Canada.

Applications to perform research with a controlled substance that is a restricted drug listed in the schedule to Part J of the Food and Drug Regulations require additional supporting documents. Upon receipt of an application, the Office of Controlled Substances will identify any additional supporting documents required.

Health Canada applies the following principles for research with controlled substances:

- there is a record of handling
- the risk of diversion in transit is reasonably addressed

- the risk of diversion at the clinical trial site or associated locations is reasonably addressed

Investigational drugs that are restricted drugs must be provided by a licensed dealer who is authorized to conduct regulated activities with the substance.

If the authorized manufacturer is located outside of Canada, a Canadian licensed dealer must import the substance. The licensed dealer must obtain an import permit from Health Canada. Only licensed dealers can apply for import permits.

Learn more about the application process for clinical trials with controlled substances:

- Controlled substances

To apply to use a controlled substance for clinical trials (must be completed by a qualified investigator):

- Application form

Researchers should familiarize themselves with all Health Canada notices to stakeholders on the requirements for conducting clinical research with specific controlled substances.

Researchers interested in conducting an expanded access clinical trial with a controlled substance should contact the Office of Controlled Substances to obtain information on associated requirements.

Email: exemption@hc-sc.gc.ca

Health Canada also conducts compliance and enforcement activities for all controlled substances and precursors and activities conducted under the CDSA and its regulations. This includes activities conducted in clinical trials. Compliance monitoring and enforcement helps to support the legitimate use of controlled substances, while reducing the risk of diversion.

For information on the principles that Health Canada follows when monitoring compliance and enforcement of controlled substances, visit:

- Compliance and enforcement policy for controlled substances and precursors (CS-POL-001)