Health Canada Santé Canada

Canada

Health Canada Office of Clinical Trials Reflections and Updates

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YOUR HEALTH AND SAFETY... OUR PRIORITY.

Learning Objectives

1. Learn more about how Health Canada's Office of Clinical Trials has worked with N2 and other clinical research organizations over the past decade.

2. Be able to apply regulatory updates (national and international) from Health Canada's Office of Clinical Trials to your own work.

Key Points

- Health Canada is the federal regulator responsible for authorizing the importation and sale of drugs for the purpose of clinical trials. As per the Food and Drug Regulations (Division 5) C.05.006(1)(b)(ii) Health Canada reviews CTAs to ensure the use of the drug for the purpose of the clinical trial:
  - does not endanger the health of clinical trial subjects (participant) or other persons,
  - the clinical trial is not contrary to the best interests of a clinical trial subject (participant), and
  - the objectives of the clinical trial may be achieved

- Health Canada leads / participates in several ongoing initiatives
  - Within Canada (e.g. Notices to stakeholders)
  - Internationally (e.g. ICH, ACCESS, ICMRA)

Clinical Trial Application (CTA) – The Basics

- Contact Info:
  - Pharmaceutical Drugs Directorate
    - oct.enquiries-requetes.bec@hc-sc.gc.ca
  - Biologic and Radiopharmaceutical Drugs Directorate
    - brdd.ora@hc-sc.gc.ca
- Clinical Trial application required for:
  - Phase I, II and III clinical trials conducted in Canada
  - If the proposed study is employing drugs that are used outside of their Canadian marketing label (i.e. via an unapproved route, dosage, patient population or indication), or an unapproved product (i.e. no DIN), a Clinical Trial Application (CTA) is generally required for the proposed study.

How to submit a Clinical Trial Application (CTA) and/or Clinical Trial Application Amendment (CTA-A)

There are 3 ways to submit a CTA or CTA-A:

1. Common Electronic Submission Gateway (CESG)

2. Courier (FedEx, Purolator, UPS, etc.) – must submit a CD or USB only

3. Email : oct.smd-dgp.bec@hc-sc.gc.ca

Note: when submitting via the CESG or email please do NOT send the documentation via mail.

Clinical Trial Application Screening Process

- 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

- All CTAs and CTA-As will be screened for completeness and if deficiencies are identified at screening, these will be addressed by a Screening Clarification Request.

- Once the application is considered administratively complete, an Acknowledgement Letter will be issued to indicate that the 30-day default period commenced on the date of receipt in Health Canada.

Clinical Trial Application Review Process

- Health Canada will conduct a clinical and quality review of the CTA. If deficiencies are identified, Health Canada will issue an Information Request. As per section C.05.009 of the FDR, the sponsors must provide the requested information within **2 calendar days**.

- As per section C.05.006(1)(b) of the FDR, the Minister must advise the sponsor within 30 days after receipt of an administratively complete CTA or CTA-A indicating that the sponsor may not sell or import the drug with specific reasons.

- Should the sponsor be unable to provide the requested information within the specified time frame, the application may be withdrawn and resubmitted without prejudice.

Audience Question #1

The only documents that need to be filed with a CTA are:

- Cover Letter
- HC/SC 3011 Form
- Product Monograph / Investigator's Brochure
- Informed Consent Form (ICF)
- Quality Overall Summary (QOS)

True or False?

Audience Question #1 – Answer

FALSE

Study Protocol

Note: A copy of the *final* study protocol should be submitted. The information in the protocol must follow the Health Canada adopted ICH guidance entitled GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2). Please refer to Section "6. Clinical Trial Protocol And Protocol Amendment(s)", as it covers essential aspects of clinical trial protocols.

List of required documents for CTA

- Cover letter
- HC/SC 3011 Form
- Product Monograph or Investigator's Brochure (IB)
- Study Protocol

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- Informed Consent Form (ICF)
- Quality Overall Summary (QOS)

QOS Templates as per Phase of Clinical Trial

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/templates-modeles/qoscecta_sgqecdec_ph_i-eng.php
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/templates-modeles/qoscecta_sgqecdec_ph_ii-eng.php
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/templates-modeles/qoscecta_sgqecdec_ph_iii-eng.php

Clinical Trial Application Amendments

When filing a CTA-A the following information should be included:

- a new HC/SC 3011 Form
- a **clear rationale** for each proposed substantial change within your CTA-A
- a copy of the clean proposed protocol, as well as a tracked protocol that clearly outlines all changes that have been made to the currently approved protocol (i.e. the most recently authorized protocol).
- an updated copy of the Informed Consent Form (ICF), as applicable, with changes clearly indicated (annotated).

NOTE: Alternatively, if the ICF is not affected as a consequence of the protocol updates, there is no need to re-submit the approved version – we only ask that you confirm this in the Cover Letter when filing.

- a clean and tracked version of the Quality Overall Summary (QOS). If a 'tracked' copy is not available, we ask that the sponsor provide a detailed summary of changes.
- <u>prior to commencing the trial</u>, the sponsor must submit a Clinical Trial Site Information (CTSI Form)

Clinical Trial Application - Notification

- As per Section C.05.007 of the FDR, these minor changes / revisions may be implemented immediately, but Health Canada must be informed in writing, within 15 calendar days of the day of the change.

- As per our online Notification Guidance, updated information regarding the change should be submitted in the form of **a cover letter** and any supporting documentation. The cover letter should indicate the file number, control number(s), and protocol number(s) of the original CTA(s).

- CTA-Ns may be submitted to our office via email: oct.ctan-ndec.bec@hc-sc.gc.ca

Pre-Clinical Trial Application (Pre-CTA) Meetings

- We strongly encourage sponsors to file for a pre-CTA meeting for the following:
  - Master Protocols / Umbrella Trials
  - new active substances
  - applications that will include complex issues that may be new to Health Canada
  - Prior to filing a new CTA (after the withdrawal of the original CTA)

- Section 2.2 of our Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications provides information on the Pre-CTA meeting process.

- We generally book pre-CTA meetings 3 months out, and we are still conducting all meetings virtually (e.g. via MS Teams).

- A Formal Pre-CTA meeting request should be directed to the following address: oct.pre.cta-dec.bec@hc-sc.gc.ca.

CTA Tips and Tricks

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  - If you are filing to amend a global protocol, provide a concise summary of only the clinically relevant changes that will impact the protocol from a **Canadian Perspective.**

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- Is the **Schedule of Events** clear?

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- Is the **Schedule of Events** clear?

- Did you provide the **Decision criteria and rationale** used to guide the opening or closing of a cohort?

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- Is the **Schedule of Events** clear?

- Did you provide the **Decision criteria and rationale** used to guide the opening or closing of a cohort?

- Is this an **amendment**? A tracking sheet documenting the life cycle of the CTA, with control numbers and NOL dates facilitates the review

CTA Tips and Tricks – Adaptive Design Trials

Although seamless design is efficient– from a regulatory perspective, there are milestones that need to be met prior to moving from one phase of the trial to the next

- for example:
  - the sponsor may be asked to commit to filing an amendment prior to initiating Part 2 (expansion) of a study, once the totality of data from the first part of the adaptive design has been considered to guide in dose selection.
- The amendment could include:
  - i) The RP2D along with rationale and why it was selected
  - ii) A concise safety update

CTA Tips and Tricks

- **Other Ways to Avoid an IR**
  - Provide a concise safety summary of all evaluable patients to date, including data cut-off date
  - When submitting a global protocol please provide details
  - Do the IB, protocol, and cover letter provide important information?
    - Is the lead-in phase complete?
    - Has a dose for the phase 2 portion of the study been determined?
    - Will Canadian patients be participating in the lead-in and expansion phase or just the expansion phase?

Audience Question #2

What are some of the ICH Guidances Health Canada is Working on Now?

A. E6

B. M11

C. E20

D. E21

E. All of the Above

Audience Question #2 – Answer

E. All of the Above

International Council for Harmonisation: E6(R3)

Good Clinical Practice

- Will build on principles outlined in E8: General considerations for clinical studies → focus on factors critical to quality
- Will provide flexibility whenever appropriate to facilitate the use of technological innovations
- Using a stakeholder engagement approach to support its development
  - N2 is a stakeholder representative on the E6 EWG

International Council for Harmonisation: E6(R3)

- A draft version of the updated principles is available on the ICH website
- Will include two annexes:
  - Annex 1: Interventional clinical trials
  - Annex 2: Additional considerations for non-traditional interventional clinical trials
- STEP 2 Public Consultation – coming in 2023

International Council for Harmonisation: M11

Clinical electronic Structured Harmonized Protocol (CeSHarP)

- Proposes to provide comprehensive clinical protocol organization with standardised content
- Will include both required and optional components
- Will apply to interventional trials
- The template will include:
  - identification of headers,
  - common text and
  - a set of data fields and terminologies
- Open for public comment in Canada until Feb 17, 2023

International Council for Harmonisation: M11

- A harmonised clinical protocol and specification for electronic exchange of protocol information will enhance the ability of sponsors, regulators, investigators, and other stakeholders to initiate, review, and conduct clinical research, resulting in more efficient drug development and delivery of medicines to patients.
- Deliverables of M11
  - M11 Guideline
  - M11 Template
  - M11 Technical Specification

International Council for Harmonisation: E20

Adaptive Clinical Trials

- Will address design, conduct, analysis and interpretation of adaptive clinical trials
- Will provide a transparent and harmonized set of principles for the regulatory review of these studies
- STEP 2 Public Consultation – June 2023

International Council for Harmonisation: E21

Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials

- Starting to draft concept paper and business plan

ACCESS Consortium Clinical Trials WG

- Consortium consists of regulatory authorities from:

  Australia, Canada, Singapore, Switzerland, United Kingdom
- Established to promote regulatory convergence and foster synergy
- Clinical trial WG established in 2021
- Goal is to:
  - Facilitate sharing of information amongst the 5 regulatory authorities
  - Establish documentation requirements and evaluation criteria amongst Access Consortium members for a list of key topics.

ICMRA Clinical Trials WG

- Working group was established in 2022
- Developing a reflection paper that discusses the challenges/ solutions/ enablers of multi(national/regional) clinical trials to address public health emergencies of international concern
- Aim is to increase pandemic preparedness, through facilitating the efficient authorization, oversight, and start-up of clinical trials

Health Canada Publication - Notice to stakeholders: Health Canada's expectations regarding risk-management measures for clinical trials involving psychedelic-assisted psychotherapy

- Published December 5, 2022
- Relevant to all clinical trials involving psychedelic-assisted psychotherapy
- Risk-management measures that will be used in proposed clinical trials involving psychedelic-assisted psychotherapy should be outlined in the protocol at the time of the clinical trial application (CTA).

Health Canada Publication - Notice to stakeholders: Health Canada's expectations regarding risk-management measures for clinical trials involving psychedelic-assisted psychotherapy

To protect the well-being of participants:

- Proof of qualifications of the therapists that will be recruited for the trial
- Rapport between Participant and therapist – through adequate sessions in the protocol
- Minimum of two therapists present at time of drug administration
- Therapists should remain the same throughout the clinical trial for each patient in order to maintain trust
- Licensed physician to provide medical oversight of the clinical trial
- A psychologically safe environment
- Report any serious unexpected adverse drug reactions (ADRs) to Health Canada
- Both the physical and psychological risks of psychedelic-assisted psychotherapy should be clearly articulated in the informed consent forms given to participants

Learning Objectives

1. Learn more about how Health Canada's Office of Clinical Trials has worked with N2 and other clinical research organizations over the past decade
   - CTAs/CTAAs/CTNs submission best practices
   - Engage with Office of Clinical Trials pro-actively for pre-CTA meetings and other regulatory questions

2. Be able to apply regulatory updates (national and international) from Health Canada's Office of Clinical Trials to your own work
   - International updates (ICH, ACCESS, ICMRA)
   - Canadian updates (Notices, consultations)

Questions?

References

List of reference material

Guidance Document : Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects" (GUI-0100)

Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications

Guidance for completing the Drug Submission Application Form (HC/SC 3011)

Guidance Document – Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals

Instructions for complete the Clinical Trial Site Information Form

Tri-Council Policy Statement : Ethical Conduct for Research Involving Humans – TCPS 2 (2022)

List of reference material – continued

ICH Guidelines

E6(R2) – Good Clinical Practices

M3(R2) – Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

M11 – Clinical electronic Structured Harmonized Protocol

Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors