Health Canada Santé Canada

Canada

PREPARING A CLINICAL TRIAL APPLICATION FOR SUBMISSION TO HEALTH CANADA

Overview of Clinical Trial Applications in Canada and Best Practices

Canadian Stroke Congress – Clinical Trials Research Coordinators Workshop
November 27, 2024

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YOUR HEALTH AND SAFETY... OUR PRIORITY.

Presentation Outline

- Overview of Clinical Trial Regulations in Canada
- Structure and Process of CTA Review at Health Canada
- Key Considerations of CTA Filing and Review, including Common Issues
- Making the most of pre-CTA meetings
- Final Reminders

Clinical Trial Regulations for Drugs in Canada

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: Part C** *[Drugs],* **Division 5** *[Drugs for Clinical Trials Involving Human Subjects]*, Clinical Trial Applications (CTAs) are required for:

- Phase I, II and III clinical trials conducted in Canada
- Study of a drug product outside the parameters of the marketing authorization.

Clinical Trial Regulations for Drugs in Canada

As per the Food and Drug Regulations (Part C, 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 (participants) 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.

The application must include sufficient information to assess the benefit and risks of the drug in the proposed trial.

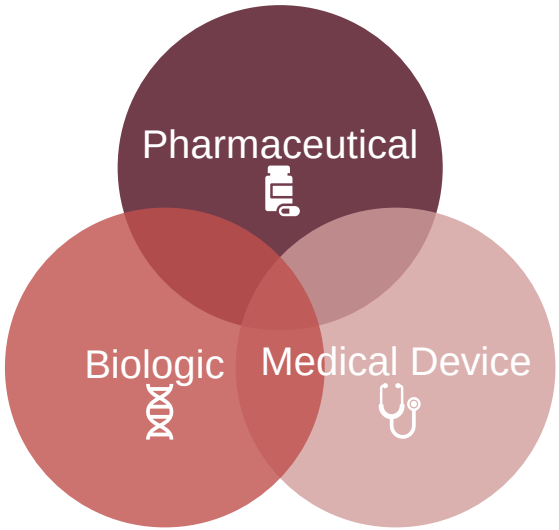
Clinical Trial Regulations for Drugs in Canada

The objective of clinical trial review is to minimize the risks that participants may be exposed to in a clinical trial setting by:

- Assessing the Study Protocol, Informed Consent Form, Investigator's Brochure and Quality-related information of the investigational drugs
- Monitoring Adverse Drug Reactions and other safety issues while trial is ongoing
- Ensuring Good Clinical Practice (GCP) is employed at clinical sites in Canada through the inspection program
- Authority to suspend or cancel the authorization of a clinical trial if required.

Clinical Trial Review Offices for Drugs at Health Canada

- Pharmaceutical Drugs Directorate (PDD).
- Biologic and Radiopharmaceutical Drugs Directorate (BRDD).
  - CTAs which involve both pharmaceutical(s) and biologic(s) or a combination product should be submitted to the Directorate of the most investigational component.

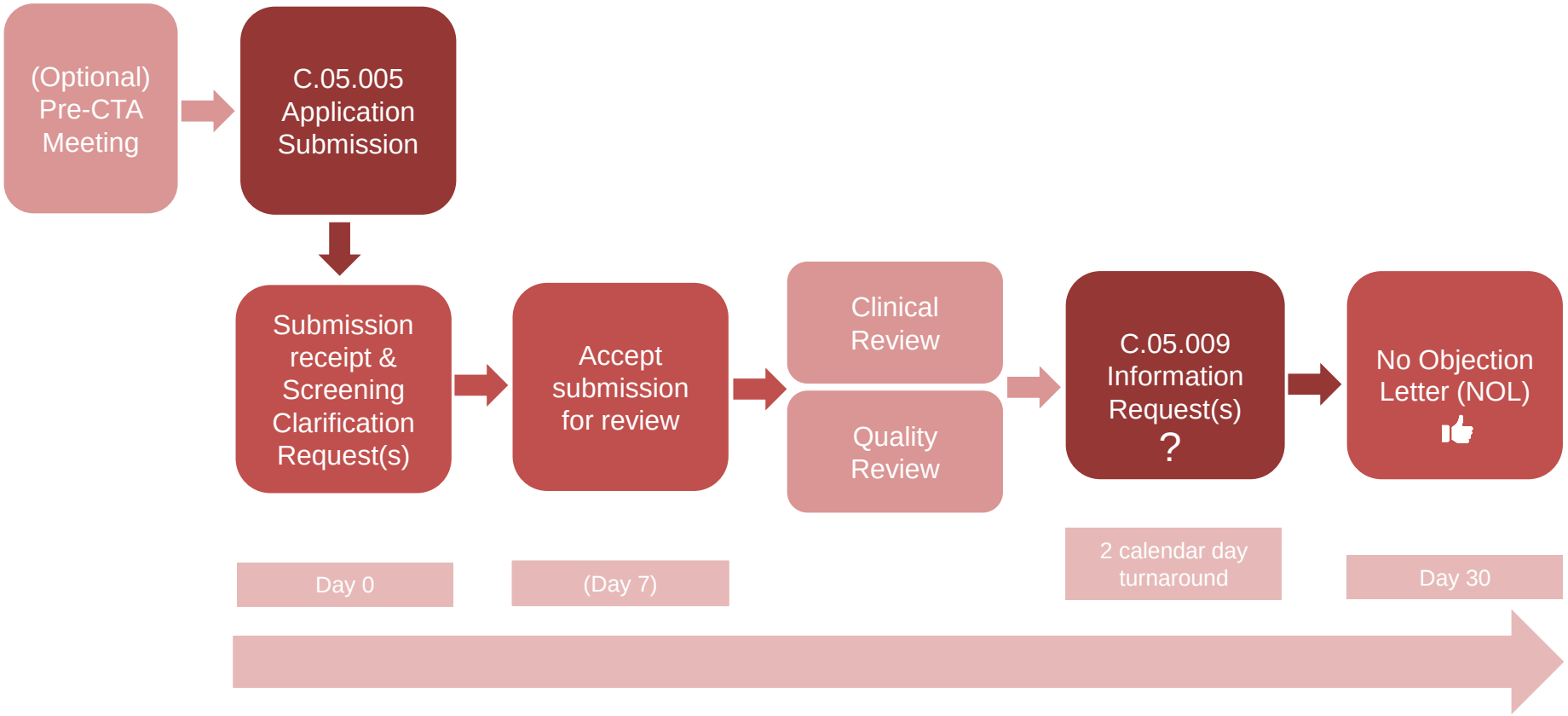


- The Medical Devices Directorate (MDD) is consulted where a device is used in a drug clinical trial.
  - ITA applications required for all unlicensed Class II, III, and IV medical devices and reviewed under the Medical Device Regulations (MDR).

- The Regulatory Operations and Enforcement Branch (ROEB) conducts inspections, compliance verification, investigations for clinical trials for drugs.

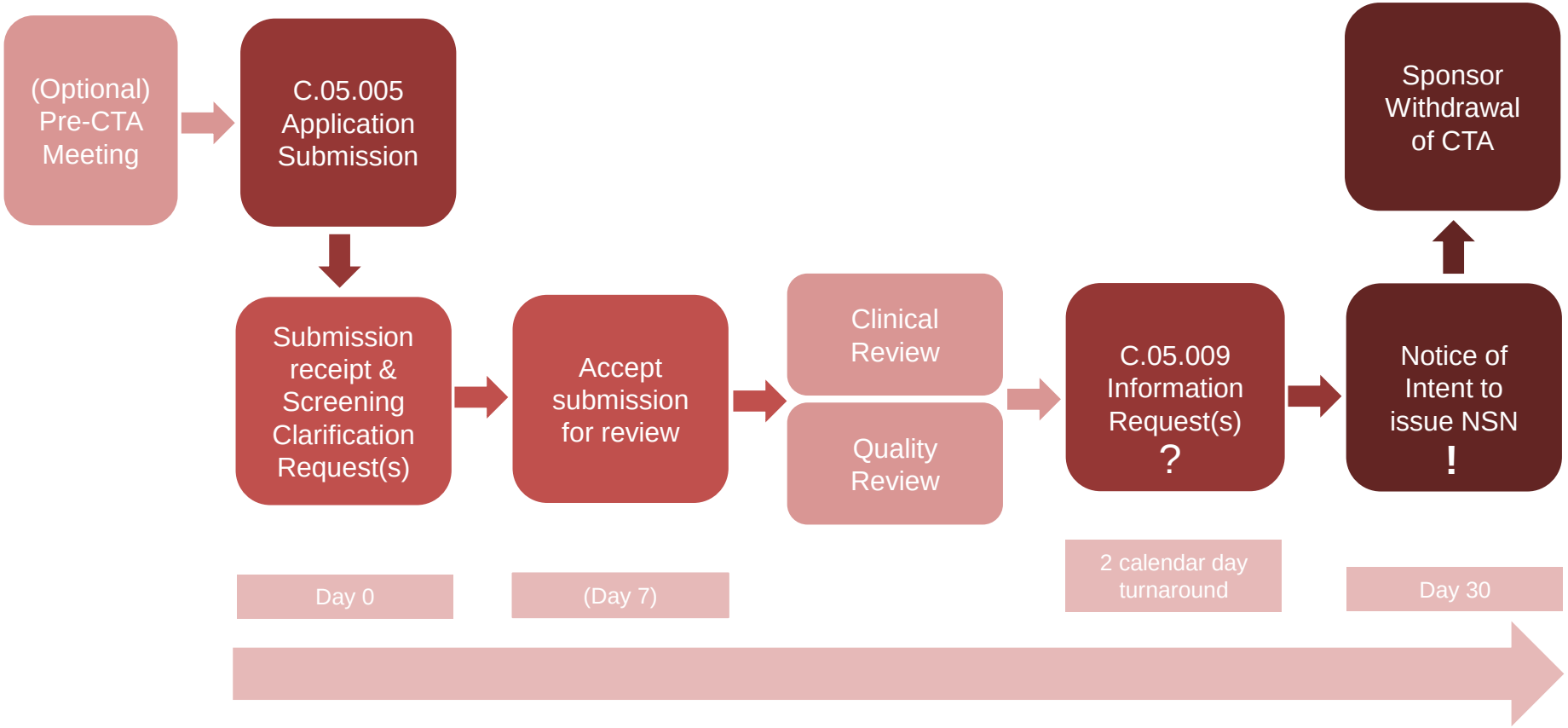
ITA: Investigational Testing Authorization

Overview of the CTA review process for Drugs at Health Canada



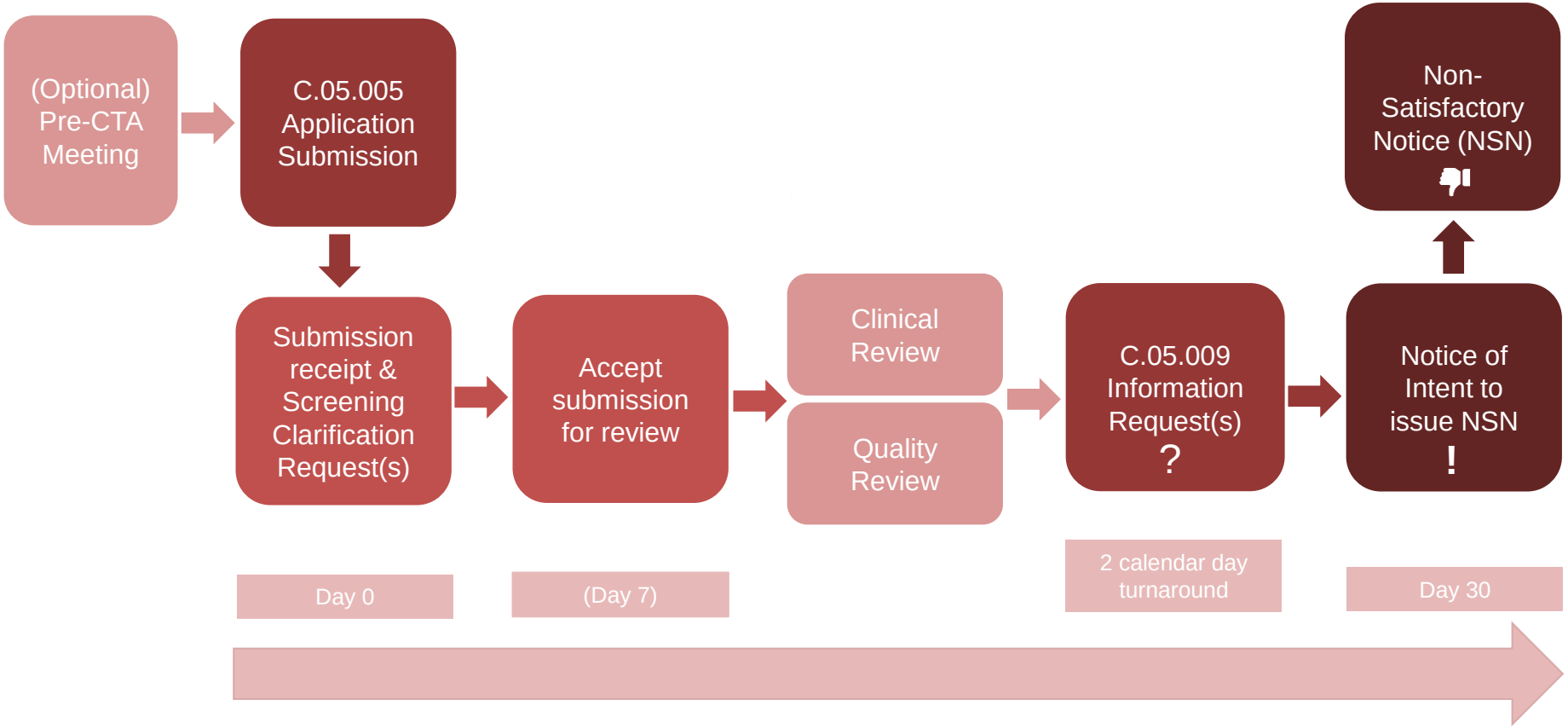
CTA: Clinical Trial Application

Overview of the CTA review process for Drugs at Health Canada



NSN: Non-Satisfactory Notice

Overview of the CTA review process for Drugs at Health Canada



Post-NOL Processes

CTSI: Clinical Trial Site Information
REB: Research Ethics Board

Post-NOL Processes

C.05.007 CTA-Notification
- Changes that do NOT affect quality of safety of drug, does NOT alter risk to health of clinical trial participants and administrative changes.
- Sponsor to notify HC within 15 days.

C.05.008 CTA-Amendment
- Changes that could impact quality or safety of the drug, or the risk to the clinical trial participants. E.g., dosing, toxicity management, changes to C&M.
- CTA-A *required prior* to implementation. Rationale to be provided with changes.

C.05.014 SUSARs
- Inform HC within 7 days if fatal/life threatening or within 15 days otherwise.

C.05.015 Study Discontinuation
- Inform HC within 15 days.

C&M: Chemistry and Manufacturing
HC: Health Canada
SUSARs: Suspected Unexpected Serious Adverse Reactions

CTA Filing

- Information about how to file a CTA is found in the *Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications.*

- Health Canada continues to accept submissions via email: *Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format.*

- The HC/SC 3011 Form is required for both CTA and CTA-As: *Guidance for Completing the Drug Submission Application Form.*

- SOAD forms are required when importing foreign-sourced drugs (from ICH countries) that have a Canadian marketed equivalent and are being used in accordance with the Canadian label.

- Sponsors may submit an ISA form for non-investigational drugs.

CTD: Common Technical Document
SOAD: Summary of Additional Drugs
ICH: International Council on Harmonization
ISA: Investigational Status Assessment

Common Clinical Issues

- **Insufficient detail in Study Protocol:**
  - Safety Monitoring or Toxicity Management guidance not provided for important safety issues related to investigational drug(s)
  - Rationales for study design not provided (e.g., dosing rationale, treatment benefit estimation, open-label vs. blinded, single-arm vs. randomization)
  - Decision criteria or stopping rules are not defined (e.g., opening/closing cohort, dose escalation, safety stopping rules).

- **Insufficient information in Investigator's Brochure**
  - Recommended to consult ICH GCP E6

- **Informed Consent Form (ICF) does not clearly state known and unknown important and potential risks of the drug(s) and/or language is not clear or in lay terminology.**

Common Clinical Issues

- **Up-to-date clinical information and data are not available at the time of submission to support the CTA or CTA-A:**
  - A trial is ongoing and up-to-date results and safety data are not incorporated in the latest version of the IB or the Study Protocol.
  - An application for a later phase trial is submitted when the related earlier phase trial has not been developed with sufficient supportive data:
    - E.g., Phase 3 CTA submitted right after Phase 1/2 initiation.
    - E.g. (oncology), Phase 3 submitted for different population than in Phase 1/2.
  - Milestones are not met prior to initiating the next part or Phase of a trial:
    - E.g., Phase 1 first-in-human (FIH) Study in US, only proposing Part 2 (dose expansion) in Canada, dose to be expanded and supportive data is not available.

Common Clinical Issues

- **Data and discussion on pharmacokinetics (PK)/ pharmacodynamics (PD) not provided:**
  - What are the relationships between the drug dose and PK [dose-exposure], dose/exposure and PD effect [dose/exposure-response], and or exposure and safety effect [exposure-safety]
  - If a combination of drugs are proposed, have they been characterized individually first? What is the contribution of effect?

- **Missing information to assess tolerability of a drug:**
  - Duration of exposure
  - Relative dose intensity
  - Frequency of dose modifications (i.e., reductions, interruptions or discontinuation) and reasons
  - Dose-limiting toxicities (DLTs)
  - Frequency Grade 3/4 adverse events (AEs), serious AEs (SAEs), including fatal events.
- **Issue(s) with statistical plan which may present pre-market review challenge(s).**

Common Screening Issues

- HC-3011 form and associated Appendices are incomplete.
- Investigator's Brochure(s) and/or Product Monograph(s) not up to date
  - IB must be <1 year old, and/or include an attestation of no changes.
- Cross-referencing of Quality information is incorrect or missing.
  - E.g., Letter of Access (LoA) to Master Files (MFs)
- Missing or discrepancy of version dates of revised study documents.
- Missing statement to whether the ICF is impacted in the Amendment.
- Summary of Changes history or annotated/tracked copies not provided for study documents.

CTA Filing – Tips

- Add any declarations or clarifying statements in your Cover Letter and use Module 1.0.7 General Note to Reviewer.

- Clearly indicate submissions that are related but filed separately and any other relevant cross-referencing information
  - E.g., Identical Amendments for multiple protocols.

- Clearly indicate when complex innovative designs are proposed
  - E.g., Master Protocols, Modular designs, Subprotocols.

- Confirm source of marketed drugs and cite the most current PMs
  - If sourced outside Canada, SOAD required, confirm that a Canadian version is available.
  - For biologics, account for C&M information.

CTA-Amendments (CTA-As)

- Same regulatory review process as CTAs, focusing on the changes.
- Always include a tracking sheet documenting the lifecycle of the CTA to facilitate review
  - Include both clinical and quality submissions, with control numbers and NOL dates.
- Provide tracked/annotated changes for Study Documents.
- Rationale, Rationale, Rationale!
  - E.g., regulatory authority request, new safety information, new standard of care, reduce burden on site or participant, REB feedback

All changes affecting participant safety or the integrity of the trial should be adequately justified with a rationale and supportive data as applicable.

Information Requests (IRs)

- Information Requests are issued by email to the submission contact listed on the HC3011 form.
  - Providing a back-up contact in the form can be useful in cases of absences.
- Ensure that you are prepared to respond to requests once a CTA is submitted:
  - IRs must be responded within 2 CALENDAR days
  - Confirm receipt of the email to notify HC that the IR has been received
  - Extensions are by exceptions only, and on a case-by-case basis.
- For eCTD submissions, please submit a courtesy copy by email.

C.05.009 Additional Information and Samples

- IRs issued when information and documents are insufficient to enable a benefit/risk assessment.
- Sponsor to submit response within 2 calendar days from receipt of the request

Clinical Review – Tips

- Always ensure the Study Protocol and IB are up-to-date with all relevant information to initiate the study in Canada.

- Avoid submitting many Addendums, Protocol Clarification Letters, Dear Investigators Letters without incorporating in the Study Protocol.

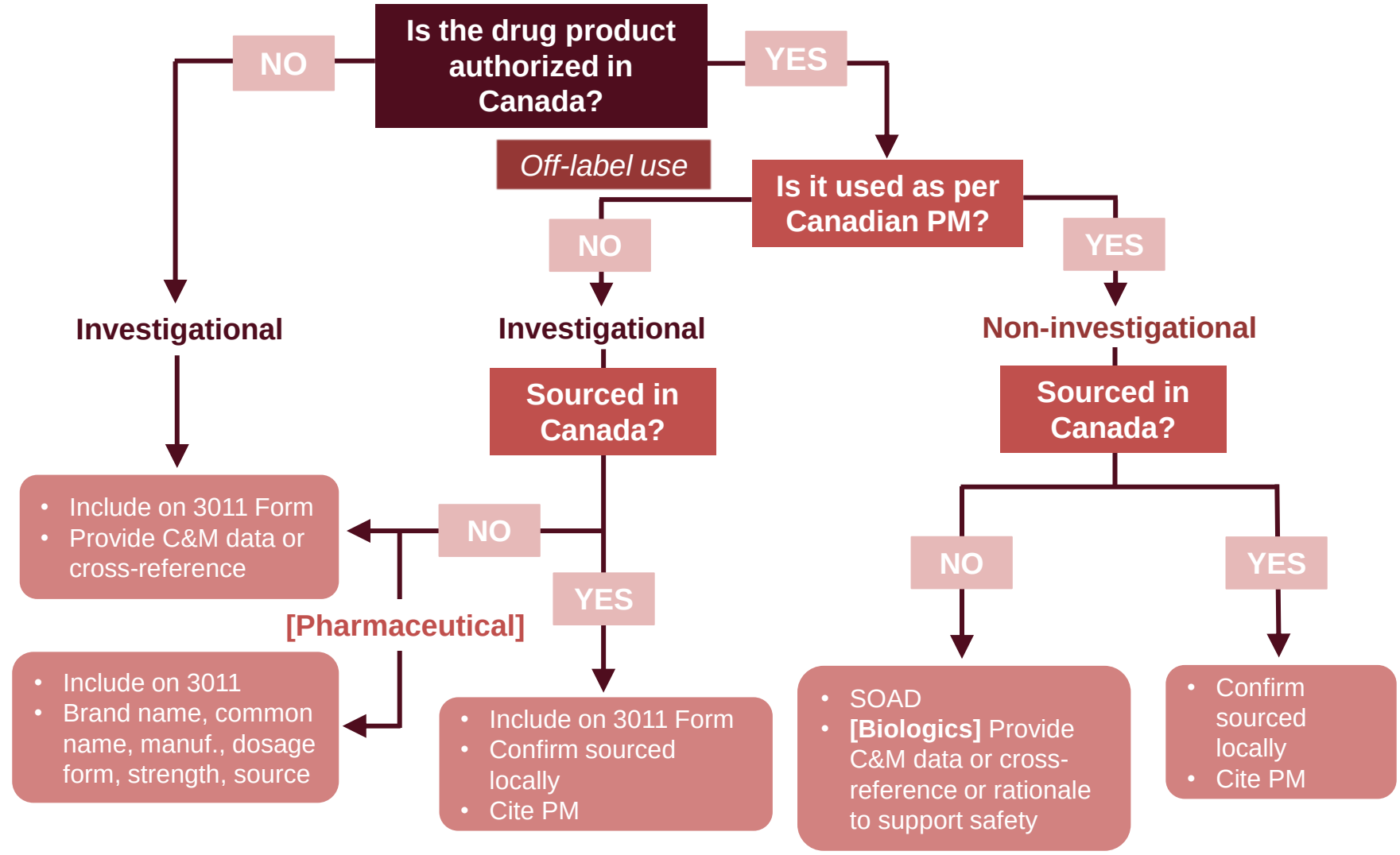
- Consider the ICH M11 Clinical Electronic Structured Harmonized Protocol (CeSHarP) *draft* template when constructing protocols:
  - Provides the format and structure of the protocol, including the table of contents, common headers, and contents
  - Ensures harmonized Global protocols, and easy-to-find information
  - Provides useful table templates for Protocol Amendment History and current Amendment Summary of Changes for sponsors and regulators
  - Indicates where rationales should be provided for various study design aspects.

General Quality Considerations

- Quality information for investigational products should always be provided, or appropriately cross-referenced.
- For marketed products, the market source should be identified and justified with adequate scientific data.
- Ensure quality information is sufficient to support the Phase of the study.
  - For multi-phase studies (e.g., Phase I/II or II/III protocols), submit CMC data according to the requirements of the highest phase.
- Alternate approaches to standard principles and practices should always be clearly described and supported by adequate scientific and/or clinical justification.

CMC: Chemistry, Manufacturing and Controls

How to determine if C&M data is required?



C&M: Chemistry & Manufacturing
PM: Product Monograph

Pre-CTA meetings

- Pre-CTA meeting requests are submitted by Sponsors when they have specific questions prior to submitting a CTA.
- Meetings are booked approximately 3 months out.
- Non-eCTD requests for meetings can be sent via email.
- Encouraged for new active substances or complex applications.
- For pre-CTAs for files that were previously withdrawn, address previously raised IR comments.
- Written advanced feedback is provided to Sponsor's questions ahead of the meeting.
  - The Sponsor may cancel the meeting if the response is deemed sufficient.

Pre-CTA meetings – Tips

- Provide a list of *specific* questions:
  - Refrain from simply asking *"is the proposal acceptable?"* or *"does the agency agree with the protocol?"*
  - Note: the acceptability of the package always remains subject to regulatory review at the time of CTA submission.

- Provide a complete package to ensure useful feedback:
  - E.g., Sponsor has a specific question about starting dose, but does not provide results of the repeated-dose toxicity studies in-line with ICH guidelines.

- Reference pre-CTA meeting minutes when CTA package is submitted.

Final Reminders

- The primary objective of CTA review is to ensure the safety of trial participants.
- Provide sufficient data in the CTA/CTA-A package to permit the benefit/risk assessment of the use of the drug(s) in the clinical trial.
- If the IB is not updated, provide updated concise safety and efficacy summaries in the Study Protocol to avoid request for data in IR.
- Alternate approaches to standard principles and practices should always be clearly described and supported by adequate scientific and/or clinical justification.
- Provide up-to-date study documents which incorporate all recent changes to ensure Good Clinical Practice and less protocol deviations.
- The more information and tracking documents you can provide in your submission, the better.
- CTAs have a 30 CALENDAR day default period. Please make sure your teams are ready to respond to IRs during this time.

Thank you!

Useful Links and Emails

CTA guidance and pre-CTA meetings	Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications Guidance on Pre-CTA meeting requests oct.pre.cta-dec.bec@hc-sc.gc.ca oct.enquiries-requetes.bec@hc-sc.gc.ca brdd.ora@hc-sc.gc.ca
ICH M11 Draft - Clinical Electronic Structured Harmonized Protocol	ICH M11 Clinical Electronic Structured Harmonized Protocol
HC/SC 3011 Form	HC/SC 3011 Form Guidance for completing the Drug Submission Application Form
Clinical Trial Site Information Form (CTSI)	CTSI Form Guidance on CTSI Form clinical.trials.site-lieu.essai.clinique@hc-sc.gc.ca brdd.ctsi-filec.dmbr@hc-sc.gc.ca
CTA/CTA-A Submissions	oct.smd-dgp.bec@hc-sc.gc.ca brdd.cta-dec.dmbr@hc-sc.gc.ca
Clinical Trial Application – Notification (CTN)	oct.ctan-ndec.bec@hc-sc.gc.ca brdd.ctan-ndec.dmbr@hc-sc.gc.ca
If Acknowledgement letter not received within 7 days of filing CTA/CTA-A	oct.smd-dgp.bec@hc-sc.gc.ca brdd.ora@hc-sc.gc.ca
ITA Guidance	Applications for medical device investigational testing authorizations guidance document