Vancouver CoastalHealth Research Institute

Standard Operating Procedure
Clinical Trial Applications (Drugs)

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Site Approval

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Document History

Version	Summary of Changes Made	Effective Date
1	Original document.	09-JUL-2010
2	This version has undergone extensive revision for administrative, educational, regulatory, and clinical changes by individual content experts and the VCHRI SOP Committee. This document has also had substantial formatting, grammatical and glossary updates. It has been classed as a rewritten document.	10-JAN-2016
3	This version has undergone revision for administrative, education, regulatory and clinical changes by individual content experts and VCHRI SOP Committee. There have been changes made to 6.2, 6.4, 6.7.3. References and definitions have been updated.	01-Jun-2021

1. PURPOSE

1.1. This Standard Operating Procedure (SOP) describes the process for submitting a Clinical Trial Application (CTA) to Health Canada, requesting approval to carry out an investigational trial on a Drug.

1.2. This SOP does not include the CTA process for Natural Health Products.

2. SCOPE

2.1. This SOP is applicable to Investigator-Initiated Clinical Trials/Studies undertaken at the Institution, and to those Research Team Members responsible for preparing, reviewing, approving, and submitting CTAs and subsequent amendments/notifications for Investigator-Initiated Clinical Trials/Studies.

3. RESPONSIBILITIES

3.1. The Sponsor-Investigator is considered to be the Sponsor for Investigator-Initiated Clinical Trials/Studies, and therefore is responsible for submitting the CTA to Health Canada.

3.2. Any or all parts of this procedure may be delegated to appropriately trained Research Team Members, but ultimately remain the responsibility of the Sponsor-Investigator.

4. RELATED SOPS/DOCUMENTS

4.1. Health Canada Guidance for Clinical Trial Sponsors: Clinical Trial Applications (last revised 2016)
4.2. Health Canada Guidance Document: Part C, Division 5 of the Food and Drug Regulations “Drugs for Clinical Trials Involving Human Subjects”. GUI-100 (2019)
4.3. Health Canada Guidance Document: Master Files (MFs) – Procedures and Administrative Requirements (2019)

5. DEFINITIONS

5.1. **Chemistry Manufacturing Control (CMC):** The quality specific information and description of the manufacturing process. It is contained in the manufacturer’s Drug Master File.

5.2. **Clinical Trial Application (CTA)**: For the purposes of this SOP, an application to Health Canada for approval to conduct Clinical Trials in Phases I through III of drug development and comparative bioavailability, according to Part C, Division 5 of the Food and Drug Act and Regulations. This term is also used in an application under Division 4 of the Regulations.

5.3. **Clinical Trial Application Amendment (CTA-A)**: A submission to Health Canada requesting approval for a change to a Clinical Trial/Study, which is running under a previously authorized CTA.

5.4. **Clinical Trial Application Notification (CTA-N):** A submission to Health Canada notifying of a minor change to a Clinical Trial/Study, or when a clinical trial is completed, or a clinical trial site is closed, which is running under a previously authorized CTA.

5.5. **Common Technical Document (CTD):** The internationally accepted format and style specifications for Clinical Trial Applications and clinical study reports. Electronic versions are permitted in Canada and are known as eCTD.

5.6. **Drug Identification Number (DIN)**: A number assigned by Health Canada to a Drug product prior to being marketed in Canada.

5.7. **Drug Master File (DMF):** A reference that provides information about specific processes or components used in the manufacturing processing and packaging of a Drug. The DMF is referenced in Clinical Trial Applications.

5.8. **No Objection Letter (NOL):** A letter issued by Health Canada when no clinical or quality deficiencies are identified during a review period and a Clinical Trial Application for a Drug Clinical Trial/Study has been deemed satisfactory.

5.9. **Notice of Compliance (NOC):** A notification issued to a manufacturer following the satisfactory review of a submission for a new Drug and signifies compliance with the Food and Drug Regulations.

5.10. **Not Satisfactory Notice (NSN):** A letter issued by Health Canada when a Clinical Trial Application is deemed deficient or a timely response to queries is not received by Health Canada.

5.11. See also VCHRI Glossary of Terms.

6. PROCEDURE

6.1. Background

6.1.1. A CTA must be filed for Clinical Trials/Studies in Phases I through III of development (including comparative bioavailability trials). Approval must be received prior to Clinical Trial/Study activation. This includes Clinical Trials/Studies in which a marketed drug is used outside of conditions specified in the Notice of Compliance (NOC) or Drug Identification Number (DIN) application, i.e., if the indication(s) and clinical use, target population(s), dosage regimen(s), route(s) of administration, or dosage form(s) differ from those described in the Product Monograph.

6.2. Preparation of Clinical Trial Application

6.2.1. Request and attend a pre-CTA consultation meeting with Health Canada, if desired. Note: Meetings are useful for new active substances, or applications with complex issues. Requests should be submitted in the form of a cover letter, proposing dates suitable for a pre-CTA consultation meeting. The cover letter should be accompanied by a brief synopsis of the proposed Clinical Trial/Study, a list of questions to be addressed by the Directorate during the meeting, and identification of specific areas, as needed.

6.2.2. The main documents required for preparation of a CTA submission include:

6.2.2.1. Drug Submission Application Form;

6.2.2.2. Study Protocol;

6.2.2.3. Protocol Synopsis (use appropriate Health Canada template, where applicable);

6.2.2.4. Informed Consent Form;

6.2.2.5. Research Ethics Board Attestation, signed by the REB (or equivalent form) and a signed Qualified Investigator's Undertaking (QIU) form; not required for submission, must be retained in the Essential Documents file;

6.2.2.6. Investigator Brochure OR Product Monograph AND Chemistry Manufacturing Control (CMC) information;** and

6.2.2.7. Chemistry Manufacturing, and Control (CMC) information*** (use appropriate Quality Overall Summary (QOS) template, where applicable).

6.2.2.8. If a controlled substance is used in the Clinical Trial/Study, a request for exemption must be made by completing *Application Form for an Exemption to Use a Controlled Substance For Clinical Studies*.

** If the manufacturer of the product in a dosage form or strength not specified in the product monograph, has previously submitted information to Health Canada about the product in question, a letter authorizing cross-reference to their information may be submitted in lieu of the Investigator's Brochure.

*** Chemistry Manufacturing Control (CMC) information: If using marketed product, the Product Monograph and Drug Identification Number (DIN) will suffice UNLESS the dosage form or strength is different from that specified in the Product Monograph. In the latter case, CMC information will be required.

6.2.3. Most Investigator-Initiated CTAs which require CMC information will use one of the following sources:

6.2.3.1. A letter of cross-reference which allows Health Canada to access the CMC information for the product through a previously approved CTA on file at Health Canada

6.2.3.2. Letter from the drug manufacturer granting access to the Drug Master File (DMF) at Health Canada for the product

6.2.3.3. Cross-referenced CMC information, if using a Canadian marketed product. Cite DIN of product

6.2.3.4. Full CMC information provided by the manufacturer for inclusion in the CTA

6.2.4. Complete and submit the CTA, CTA-A, any CTA-Notifications, Clinical Trial Site Information (CTSI) forms and pre-CTA meeting information electronically to Health Canada. Ensure that no Clinical Trial/Study activities begin before the No Objection Letter (NOL) is received.

6.2.5. Note: Detailed information and forms/templates to be used for a CTA are available on Health Canada's website: http://www.hc-sc.gc.ca

6.3. Health Canada Screening and Review

6.3.1. Health Canada reviews the application, and if any deficiencies are detected, should inform the Sponsor-Investigator within 30 days. Submit further information, as/if requested.

6.3.2. Submission Screening: Minor issues with documentation or deficiencies with the package will be addressed by either:

6.3.2.1. Screening Rejection Letter, itemizing deficiencies/significant information lacking from the CTA or CTA-A. All information will require re-submission and will be processed as 'new' information, and hence will be assigned a new control number; or

6.3.2.2. Request for Clarification, sent via fax, email, or phone. Response is required within 2 calendar days.

6.3.3. Receive the acknowledgement letter from Health Canada, to indicate that screening is complete, and the review has commenced (usually by fax, within 2-3 days of submission). Contact Health

Canada if acknowledgment letter is NOT received, to ensure that submission has been received safely. The default/target review period from receipt of a completed application package is 30 days.

6.3.4. Receive queries (if any) for specific issues with the Protocol, Informed Consent, or the submission from Health Canada reviewer via fax, email, or phone (Information Request).

6.3.5. Respond to Health Canada (to any form of communication) within two (2) calendar days, in order to maintain the 30-day review period.

6.3.6. The reviewer may ask the Sponsor-Investigator to withdraw the CTA, to avoid receiving a Not Satisfactory Notice (NSN), if any deficiencies remain that Health Canada does not consider to have been satisfactorily addressed.

6.3.7. An NSN will be issued if a timely response is not received, or significant deficiencies are identified during the review, and the applicant does not withdraw the CTA. Note: A new 30-day review period will be applied to this new CTA. The resubmission will be reviewed without prejudice, if the CTA is withdrawn.

6.3.8. Note: Withdraw the CTA, if amendment-worthy modifications are desired by the Sponsor-Investigator, while the review is underway. Re-submit a new CTA for approval, as described above.

6.3.9. Maintain all submission documents and correspondence in the Essential Documents file.

6.4. Trial Commencement

6.4.1. Wait for the No Objection Letter (NOL), indicating a satisfactory review and approval, before commencing Clinical Trial/Study activities. Submit copy of NOL to Research Ethics Board.

6.4.2. Complete and submit a completed Clinical Trial Site Information (CTSI) form (for each Clinical Trial/Study site in Canada) to Health Canada if not submitted with the CTA OR CTA-A. Ensure that the Health Canada control number and Clinical Trial/Study start date information are included on the form. Submit the CTSI form prior to the start of the Clinical Trial/Study at the site.

6.4.3. Register the Clinical Trial/Study with a publicly accessible registry, such as clinicaltrials.gov.

6.5. Clinical Trial Application Amendment (CTA-A)

6.5.1. Submit CTA-A, as/if required. Reasons for amendments include, but are not limited to, changes to the following:

- Clinical trial drug supplies (e.g., manufacturing process, dose strength);
- Dosing regimen, inclusion/exclusion criteria;
- Selection, selection criteria, monitoring, follow-up, or withdrawal of a Participant;
- Evaluation of the clinical efficacy of the drug;
- Alteration of risk to the health of a Participant;
- Drug safety assessment (changed or additional);
- Extended Clinical Trial/Study duration; and
- CMC information affecting safety or quality of the drug.

6.5.2. CTA amendments are subject to a 30-day review period, and require approval from Health Canada before implementing the changes.

6.5.3. Exception to 30-day review period: Implement Protocol changes immediately only if there are serious safety concerns to Participants (or others). Submit the changes to Health Canada immediately, as a Notification. Ensure that the reasons for immediate change are fully explained. Submit the full CTA-A, within 15 days of implementing the amended Protocol.

6.5.4. Complete and submit a completed Clinical Trial Site Information Form (for each Clinical Trial/Study site in Canada) to Health Canada for the CTA-A. Ensure that the Health Canada control number issued to the CTA-A and Clinical Trial/Study start date information are included on the form.

6.6. Notifications to CTA, CTA-A, and CTA-N

6.6.1. Inform Health Canada when implementing any of the following types of Protocol changes following the timelines on the current version of the Health Canada forms or guidance information:

6.6.1.1. Changes to the Protocol that do not compromise the safety of Participants, and are not classed as amendments (see CTA-A section);

6.6.1.2. Information about a site closure or completion of a Clinical Trial/Study;

6.6.1.3. Premature discontinuation of a Clinical Trial/Study, at one or all of the study sites, for any reason, as specified in the Protocol (e.g., safety, efficacy, administrative, recruiting issues, Sponsor choice, etc.).

6.6.2. Notification information for continuing Clinical Trials includes changes in data quality (chemistry and manufacturing) that do not affect drug quality or safety, such as:

- Pharmaceutical products: increase in production without any change in process;
- Narrowing of actual test specifications;
- Changes related to research laboratories under contract;
- Changes in packaging material;
- Pharmaceutical products: extension of shelf life; and
- Pharmaceutical products: all changes to the chemistry and manufacturing of the drug which do not affect its quality or safety (according to the criteria described elsewhere in this SOP).

6.6.3. Notification information for discontinued Clinical Trials/Studies includes:

6.6.3.1. A description of the effect of discontinuation on projected or ongoing trials of the drug in Canada;

6.6.3.2. A statement confirming that each Principal Investigator has been duly notified of the Clinical Trial/Study discontinuation and the reasons thereof, and that they have been sent a written notice regarding the potential health risks to study Participants or others;

6.6.3.3. Confirmation that the sale or importation of the drug at each involved Clinical Trial/Study site has been discontinued; and

6.6.3.4. Confirmation that reasonable measures will be taken to ensure the return of all unused Drug.

6.6.4. Other types of Notification include:

6.6.4.1. All information regarding refusals to approve the Clinical Trial/Study by other regulatory authorities, or Research Ethics Boards, at any time before or during the Clinical Trial/Study.

6.6.4.2. Discontinuation or partial/full Clinical Hold of a trial outside of Canada, when equivalent trials are being conducted in Canada.

6.6.4.3. If the Clinical Trial/Study Drug is being imported: provide a NOL at the importation to facilitate shipment, and to demonstrate regulatory compliance.

6.6.4.4. If the product is imported by a third party: ensure that the Sponsor-Investigator has a written agreement and systems in place for handling and storage of the product.

6.6.4.5. If additional drugs are imported for the Clinical Trial/Study: provide a list of these drugs in the CTA.

6.6.5. A CTA-N is filed when any other change, not covered by a CTA-A occurs, including:

- Clinical Trial/Study site closure,
- completion of the Clinical Trial/Study,
- the evaluation of the clinical efficacy of the Investigational Product,
- discontinuation of a Clinical Trial/Study or site for non-safety related issues, or
- An update to the Investigator Brochure.

NOTE: CTA issuance of acknowledgment of notification letter for CTA-N are not in effect. They are issued for a CTA-A only.

6.7. Suspension and Cancellation

6.7.1. If you receive a notice of suspension or cancellation for your Clinical Trial/Study immediately notify Research Team Members, REB, VCHRI Clinical Trials Administration and pharmacy (if applicable) as well as other Clinical Trial/Study sites if you are the coordinating site.

6.7.2. Follow instructions provided by the regulator authority. The conditions/instructions are outlined in the notice provided.

6.7.3. Division 5, Section C of the Food and Drug Regulations allows for the authorization to sell or import a drug for investigational purposes, in its entirety or at a Clinical Trial/Study site. The conditions for a suspension are outlined in subsection C.05.016 (1) paragraphs (a) to (d).

6.7.4. Prior to suspending an authorization, Health Canada will send a notice to the Sponsor/Sponsor-Investigator detailing the reason for the suspension, the date the suspension begins and if the authorization to suspend is in its entirety or at a particular Clinical Trial/Study Site.

6.7.5. The authorization for the Clinical Trial/Study will be restored if, within 30 days after the day on which the suspension is effective, Health Canada is provided with information demonstrating that the situation causing the suspension either did not exist or has been corrected. If the information has not been provided to Health Canada within those 30 days, the authorization for the Clinical Trial/Study will be cancelled in its entirety or at a particular site.

6.7.6. If the Clinical Trial/Study is reinstated, immediately notify REB and VCHRI Clinical Trials Administration.

6.8. Investigator Brochure Updates

6.8.1. Submit updated Investigator Brochure (annually or more often if needed) as a CTA-Notification to Health Canada, unless included as a part of a planned CTA-A. Include complete safety data and a general overview of the Clinical Trial/Study. Highlight/summarize changes for ease of review and evaluation.

6.8.2. Distribute updated Investigator Brochure to all sites and to the REB.

6.9. Submission of Adverse Drug Reactions (ARs)

6.9.1. See specific SOP on Serious Adverse Drug Reaction Reporting in Clinical Trials/Studies (See VCHRI SOP012 Safety Reporting Requirements)

6.10. Ongoing Sponsor-Investigator Responsibilities

6.10.1. Refer to Sections 4 and 5 of the GCP Consolidated Guideline (ICH Topic E6 (R2)).

7. REFERENCE(S)

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, TCPS 2 (2018), December 2018.

Department of Justice (Canada), Personal Information Protection and Electronic Documents Act (PIPEDA), last amended June 21, 2019, current to February 15, 2021.

Government of Canada, Exemptions, Controlled Drugs and Substances Act, Exemptions, Section 56(1), amended September 19, 2019, current to February 15, 2021.

Government of Canada, Medical Devices Regulations, Part 3 Medical Devices for Investigational Testing Involving Human Subjects, SOR/98-282, May 7, 1998; last amended February 13, 2017, current to March 20, 2017.

Government of Canada, Natural Health Products Regulations, Part 4 Clinical Trials Involving Human Subjects, SOR/2003-196, June 5, 2003; last amended October 17, 2018, current to February 14, 2019.

Health Canada, Food and Drug Regulations, Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects, (Schedule 1024), June 20, 2001.

Health Canada, Guidance Document: Part C, Division 5 of the Food and Drug Regulations “Drugs for Clinical Trials Involving Human Subjects”. GUI-0100. August 20, 2019.

Health Canada, Guidance for Clinical Trial Sponsors: Clinical Trial Applications, June 25, 2003 (includes administrative changes, February 27, 2008, March 12, 2009), revised March 17, 2016.

Health Canada, Release of Electronic Specifications for Clinical Trial Applications and Amendments filed in accordance with Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications, July 2, 2009, and Notice of Revisions, May 29, 2013.

Health Canada, Notice: Preparation of Clinical Trial Regulatory Activities in the “Non-eCTD Electronic-Only” Format, March 2, 2016.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Harmonised Guideline, Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, E6(R2), November 9, 2016.

Network of Networks (N2) Clinical Trial Application (Drugs) SOP018_09. Effective Date: 15 May 2021.

US Food and Drug Administration, Code of Federal Regulations, Title 21, Volume 1:
- Part 11, Electronic Records; Electronic Signatures, (21CFR11).
- Part 50, Protection of Human Subjects, (21CFR50).
- Part 54, Financial Disclosure by Clinical Investigators, (21CFR54).
- Part 56, Institutional Review Boards, (21CFR56).
- Part 312, Investigational New Drug Application (21CFR312).
- Part 314, Applications for FDA Approval to Market a New Drug (21CFR314).

US Department of Health and Human Services, Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects (45CFR46).

US Department of Health and Human Services, Guidance for Industry: Computerized Systems Used in Clinical Investigations, May 2007.

8. ATTACHMENT(S)

None.