Title: Health Canada Requirements for Research Involving an Experimental Drug	
Manual: RI MUHC – Policies and Procedures – Human Research SOPs	**Originating Dept/ Service:** RI MUHC Division of Clinical Research
SOP: ☐ New ■ Revised ☐ Reviewed	**Effective Date**: 08 October 2009
Key Words: Health Canada, Experimental Drug, CTA	
Approved by : ☐ Supervisor/Manager ☐ Risk/Ethics ■ Sr. Mgmt Committees ■ Board/Councils	
Scope: ☐ Research wide ☐ Dept. specific ■ Other: Research involving Human Subjects	
Site Specific: ☐ Yes ■ No	**Distributed to:** ■ Staff ☐ Mgmt ☐ Others

Objective(s)

The objective of this standard operating procedure (SOP) is to guide the sponsor-investigator in the conduct of a clinical trial when the trial is the subject of a Clinical Trial Application (CTA) to Health Canada.

Persons/Areas Affected

This SOP concerns the MUHC research community (employees, investigators, physicians, management, consultants, students, volunteers or other persons) involved in conducting research with an experimental drug in human subjects.

Definition(s)

I. **Notice of Compliance (NOC)**: Notification issued pursuant to paragraph C.08.004(1)(a), indicating that a manufacturer has complied with sections C.08.002 or C.08.003 and C.08.005.1 of the *Food and Drug Regulations.*

II. **Drug Identification Number (DIN)**: Number located on the label of prescription and over-the-counter drug products that have been evaluated by the Therapeutic Products Directorate (TPD) and approved for sale in Canada.

III. **Experimental Drug**: Any drug intended for the use of an experimental protocol of phase I, II, III, or IV studies or expanded access.

IV. **Sponsor**: An individual, company, institution or organization which takes responsibility for the initiation, management or financing of a human research study (modified from ICH, E6 1.53).

V. **Sponsor-Investigator**: An individual who both initiates and conducts alone or with others a research study. The term does not include any person other than an individual (it does not include a corporation or an agency). The obligations of a Sponsor-Investigator include both those of a Sponsor and those of a Principal Investigator/Qualified Investigator (ICH, E6 1.54).

VI. **Principal Investigator (PI)**: A person responsible for the conduct of the research study at a study

site. If a study is conducted by a team of investigators at the same study site, the Principal Investigator is the responsible leader of the team (ICH, E6 1.34).

VII. **Qualified Investigator**: The person responsible to the Sponsor/Sponsor-Investigator for the conduct of a clinical research study with an experimental drug at the study site, who is entitled to provide health care under the laws of the province where that study is located, and who is (HC, C.05.001):

a. In the case of a clinical research study with an experimental drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association;

b. In any other case, a physician and a member in good standing of a professional medical association.

Procedures

1. Clinical Trial Application (CTA)

1.1.1. Health Canada's Food and Drugs Act and Regulations, controls the sale and importation of drugs for clinical trials in human subjects. Division 5 of Regulations Section C depicts the requirements concerning applications submitted by Sponsor-Investigators who want to conduct clinical drug trials in humans. Detailed information and forms to be used for a CTA are available on Health Canada's web site at the following address: http://www.hc-sc.gc.ca

1.1.2. In Canada, a *Clinical Trial Application* (CTA) should be filed before initiating a clinical trial involving an experimental drug. Health Canada reviews the application and, if any deficiencies are detected, should inform the sponsor-investigator within 30 days.

1.1.3. CTAs are required from sponsor-investigators for:

i. All Phase I to III studies on drug development;
ii. Bioavailability comparison studies;
iii. Clinical trials of marketed drugs, which are used, off-label (i.e. whose use exceeds the parameters of the notice of compliance (NOC) or the drug identification number (DIN)).

1.1.4. If no deficiency is detected and the CTA is considered acceptable, within 30 days, Health Canada issues and sends a NOL to the Sponsor-Investigator. This letter should be kept with the study-related essential documentation as described in SOP03.

1.1.5. Before initiating the clinical trial or clinical trial amendments, the Sponsor-Investigator should fill out and submit a Clinical Trial Site Information Form. This form should be filled out for each clinical trial site.

2. CTA Amendment

2.1.1. Amendments to a CTA (CTAM) are requests by which the Sponsor-Investigator provides information in support of a pre-approved request for modifications (HC C.05.008). CTA modifications may deal with changes to the clinical trial drug supply (i.e. drug manufacturing process modification), approved protocol amendments (i.e. revised dosage regimen), or both.

2.1.2. Health Canada should approve of the CTA before implementing the modifications (HC C.05.008).

2.1.3. Should a Sponsor-Investigator wish to modify a CTA under review, he should withdraw the active CTA and resubmit another one.

2.1.4. Should a Sponsor-Investigator have to immediately initiate one or more of the amendments described in paragraph (2) of section C.05.008, because the clinical trial or use of the drug within the study framework of the clinical trial is endangering the health of a participating subject or someone else, he may do so without waiting for Health Canada's review. However, he should provide Health Canada with the required information, within 15 days of the date of the amendment, according to paragraph (2) of section C.05.008

2.1.5. The Sponsor-Investigator should present a CTAM when:

I. A protocol amendment affects the selection, selection criteria, follow-up or withdrawal of a clinical trial subject;

II. A protocol amendment affects the evaluation of the clinical efficacy of the drug;

III. A protocol amendment alters the risk to the health of a clinical trial subject;

IV. A protocol amendment affects the drug safety assessment;

V. A protocol amendment extends the duration of the clinical trial;

VI. An amendment to information about drug chemistry and manufacturing affects the safety or quality of the drug.

3. Notification to Health Canada

For amendments to an already approved CTA and CTAM other than those described in section 2 above, Health Canada should be notified within the following 15 working days even though the amendments may be implemented right away. The following changes warrant a notification:

3.1.1. Changes to the protocol that do not compromise the safety of clinical trial participants and that are not viewed as amendments according to section 2 above;

3.1.2. Information about a site closure or completion of a clinical trial;

3.1.3. Premature discontinuation of a trial, at one or all of the study sites, for reasons other than the safety of the trial participants (i.e. administrative reasons, recruiting problems, etc.);

3.1.4. Changes in data quality (chemistry and manufacturing) that do not affect drug quality or safety, such as:

I. Pharmaceutical products: increase in production without any change in process;

II. Narrowing of actual test specifications;

III. Changes related to research laboratories under contract;

IV. Changes in packaging material;

V. Pharmaceutical products: extension of shelf life;

VI. 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 in 4.3.

4. Evaluation of a CTA Follow-up or Discontinuation

4.1.1. Following regulatory approval of a CTA or CTAM, the Sponsor-Investigator should present in notification format, all information regarding refusals by other regulatory authorities or REB.

4.1.2. In the case of discontinuation, at one or all of the selected sites, of a clinical trial for which a CTA or CTAM has been submitted in Canada, the Sponsor-Investigator should notify the authorities concerned as soon as possible, within 15 days following the date of discontinuation (HC C.05.015). The notification should include the following information:

I. A detailed report of the reasons for discontinuation;

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

III. A statement confirming that each Qualified Investigator has been duly notified of the trial discontinuation and the reasons thereof, and that they have been sent a written notice regarding the potential health risks to participating subjects or others;

IV. Confirmation that the sale or importation of the drug at each involved trial site has been discontinued;

V. Confirmation that reasonable measures will be taken to ensure the return of all unused drug.

4.1.3. The Sponsor-Investigator should also notify the appropriate authorities' of the discontinuation of a clinical trial outside Canada when equivalent trials are being conducted in Canada.

4.1.4. The Sponsor-Investigator should promptly report to Health Canada any serious, unexpected adverse drug reactions. Serious but foreseeable reactions, as well as serious adverse events observed in the course of a clinical trial but not considered product-related do not require immediate reporting whether expected or not. For more details regarding adverse reactions declaration, see SOP09.

4.1.5. Once a year the Sponsor-Investigator should submit an updated Investigator's Brochure including complete safety data and a general overview of the situation. Additional information and all modifications included in the Brochure should be highlighted. If the Investigator's Brochure is updated more often it should be submitted accordingly.

5. Records Related to the CTA or CTAM

5.1.1. The Sponsor-Investigator should record, manage and preserve all clinical study related information so that complete and accurate reports may be presented, interpreted and audited.

5.1.2. The Sponsor-Investigator should keep complete and accurate records in order to demonstrate that the clinical trial is conducted in compliance with *Good Clinical Practice* and Health Canada, *Food and Drug Regulations* and to offer guidelines for Sponsors of clinical trials who file clinical trial applications.

5.1.3. The Sponsor-Investigator should keep complete and accurate records on the use of a drug during a clinical trial as described in ICH section 8.

5.1.4. The Sponsor-Investigator should retain records for a period of twenty-five years. At Health Canada's request, these records should be available within 2 days if the use of a drug in the course of a clinical trial causes concern and endangers the health of trial participants. Otherwise, records should be provided within 7 days of receipt of the request.

5.1.5. The retention period for clinical trial related documents (25 years) starts with the document creation date. For practical reasons, it is strongly recommended that the retention period of the study-related documents start on the study completion date. However, it is important to check with the Sponsor-Investigator, Institution or REB if any specific additional study related requirements exist (i.e. pediatric studies).

6. Research Ethics Board (REB)

6.1.1. Prior to starting a clinical study or a CTAM at a site, the proposed protocol and all documents listed in section 2.2.2 of SOP13 should be reviewed and approved by the REB as described in Health Canada *Food and Drugs Act*.

6.1.2. The Sponsor-Investigator should submit to Health Canada the name of the REB who has approved the trial or amendment before the trial or amendment can begin at the selected site. Section C, of the Clinical Trial Site Information form should be completed to that effect.

6.1.3. The Sponsor-Investigator should keep in the files a statement issued and signed by the REB which has approved the protocol and according to which he undertakes to fulfill his functions in compliance with *Good Clinical Practice.* The REB may elect to use Health Canada Research Ethics Board Attestation form or create a similar one that meets the conditions of the *Food and Drug Regulations,* Division 5.

6.1.4. The Sponsor-Investigator should provide Health Canada with specifics regarding any refusal of a protocol or protocol amendment by an REB for any reason~~s~~ whatsoever. (HC C.05.008 par. 1c [II])

6.1.5. It is strongly recommended that the NOL to a CTA from Health Canada be submitted to the REB.

6.1.6. The Research Ethics Board Attestation Form is to be provided to Health Canada only upon their request.

7. Qualified Investigators

Prior to each clinical study in Canada, the Sponsor-Investigator should complete:

7.1.1. The Clinical Trial Site Information form (http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/clinicalsiteinfo_e.html). This form should be completed for each clinical trial site and submitted to Health Canada.

7.1.2. The Research Ethics Board Attestation form (http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/rebattestation_e.html). The REB may elect to use this form or create a similar one that meets the conditions of the Food and Drug Regulations, Division 5. This form is to be provided to Health Canada only upon their request.

7.1.3. The Qualified Investigator Undertaking form (http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-

dpt/qualifiedinvestigator_e.html). The Qualified Investigator may elect to use this form or create a similar one that meets the conditions of the *Food and Drugs Regulations,* Division 5. This form is to be provided to Health Canada only upon their request.

Reference(s)

- HC: Health Canada, Therapeutic Products Directorate (DPT), Food and Drug Act (Includes Food and Drug Regulations, Medical Device Regulations, Natural Health Product Regulation), August 2004.