

INSTITUTION / INVESTIGATOR-INITIATED CLINICAL TRIALS IN CANADA

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ABSTRACT

Institution/investigator-initiated clinical trials in Canada require adherence to similar regulations and processes required of large pharmaceutical manufacturers. This may require an investigator to file a Clinical Trial Application. This article outlines the responsibilities and actions that are required prior to, during, and after the conduct of an institution/investigator initiated trial.

Key Words: *Regulations, clinical trials, Health Canada*

An earlier article in this series reviewed the general regulatory requirements for Clinical Trial Applications in Canada.¹ The current article discusses the specific regulatory requirements for a sub-set of clinical trials, those that are initiated and conducted by an institution or an individual investigator. Investigators may not be aware of all of the regulatory requirements that they are obliged to meet, or that these requirements are generally the same as those applied to drug manufacturers, from large pharmaceutical companies to small biotechnology start-up companies. Investigator-initiated clinical trials and Clinical Trial Applications (CTAs) are also covered by Division 5 of the Food and Drug Regulations, which came into force on September 1, 2001.

Sponsoring a Clinical Trial

Most researchers are familiar with the situation where a pharmaceutical or biotechnology company contracts with them to participate in a clinical trial that is being conducted by the company. Typically, the researcher's institution represents one clinical trial site in a multi-centre trial and the company usually takes care of all regulatory interactions with Health Canada, including the filing of the requisite paperwork to gain clearance to conduct the clinical trial in Canada (i.e. the Clinical Trial Application). In this situation, the company is the sponsor of the study and has clear responsibilities relating to the filing and maintenance of the Clinical Trial Application

(CTA), the manufacturing and control of the clinical trial supplies according to Good Manufacturing Practices (GMPs), as well as for Good Clinical Practices (GCPs). The investigator also has his/her own responsibilities relating to the conduct of the clinical trial according to Good Clinical Practices (GCPs).

However, in some cases the investigator may be conducting a study that is considered to be an investigator-initiated clinical trial. Even though the study may be funded by a grant from a pharmaceutical company, or other source, the investigator (or their institution) takes full responsibility for all regulatory activities as well as the conduct of the clinical trial, and in this situation the investigator is acting as the sponsor of the clinical trial.

It is important for both the investigator (sponsor) and the pharmaceutical company (or other donor of funds or drugs) that the responsibilities of each party are clearly understood before proceeding. The key responsibilities of the investigator in this situation are described below.

Clinical Trial Application (CTA)

Before any clinical trial can start in Canada, the sponsor (in this case the investigator) must have filed a CTA with Health Canada and must have received a No Objection Letter (NOL) from Health Canada. This NOL effectively constitutes approval to proceed with the study. In most cases, an investigator-initiated clinical trial is conducted

with drug products that are already available on the market in Canada. That means that the content of the CTA is relatively simple. The core components of the CTA are the study protocol, the informed consent documents, and the Investigator's Brochure (containing all available information on the drug at the time of study start), or in the case of a marketed product, a copy of the current product monograph for the product may be included instead. The remaining components of the CTA include certain Health Canada required forms/templates, information relating to any refusals by a Canadian Research Ethics Board to approve the clinical trial protocol, or refusals by foreign regulatory bodies to approve the clinical trial protocol. Some information must be supplied in electronic format: the clinical trial protocol, the Investigator's Brochure or Product Monograph, the Health Canada required template that provides a synopsis of the clinical trial protocol, and information on the clinical trial supplies (if applicable).

It is worth pointing out that the Clinical Trial Regulations cover all clinical trials that involve the use of products in a manner that is outside of the scope of the current approval in Canada (i.e. the Product Monograph or labelling for the drug product). That means that even though a product is marketed in Canada, a study conducted with that product is not automatically considered a Phase IV study. For example, an investigator who wishes to study the effects of a drug that is already approved for the treatment of depression, in a new indication such as panic disorder, must file a CTA and comply with all the other regulatory requirements associated with clinical trials in Canada.

A CTA is also required for studies involving drugs that are already approved in other jurisdictions, but have not yet been cleared by Health Canada. Note that the importation of foreign sourced clinical trial supplies into Canada requires that Customs Canada be provided with a copy of the Health Canada No Objection Letter. There are additional requirements for the importation of controlled substances.

Drugs that are already approved in another jurisdiction but are not yet marketed in Canada may be made available to Canadian patients with Health Canada approval as part of a Special Access Programme (SAP). This is not discussed

further in this article, but additional information on SAP can be obtained from Health Canada's website at http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_sap_drugs_e.html.

Clinical Trial Supplies

Many investigator-initiated clinical trials are conducted with products already marketed in Canada. In such cases it is not necessary for the investigator-sponsor to provide detailed chemistry, manufacturing and controls information as part of the institution/investigator-initiated CTA. However, if the products to be used (either the test product or a comparator product) are to be modified in some way prior to use, additional information must be provided as part of the CTA. For example, if the product is to be blinded (encapsulation of whole tablets, crushing/filling of tablets into capsules etc.), then a description of the modification must be provided, along with evidence demonstrating that the modification has not adversely affected the release characteristics or bioavailability of the marketed product. Often comparative dissolution profiles of the modified (blinded) product vs. the unmodified product will suffice. Additional testing of each batch of modified product may be necessary before it can be used in the clinical trial. The scope of information and testing required will vary depending on the extent of product modification.

Other non-investigational products that may be used during the conduct of a clinical trial (i.e. products used for diagnostic, support, or therapeutic reasons) but which are not the subject of the clinical trial investigation, do not fall into the category of "clinical trial supplies" and may be administered to clinical trial participants as long as their use has been clearly outlined in the clinical trial protocol and they are of an appropriate quality.

Where chemistry, manufacturing and controls information is required, a summary of the relevant information must be provided in the format of a Quality Overall Summary (QOS), as required by Health Canada, along with any supporting data. The QOS must also be provided in electronic format as part of the CTA. Templates are provided on Health Canada's website, for both drugs and biologics.

There are specific requirements for biologics that differ from non-biological drugs; for

example, additional copies of the CTA or sections of the CTA are required.

Review of the CTA

Clinical Trial Applications are subject to a 30-day target for completion of the Health Canada review, and the issuance of a No Objection Letter (provided that the application is cleared). For some studies, (i.e. bioequivalence studies in healthy volunteers) a 7 day administrative target applies. In either case, a No Objection Letter must be received prior to initiating the study.

Once the CTA has been delivered to Health Canada, it undergoes an initial screening phase to check that the application is complete. Once screening is complete the sponsor will receive a letter acknowledging receipt and indicating when the 30-day review period starts. Questions may be asked of the sponsor during either the screening period or the review period. These may come in the form of a phone call, or a “clarifax” (a faxed request for clarification). The sponsor must respond to any clarifaxes within 2 calendar days. In exceptional circumstances, the sponsor may request, and be granted an extension to this 2-day deadline. However, it is recommended that such requests be kept to a minimum in order to allow Health Canada to complete their review within the 30-day timeframe. Otherwise, there is a risk that the CTA will not be approved (a Not Satisfactory Notice will be issued) and the CTA will have to be re-filed, and another 30-day review period assigned.

Post-Approval Commitments

Even after Health Canada has confirmed that there are no objections to the clinical trial proceeding, the sponsor may not commence the study until the relevant Research Ethics Board’s (REB) approval for the protocol has been obtained. The sponsor must have on file a signed REB attestation form indicating that the REB has reviewed and approved the clinical trial protocol (for the same version of the protocol that has been cleared by Health Canada). This form does not have to be submitted to Health Canada but must be retained on file by the sponsor and be made available for inspection by Health Canada. The investigator must also complete a Qualified Investigator Undertaking (QIU) or similar form. There must be no more than one Qualified Investigator at each

site. Typically an investigator-initiated clinical trial is carried out at only one site, so the QIU will likely be completed by the principal investigator at that site (although in some cases the principal investigator may not be the same as the qualified investigator). The QIU does not have to be submitted to Health Canada but should be retained on file by the sponsor and should be made available for inspection by Health Canada.

The sponsor must complete a Clinical Trial Site Information form, which includes the date of the REB approval for the clinical trial protocol. This form can be completed after the CTA has been cleared to proceed, but must be submitted to Health Canada prior to study start. The form can be faxed or e-mailed to Health Canada. There will be no acknowledgement or “approval” of this form. The requirement is simply to complete and submit it before the study actually starts.

Health Canada may require additional post-approval commitments as a condition of issuing the No Objection Letter. For example, they may request that annual safety updates be provided for all or some clinical trial subjects, or they may require stability data updates on marketed products that have been modified in some way (see Clinical Trial Supplies, above).

Amendments and Notifications

Once the study has begun, it may be necessary to revise the protocol, or to make other changes to the information provided in the original Clinical Trial Application. Changes, which affect the selection of subjects (i.e. inclusion/exclusion criteria, discontinuation), monitoring of the subjects, the evaluation of efficacy or safety, the risk to the subject, or extending the duration of the clinical trial must be submitted as a Clinical Trial Application Amendment (CTA-A). Certain chemistry, manufacturing and controls changes must also be submitted as a CTA-A, but this is less likely to be the case for an investigator-initiated CTA where marketed products are typically used. Amendments are also subject to a 30-day review period before they can be implemented. While the CTA-A is under review, the study may continue under the parameters of the already approved CTA, until a No Objection Letter has been received for the CTA-A, and all of the other requirements regarding the Amendment (i.e. REB approval, submission of the Clinical

Trial Site Information and Qualified Investigator Undertaking forms etc.) have been fulfilled. The exception is if the amendment must be implemented immediately to avoid endangering the health of a clinical trial subject. In this case, the amendment may be made immediately but a CTA-A must be filed within 15 days of implementation.

Minor changes to the CTA (those not considered to materially affect the conduct of the study) may be filed as a notification, within 15 days of the change being made. Any notification submitted to Health Canada will be reviewed and added to the CTA file. The review may result in the notification being re-assessed as an amendment. In this case, the sponsor will be asked to re-submit the change as a CTA-A and a 30-day review period applies before the change can be implemented.

Discontinuation of a Study

If a study is discontinued prematurely, for any reason, Health Canada must be notified within 15 days of the date of discontinuance.

Adverse Event Reporting

Adverse event reporting has been discussed briefly in a previous article.¹ Of note is the requirement that a specific form should be used for expedited reporting, “ADR Expedited Reporting Summary Form” and that this form is available from Health Canada, http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/ct_adr_e.html. Safety information on an investigational drug should be conveyed promptly to other participating investigators and the REB.

Site Inspections

Clinical trial sites may be subject to inspection by Health Canada at any time. The sponsor may be asked to provide evidence that the clinical trial is being (or has been) conducted, according to Good Clinical Practices. Clinical trial supplies are also subject to Good Manufacturing Practices and must be stored and handled accordingly. Records relating to clinical trials must be maintained for 25 years. These records must be made available to Health Canada within 2 days if there is a risk to the health of trial subjects, otherwise they must be made available within 7 days of a request from Health Canada.

Other Products

Biological, radiopharmaceutical, and biotechnology products are also covered by the same drug regulations as pharmaceutical products. However, there are separate regulations for medical devices and for natural health products (for which the requirements are generally similar to those outlined for drugs). Combination products may have to comply with multiple regulations, and may be considered primarily as a drug, a biologic, or a device.

Further Information

Health Canada has published a guidance document “Guidance for Clinical Trial Sponsors, Clinical Trial Applications” and it is available on their web-site at http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ctdcta_ctddec_e.pdf

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REFERENCES

1. Klein AV, Tomalin AM. Clinical trial applications in Canada. *Can J Clin Pharmacol* Vol 12(3) Fall 2005:e246-e250; Oct. 24, 2005.