

**Baker
McKenzie.**

CLINICAL TRIALS HANDBOOK Americas



CANADA

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Canada

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Introduction

In Canada, a clinical trial for a drug product (CT) comprises an investigation for use in humans that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug; identify any adverse events in respect of the drug; study the absorption, distribution, metabolism and excretion of the drug; or otherwise assess its safety or efficacy.² The data generated from a clinical trial may be used for multiple purposes. Primarily, such data are used to support a request for the approval for market authorization for a new (yet to be marketed) drug, as well as a request to market a previously approved drug for a new use or indication, or a new dose.

Clinical trials for pharmaceutical products, biologics and Natural Health Products fall primarily under the authority of Health Canada's Health Products and Food Branch (HPFB).³ This federal government department is generally responsible for administering the federal *Food and Drugs Act* ("Act")⁴ and the *Food and Drug Regulations* ("Regulations").⁵ The regulatory framework governing CTs for drugs (both pharmaceutical and biologic) involving human subjects is derived from a combination of the Act and the Regulations since any product falling within the definition of a drug in the Act,⁶ are federally regulated by Health Canada under these two pieces of legislation.⁷ Natural Health Products and medical devices are subject to similar regulatory procedures for clinical investigations. (Medical devices are outside the scope of this chapter.)

CTs for drugs involving human subjects are regulated specifically pursuant to Division 5 of Part C of the Regulations,⁸ which came into force in September 2001. That said, other federal and provincial laws may also regulate certain aspects of CTs. For example, there are both federal and provincial/territorial laws that formally govern the protection of patient information, including the *Privacy Act*⁹ governing the federal public sector and the Ontario provincial *Personal Health Information Protection Act, 2004*.¹⁰

In addition, provincial laws generally impose conflict of interest requirements on healthcare professionals in their interaction with those promoting and selling drugs, biologics and medical devices.¹¹ Similarly, the Canadian Medical Association (CMA) has also established standards of ethical behavior regarding Canadian physicians' involvement in CTs. CMA codes and standards of conduct have been adopted or used as models by provincial self-regulatory

¹ The author wishes to express her appreciation to Andrew Chien and Megan Paterson for their patience and assistance in preparing this Chapter.

² *Food and Drug Regulations*, s. C.05.001.

³ Health Products and Food Branch, Health Products and Food Branch, (Ottawa: Health Canada, 2016), available at <http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/tpd-dpt/index-eng.php>

⁴ RSC 1985, c F-27 [Food and Drugs Act].

⁵ CRC, c 870 [Food and Drug Regulations].

⁶ *Food and Drugs Act*, *supra* note 4, s 2.

⁷ Clinical trials for natural health products are governed by Part 4 of the *Natural Health Products Regulations*, SOR/2003-196 [NHP Regulations].

⁸ *Food and Drug Regulations*, *supra* note 5, C.05.001-C.05.017.

⁹ RSC 1985, c P-21.

¹⁰ SO 2004, c 3, Sched A.

¹¹ See *e.g.* the power bestowed upon the College of Physicians and Surgeons of Ontario under the *Regulated Health Professions Act, 1991*, SO 1991, c 18, and a list of the College's policies available at: <http://www.cpso.on.ca/Policies-Publications/Policy>.

authorities.¹² For example, the College of Physicians and Surgeons of Ontario has issued its own policy statement on conflicts of interest in clinical research, which addresses the recruitment of human subjects.¹³

Despite the other sources of law and guidance that can impact the conduct of a CT, this chapter is focused on the process of approval and conduct of a CT under the regulatory framework administered by Health Canada, unless otherwise noted.

Clinical trial applications

A CT sponsor must submit a clinical trial application (**CTAP**) for authorization to sell or import the following for the purpose of a clinical trial:

- A drug product that is not authorized for sale in Canada
- Marketed drug product where the proposed use of the drug is outside the parameters of the prior market authorization

Pre-clinical trial application consultation meeting

Before filing a CTAP, the sponsor may request a pre-filing consultation meeting with Health Canada to present relevant data, discuss concerns or resolve issues with respect to the drug at issue.¹⁴ This step is not required but can be useful for new active substances or applications that deal with complex issues that are unfamiliar or new to Health Canada. Such a meeting also provides Health Canada with an opportunity to provide guidance on the acceptability of the proposed trial.

Introducing the Clinical Trial Application and Key Personnel

Following the optional pre-CTAP consultation meeting, the Regulations require that the sponsor submit a CTAP. This regulatory requirement must be followed before drugs can be used in CTs involving humans.¹⁵ One of the most basic functions that CTAPs fulfill is the establishment of a research protocol to be followed.

The roles and responsibilities of Health Canada, the sponsor(s), the Research Ethics Board (**REB**), and the Qualified Investigator (**QI**) in the conduct of CTs are as follows¹⁶:

- Health Canada reviews CTAPs to assess the drugs to be included in trials, verifies the qualifications of CT investigators, assures review by an REB, and monitors adverse drug reactions. Health Canada ensures that the CT is scientifically sound and clearly described in the protocol. As such, it has endorsed the principles and practices of the International Conference on Harmonization (**ICH**) on good clinical practice (**GCP**) and has issued a specific guidance document ("**ICH Guidance**")¹⁷ that describes the practices that sponsors must follow, i.e., setting out the procedural and ethical requirements.

¹² To access the CMA's policy base, please visit: <https://www.cma.ca/En/Pages/policy-base.aspx>.

¹³ College of Physicians and Surgeons of Ontario, Conflict of Interest: Recruitment of Subjects for Research Studies, (Toronto: CPSO, 2006), available at: https://www.cpso.on.ca/uploadedFiles/policies/policies/policyitems/conflict_recruit.pdf.

¹⁴ Health Canada, *Pre-Clinical Trial Application (CTA) Consultation Meeting*, (Ottawa: Health Canada, 2010), available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_pre_application-eng.php.

¹⁵ *Food and Drug Regulations*, *supra* note 5, C.05.005.

¹⁶ Health Canada, *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*, (Ottawa: Health Canada, 2013, rev'd 2016), available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.pdf.

¹⁷ Health Canada, *ICH Guidance E6: Good Clinical Practice: Consolidated Guideline*, (Ottawa: Health Canada, 2004), available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e6-eng.pdf.

- The sponsor may be an individual, corporate body, institution or organization that submits the CTAP and is ultimately responsible for the conduct of a CT. The sponsor must notify Health Canada of any changes to the CTAP and of any adverse drug reactions, keeps records in accordance with the Regulations, and is required to follow GCP for the proper use of drugs involved in the CT.
- The REB is a body that is independent of the sponsor and is comprised of at least five members (including both men and women and at least two members with expertise in a scientific or medical discipline). The REB's primary role is to approve or reject the protocol(s) put forward by sponsors for proposed CTs, as well as the informed consent document given to each human subject by assessing any ethical issues that may arise during or as a result of a CT.¹⁸
- The QI is a physician in good standing with a professional medical association and is responsible to the sponsor for conducting the CT at the CT site in accordance with the protocol approved under the CTAP, including obtaining informed consent from subjects and reporting to the sponsor and the REB in the event of any adverse drug reactions.

Contents of clinical trial application

The CTAP contains information and documentation that outline and support the objectives, methodology and goals of a proposed CT. The core components of a CTAP are the proposed clinical protocol; informed consent documents; the investigator's brochure (which contains available pre-clinical and clinical information on the drug at the time of the CT); the contact information of any REB that has reviewed and either rejected or approved the clinical protocol and informed consent documents; the name of the QI; and information on each proposed CT site.¹⁹

Because most CTs are seeking to investigate new drugs that have not yet been approved by Health Canada (i.e., in Phase I to III CTs) or new indications for a marketed drug, Health Canada requires a basis on which to allow the use of the drug on human subjects from a safety and efficacy perspective. Prior to Health Canada granting approval, which is denoted by a Notice of Compliance (NOC) or Drug Identification Number (DIN),²⁰ sponsors are required to submit a CTAP for unapproved drugs and drugs that have been approved for uses other than the CT's intended use (i.e., if the drug is being used in the CT for a new indication or in a new dosage). Similarly, a CTAP is required where a sponsor seeks to conduct a CT with a product that has received a Notice of Compliance with Conditions.²¹

Format of clinical trial application

The sponsor must file a CTAP in the format required by Health Canada. As a rule, the application must be organized into three different modules, each containing the following information:²²

- Module 1 – contains administrative and clinical information about the proposed trial
- Module 2 – contains quality (being chemistry and manufacturing) information about the drug product(s) to be used in the proposed trial
- Module 3 – contains additional supporting quality information

¹⁸ *Food and Drug Regulations*, *supra* note 5, C.05.006(1)(c).

¹⁹ *Ibid*, C.05.005.

²⁰ *Ibid*, C.01.014(a), C.08.004(1)(a).

²¹ A Notice of Compliance with Conditions (NOC/c) is authorization to market a drug on the condition that the sponsor undertake additional studies to verify the clinical benefit. Market authorization under the NOC/c Policy allows Health Canada to provide earlier market access to potentially life-saving drugs

²² Health Canada, *Clinical Trial Applications (CTAs)*, (Ottawa: Health Canada, 2015), available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_application-eng.php.

Effective 1 June 2016, Health Canada no longer accepts paper copies of CTAPs. Any paper CTAP received will be shredded or returned at the sponsor's expense.²³ Each of the CT modules must be submitted in electronic format using a folder structure that easily delineates each module and sub-folders within each module.²⁴ Health Canada recommends that sponsors submit the CTAP in the "Common Technical Document" format.²⁵ For a complete review of the format and submission requirements, please review the "Updated - Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format" document published by Health Canada.²⁶

Further special requirements for radiopharmaceutical and biological drugs

The types of drugs that are studied in CTs are recognized by Health Canada as one of three main categories of drugs: pharmaceuticals, biologicals and radiopharmaceuticals.²⁷ While CTAP requirements are generally the same for all three types of drugs, there are some differences in the amount of information disclosed when completing a CTAP, and there are different Directorates within the HPFB responsible for reviewing CTAPs for CTs studying certain types of drugs.²⁸

For pharmaceutical drugs, CTAPs in Canada are only required to include summarized information about the drug, while biological or radiopharmaceutical drugs are subject to more stringent requirements. This is due to the additional risks associated with the complexity and variability inherent in the manufacturing process utilized for these types of drugs. This complexity and variability can result in "lot-to-lot variations," which creates a potential for introducing adventitious agents, such as viruses, bacteria, mycoplasma, fungi, protozoa or parasites.²⁹

In order to satisfy these further requirements, CTAPs for biological and radiopharmaceutical drugs must contain additional information, including with respect to the chemical and manufacturing processes.³⁰ Moreover, each "lot" of biologics to be used in the CT must be submitted to the Biologics and Genetics Therapies Directorate for release, prior to use.³¹

²³ Health Canada, Updated - Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format, (Ottawa, Health Canada, 2016), available at: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html>

²⁴ *Ibid.*

²⁵ *Clinical Trial Applications (CTAs)*, *supra*, note 22.

²⁶ *Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only Format"*, *supra*, note 23.

²⁷ *Food and Drugs Act*, *supra* note 4, Sched C, Sched D set out the list of drugs that are considered to be biological and radiopharmaceutical drugs, respectively.

²⁸ The Biologics and Genetic Therapies Directorate reviews CTAPs for CTs that study biologics and radiopharmaceutical drugs while the Therapeutic Products Directorate reviews CTAPs for CTs that study pharmaceutical drugs.

²⁹ Health Canada, *Clinical Trial Applications for Biologics and Radiopharmaceuticals*, (Ottawa: Health Canada, 2004), available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_biologics-eng.php; Health Canada, Canada, Health Canada, *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*, (Ottawa: Health Canada, 2013, rev'd 2016), available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.pdf.

³⁰ *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*, *supra* note 16

³¹ Health Canada, *Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs*, (Ottawa: Health Canada, 2005), available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/gui_sponsors-dir_promoteurs_lot_program-eng.pdf.

Classifying and approving clinical trials

The four phases of clinical trials

Health Canada classifies CTs under one of four phases, each of which has its own set of requirements prior to implementation³²:

- Phase I CTs – initial safety studies on a new drug, including the initial administration of the drugs to humans, usually healthy volunteers
- Phase II CTs – used to evaluate the efficacy of a drug in patients with a medical condition to be treated, diagnosed or prevented, and to determine the side effects and risks associated with the drug
- Phase III CTs – controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the drug has been demonstrated
- Phase IV CTs – all studies performed after the drug has been authorized by the regulator for the market, and related to the authorized indication

Clinical trial application review and approval

For CTs in Phases I through III, a CTAP is required for drug development and comparative bioavailability studies.³³ In contrast, a CTAP is not required to conduct Phase IV trials since the drug being studied will have already been approved for marketing by Health Canada.³⁴ Despite not requiring a CTAP, sponsors should ensure that Phase IV trials are still conducted in accordance with Division 5 of the Regulations.

The CTAP process is generally the same for Phase I to III trials. However, one significant difference is the estimated amount of time that Health Canada takes to review CTAPs. Particularly, Health Canada aims to review Phase I CTAPs within seven days, and Phase II and III trials within 30 days, subject to some exceptions.³⁵

Once a CTAP is reviewed and the CT is approved by Health Canada, a No Objection Letter (NOL) will be issued, authorizing the CT to proceed using the named drug. Although the Regulations permit a CT to be commenced after 30 days unless the sponsor has received a Not Satisfactory Notice (**NSN**), a sponsor will generally not commence a CT until an NOL has been received.³⁶

If there are deficiencies in the sponsor's CTAP, Health Canada will communicate to the sponsor through a Request for Clarification (**Clarifax**) or a Screening Rejection Letter.³⁷ A Clarifax is issued during the screening process, and a sponsor is required by the Regulations to respond within two calendar days.³⁸ On the other hand, a Screening Rejection Letter is issued where there is significant information missing from a CTAP, and each deficiency is

³² *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*, *supra* note 16.

³³ Health Canada administratively defines "Comparative Bioavailability Studies" as "studies comparing the pharmacokinetics of two drug formulations in healthy adult volunteers."

³⁴ *Food and Drug Regulations*, *supra* note 5, C.05.006(2); *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*, *supra* note 13, s 2.3.

³⁵ *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*, *supra* note 16 s 2.5.

³⁶ *Ibid*, s 2.5.2.

³⁷ *Food and Drug Regulations*, *supra* note 5, C.05.009; Canada, Health Canada, *Review of your Application*, (Ottawa: Health Canada, 2006), available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_review-eng.php.

³⁸ *Ibid*.

itemized.³⁹ Failure to rectify deficiencies to Health Canada's satisfaction will result in the issuance of an NSN, which means that the CT cannot proceed.⁴⁰

Clinical trial agreements (CTAs)

Introduction to clinical trial agreements

Clinical trial agreements will ordinarily be concluded between the sponsor and the medical or research organization engaged to conduct the CT. Historically, the sponsor may have been in a position to impose its own favorable terms on such institutions in developing a CTA. Today, however, most institutions will seek to use their own template CTA terms.

Some common provisions of CTAs deal with the provision and disposal of the study drug, record-keeping and reporting obligations, IP rights, REB approvals, site access, and compliance with legal obligations, as well as standard commercial terms.⁴¹

A physician or other permitted practitioner who serves as the QI will usually be a signatory to the CTA. This is the case even if the QI is an employee of the medical or research institution since:

- The QI must agree to specific record-keeping and reporting obligations as required by the Regulations and ICH Guidance.⁴²
- The institution will typically not wish to be directly responsible for these obligations.

Physician's considerations in signing clinical trial agreements

A major consideration for a physician when signing a CTA is whether or not they will be insured for their actions in connection with the fulfillment of a CTA. In Canada, physicians, including those who participate in CTs, are insured through the Canadian Medical Protective Association (CMPA), an industry-wide, member-based program.⁴³ When signing CTAs, physicians must consider the many rules and restrictions that the CMPA imposes. For example, the CMPA will generally indemnify physicians and their employees only for claims under a CTA relating to the practice of medicine, and will generally not cover acts or omissions relating to administrative or non-medical functions. The CMPA will also generally not provide coverage to its members who act as QIs for CTs performed on healthy volunteers, providing coverage only where the subjects are patients with a medical condition.

Given the limitations of CMPA's coverage, contracted institutions, research organizations and the QI will frequently require that the sponsor obtain insurance and provide adequate indemnities before they agree to enter into a CTA. The coverage amount will generally depend on the phase and risk of the CT in question.

The sponsor will also usually require the QI to sign a confidentiality agreement as a condition of the CTA. Both physicians and institutions are likely to use an agreement adapted from the template confidentiality agreement that has been developed by the Canadian Medical Association, the CMPA and the Federation of National Specialty

³⁹ *Ibid.*

⁴⁰ *Ibid.*

⁴¹ See for example Canadian Clinical Trials Coordinating Centre, *model Clinical Trials Agreement (mCTA)* (Ottawa, Canada: CCTCC) available at: <http://www.cctcc.ca/index.cfm/our-initiatives/model-clinical-trials-agreement-mcta/>

⁴² *Food and Drug Regulations*, *supra* note 5, C.05.012; *ICH Guidance E6: Good Clinical Practice: Consolidated Guideline*, *supra* note 17 s 4.9.

⁴³ The Canadian Medical Protective Association online: CMPA <<https://www.cmpa-acpm.ca/home>>.

Societies of Canada.⁴⁴ Furthermore, the different provincial professional Colleges or applicable provincial laws may impose limitations on a physician's ability to enter into a confidentiality agreement, for example, by prohibiting physicians from concealing the negative findings of research projects in which they have participated.⁴⁵

Sponsor and contract research organizations (CROs)

Sponsor's responsibilities

The Regulations apply to all sponsors conducting CTs in Phases I to III in Canada⁴⁶ and define "sponsor" as "an individual, corporate body, institution or organization that conducts a clinical trial."⁴⁷ In Canada, the sponsor is responsible for ensuring compliance of the CT with the Regulations – this includes compliance with the requirement to follow good clinical practices, proper labelling of the drugs, maintenance of required records for a specified period of time, submission of required information and samples of the drug, reporting of serious adverse drug reactions, and reporting to Health Canada where the CT has been discontinued.⁴⁸

In addition to the enumerated responsibilities in the Regulations, the sponsor is also required, as a general matter, to follow the ethical and procedural guidelines under Health Canada's ICH Guidance. The sponsor must implement and maintain quality control systems that will govern the conduct of CTs, provide medical expertise through qualified medical personnel, and design and manage the CT so as to keep proper records. The ICH Guidance makes the sponsor responsible for selecting the QI for the CT and provides that there should be an agreement that clearly allocates responsibility between the sponsor and the QI.⁴⁹

There is no requirement that the sponsor for a CT be located in Canada. However, the Regulations require that if a drug is imported, there must be a representative in Canada responsible for the sale of the drug.⁵⁰

The relationship between sponsor and contract research organization

The ICH Guidance provides that the sponsor may transfer any or all of its trial-related duties and functions to a CRO.⁵¹ However, the sponsor retains ultimate responsibility for approval of the CTAP, and for the quality and integrity of the CT data.⁵² Pursuant to the ICH Guidance, any duty or function that is not specifically transferred to a CRO is retained by the sponsor.⁵³ There are no specific legal requirements governing the choice of a CRO in Canada, and it is the sponsor's decision whether to retain a CRO, and which CRO to retain.

The CTA between sponsor and CRO is not subject to review by Health Canada, but in the event that the sponsor contracts a CRO to conduct the CT, the sponsor is required to provide contact information for and summarize the scope of duties of the CRO in the CTAP for review by Health Canada.⁵⁴

⁴⁴ See *e.g.* the CMPA's template confidentiality agreement here: https://www.cmpa-acpm.ca/documents/10179/25003/confidentiality_agreement_template-e.pdf.

⁴⁵ College of Physicians and Surgeons of Ontario, *Physicians' Relationship with Industry: Practice, Education and Research*, (Toronto: CPSO, 2014), available at: http://www.cpso.on.ca/CPSO/media/images/Policies%20and%20Publications/Rel_Industry.pdf?ext=.pdf.

⁴⁶ *Food and Drug Regulations*, *supra* note 5, C.05.002(2).

⁴⁷ *Ibid*, C.05.001.

⁴⁸ *Ibid*, C.05.010–C.05.015.

⁴⁹ *ICH Guidance E6: Good Clinical Practice: Consolidated Guideline*, *supra* note 17.

⁵⁰ *Food and Drug Regulations*, *supra* note 5, C.05.005(viii).

⁵¹ *ICH Guidance E6: Good Clinical Practice: Consolidated Guideline*, *supra* note 17 s 5.2.1.

⁵² *Ibid*.

⁵³ *Ibid*, s 5.2.3.

⁵⁴ *Food and Drug Regulations*, *supra* note 5, C.05.005(c).

The qualified investigator

Introduction to qualified investigators

The term “qualified investigator” is defined in the Regulations and must be a physician (or a dentist where the trial involves a drug for dental purposes only) who is a member of the applicable professional medical (or dental) association.⁵⁵ The QI is generally accountable to the sponsor for the conduct of the CT at a given site. In Canada, there can only be one QI per site.⁵⁶ More specifically, the QI is generally responsible for the supervision of medical care and medical decisions relating to the CT at each site. The QI is required to sign an undertaking that he/she will conduct the CT in accordance with good clinical practices and that in the event of a discontinuance of the CT, he/she will immediately inform the trial subjects and the REB of the discontinuance, the reasons for the discontinuance, and any potential health risks.⁵⁷ The written undertaking must be retained together with the records for the CT, and all of these records must be kept by the sponsor for a minimum period of 25 years.⁵⁸

The functions of a QI are also outlined in the ICH Guidance, which sets out the processes and practices for obtaining informed consent from the trial subjects, assigns responsibility for the study drugs at the trial site to the QI, and provides details on the reporting duties of the QI.⁵⁹

Reporting of adverse drug reactions

The reporting of adverse drug reactions (**ADRs**) is required under both the Regulations and the ICH Guidance.⁶⁰ In general, only ADRs that are both (i) serious and (ii) unexpected are subject to expedited reporting to Health Canada.⁶¹ Expedited reporting for ‘expected’ reactions or reactions unrelated to the study drugs is generally not required.

During the CT, the QI must notify the sponsor immediately of any ADRs, and after such report, submit a more detailed, written follow-up report to the sponsor. The sponsor is then required to inform Health Canada of ADRs, regardless of whether they have occurred within or outside Canada.⁶² A report must generally be filed within 15 days of the sponsor becoming aware of the ADR if the ADR is neither fatal nor life-threatening, and immediately or within a maximum of seven days where the ADR is fatal or life-threatening.⁶³ In addition, when dealing with fatal or life-threatening ADRs, the sponsor must submit a report assessing the impact of the ADR on the CT within eight days of informing Health Canada.⁶⁴

Study drugs

As outlined above, in order to administer a study drug in a Phase I, II or III CT in Canada, a sponsor must generally have filed a CTAP and either: (i) not have received an NSN within the applicable review period; or (ii) more commonly, have received an NOL from Health Canada confirming that the drug can be administered in a CT.⁶⁵ For Phase IV CTs,

⁵⁵ *Ibid*, C.05.001.

⁵⁶ *Ibid*, C.05.010(e).

⁵⁷ *Ibid*, C.05.012(3)(e).

⁵⁸ *Ibid*, C.05.012.

⁵⁹ *ICH Guidance E6: Good Clinical Practice: Consolidated Guideline*, *supra* note 17, s 4.

⁶⁰ *Ibid*, s 5.17; *Food and Drug Regulations*, *supra* note 5, C.05.014.

⁶¹ *Ibid*.

⁶² *Ibid*.

⁶³ *Food and Drug Regulations*, *ibid*, C.03.314.

⁶⁴ *Ibid*.

⁶⁵ *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*, *supra* note 16, s 2.5.2.

CTAPs are not required, and the sponsor may generally administer the drug within the parameters of its market authorization without further approval.⁶⁶

Provision and cost of the study drug

Who covers the cost of providing a study drug is not specifically regulated in Canada. The general practice is that the sponsor provides the study drug free of charge to the CT subjects. In fact, many CTs offer some form of additional financial remuneration. In the event that the sponsor itself cannot provide the study drug for use in a CT, the sponsor will generally reimburse the QI or the institution conducting the CT for the cost of the study drug.

The cost of medical procedures and tests that are part of the CT protocol is typically negotiated by the sponsor and the QI and/or institution involved in conducting the CT, and is covered under the CTA. If the CT involves a normal standard of care for patients, the cost is typically covered by the medical or research institution. Where the required care, however, is outside the normal standard, the sponsor is more likely to cover the cost of the tests and procedures.

As noted earlier, the sponsor retains sole responsibility for compliance of a CT with the Act and Regulations, subject to its ability to delegate its duties and responsibilities and provided that this is disclosed to Health Canada as part of the CTAP.⁶⁷ Liability relating to study drugs, however, is a separate issue and a legal proceeding could potentially be commenced against any party involved in the commission, design or performance of the CT. Liability and indemnification for such claims are normally addressed in the CTA.

The ability of a sponsor to provide study drugs to subjects after the completion of a CT should also be considered as it may give rise to issues under the drug sampling provisions of the Act (if drugs are provided at no cost)⁶⁸ or provincial/territorial pharmacy laws governing the dispensing and pricing of drugs.⁶⁹

Natural health products

The requirements of an NHP CT are similar to the requirements of a pharmaceutical drug CT, as described above.⁷⁰ A Phase I, II or III NHP CT in Canada must be approved by the issuance of a Notice of Authorization by the Natural and Non-prescription Health Products Directorate (**NNHPD**). The sponsor must notify the NNHPD of the date of CT commencement at least 15 days in advance.⁷¹ A CTA does not need to be submitted to Health Canada for observational studies or Phase IV CTs.⁷²

A CTAP should be submitted to the Therapeutic Products Directorate (**TPD**) for NHP/drug combinations where the drug is being used outside of the conditions of use approved by Health Canada or is not approved for sale in Canada.⁷³ The TPD will also authorize and monitor CTAPs for an NHP that contains certain ingredients listed in the Prescription Drug List of the *Regulations*.⁷⁴

⁶⁶ *Food and Drug Regulations*, *supra* note 5, C.05.006(2); *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*, *ibid*, s 2.3.

⁶⁷ *Food and Drug Regulations*, *supra* note 5, C.05.010-C.05.015.

⁶⁸ *Food and Drugs Act*, *supra* note 4, s 14.

⁶⁹ See, e.g., Ontario's restrictions on dispensing drugs in the *Drug and Pharmacies Regulation Act*, RSO 1990, c H.4, s 149.

⁷⁰ Health Canada, *Guidance Document for Clinical Trials for Natural Health Products*, (Ottawa, Health Canada, 2016), available at: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/clinical-trials.html>>

⁷¹ *NHP Regulations*, *supra* note 7 s. 69.

⁷² *Guidance Document for Clinical Trials for Natural Health Products*, *supra* note 70.

⁷³ *Ibid*.

⁷⁴ For example a CT testing a multivitamin that contains more than 10,000 IU of Vitamin A per day would fall under this category and need to be submitted to the TPD.

Publishing results and intellectual property (IP) issues

Publishing results of the clinical trial

With respect to the publication and confidentiality of the results of CTs, Canadian rules are generally designed to promote publication. In fact, Health Canada released a draft guidance document on 10 April 2018 entitled “Public Release of Clinical Information” to guide the proactive release of de-identified (confidential personal information removed) clinical information following completion of the regulatory process, such as upon issuance of market authorization. The clinical information that Health Canada is proposing to release includes information on the drug’s safety and efficacy; it will not include chemistry, manufacturing and other non-clinical information. Balanced against this objective to publish clinical information is the acknowledged risks inherent to the premature disclosure of clinical data on an interim basis and prior to finalization of the CT. Health Canada notes that such premature disclosure could jeopardize the reliability of the trial data, bias data collection or weaken confidence in the study’s conclusions. Accordingly, interim analyses will be determined on a case-by-case basis and will not be released if disclosure risks affecting the integrity of the study.⁷⁵

Moreover, on this point of transparency, the CMA policy titled “Guidelines for Physicians in Interactions with Industry” takes the position that physicians should not participate in industry-sponsored research unless the study is registered prior to its commencement in a publicly accessible research registry.⁷⁶

Similarly, the “Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans” adopted by three Canadian public research agencies⁷⁷ takes the view that researchers have a duty to disseminate the analysis and interpretation of their results from CTs to the research community, and that non-publication may foster inappropriate or potentially harmful clinical practices, or unnecessary duplication of research.⁷⁸ In some Canadian jurisdictions, physicians may also be prohibited from concealing the negative findings of a research project in which they were involved.⁷⁹

Intellectual property issues

As most CTs in Canada are conducted pursuant to a CTA or some other written contract, issues of IP rights and ownership are primarily a matter of contract law, subject to the provisions of relevant federal statutes governing patents and other areas of IP.⁸⁰

Typically, the sponsor will negotiate terms that give it ownership in all study data and inventions arising from the CT, and it will require the QI or institution to assist in any application to obtain patent protection or secure other IP rights. Some institutions, however, may insist on retaining ownership of inventions that are conceived by their institutional employees, and in such cases, the sponsor may negotiate an exclusive license or a right of first refusal.

⁷⁵ Health Canada, *Draft Guidance Document: Public Release of Clinical Information*, (Ottawa, Health Canada, 2018), available at: <https://www.canada.ca/content/dam/hc-sc/documents/programs/consultation-public-release-clinical-information-drug-submissions-medical-device-applications/draft-guide-public-release-clinical-information.pdf>

⁷⁶ Canadian Medical Association, *Guidelines for Physicians in Interactions with Industry*, (Ottawa: CMA, 2007), available at: <http://policybase.cma.ca/dbtw-wpd/Policy/pdf/PD08-01.pdf>.

⁷⁷ The Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC)

⁷⁸ Secretariat on Responsible Conduct of Research, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, (Ottawa: Government of Canada, 2014), available at: http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf.

⁷⁹ See e.g. Ontario’s position on concealing negative findings in *Physicians’ Relationship with Industry: Practice, Education and Research*, *supra* note 45.

⁸⁰ See for example, Patent Act, RSC 1985, c P-4.

Investigator-initiated trials are generally permitted under Canadian law.⁸¹ Expectedly, all regulatory requirements in respect of a CT apply to investigator-initiated trials, and the investigator/institution is considered to step into the shoes of the sponsor. This generally applies even where an investigator has received a grant from a commercial entity to conduct the CT. Accordingly, the procedures for investigator-initiated trials are largely the same as those for commercial sponsors, save for certain administrative differences, such as who may sign documents relating to the CTAP.

⁸¹ Health Canada, *Institution / Investigator Initiated Clinical Trials*, (Ottawa: Health Canada, 2006), available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_for_sponsors-eng.php.



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