Health Canada’s modernized clinical trial framework: Implications for stakeholders

June 28, 2021

As one of the five key pillars of the Government of Canada’s Regulatory Innovation Agenda for health products, Health Canada recently released its vision for the modernization of Canada’s clinical trials regulatory framework.

Health Canada is proposing a single clinical trial framework for drugs, medical devices, and natural health products (NHPs) as the foundation for the new regulatory regime, which will provide:

- proportional risk-based oversight;
- regulatory agilities over the life-cycle of a clinical trial;
- greater transparency; and
- a modernized compliance and enforcement regime.

The proposal incorporates regulatory flexibilities introduced by Health Canada under the Interim Order processes for clinical trials for medical devices and drugs related to COVID-19 (IO and IO-2, collectively, the "Interim Orders"). While the measures introduced under the Interim Orders are temporary in the context of the pandemic, they provide an important proof of concept for the regulatory amendments under review by Health Canada.

A brief overview of Health Canada’s proposal and the potential implications for Canadian clinical trial stakeholders is provided below.

Proportional risk-based oversight

Clinical trial authorization

Health Canada is proposing changes to Canada’s clinical trial framework that will allow the regulator to oversee the safe conduct of the clinical trial in its entirety, while enabling sponsors to conduct innovative trial types, such as master protocols (trials studying multiple therapies) and adaptive trials (trials that allow for planned changes to the study protocol at pre-specified times).

According to the proposal, Health Canada will transition from its current framework, which requires an authorization of the sale or importation of the health product used in the clinical trial, to a comprehensive authorization of the trial as a whole, as well as the products being tested. A key part of this proposal involves the implementation of a single authorization pathway for clinical trials involving multiple health products from different categories, such as drugs, medical devices, and NHPs. The effect of this change is that sponsors would no longer have to file separate drug and/or NHP clinical trial authorizations and/or medical device Investigational Testing Applications (ITAs) for a single clinical trial. Clinical trial regulatory requirements across health product lines would also be aligned to ensure coherence and predictability for sponsors. This would include defining review timelines in policy and ensuring alignment across product lines.

Categorization of clinical trials

Health Canada's proposal also includes categorizing clinical trials that fall under the scope of the *Food and Drugs Act* and its regulations into one of three categories (A, B or C) and two subcategories for Category B (B1 and B2). These categories represent the level of risk, uncertainty and safety information available for each product used in the trial. A trial with multiple product types would be classified by the product with the highest level of risk.

Category A would include clinical trials involving products or therapies with a known safety profile that pose minimal risk to participants compared to usual medical practice. Category A trials would not require the submission of a clinical trial application and would therefore be exempt from authorization.

Category B would include clinical trials involving unlicensed medium risk medical devices, drugs or NHPs that have well-established safety information available. For drugs and NHPs, Category B would be further divided into subcategories B1 and B2 depending on the level of evidence available to support testing outside the authorized indication. These trials would require authorization but with tailored requirements based on the level of risk of the product or trial type.

Category C would include trials involving unlicensed high-risk medical devices and/or new drugs or NHPs or therapies, as well as bioequivalence studies. These trials would require submission of a full clinical trial authorization. The full set of post-authorization requirements, consistent with the current regulations, would continue to apply for Category C clinical trials.

Flexibility for independent investigators

Health Canada is proposing to amend the *Medical Devices Regulations* to enable independent investigators (such as a researcher, clinician, or healthcare facility), independent of a device manufacturer, to apply for an ITA. Currently, only manufacturers and importers of medical devices can apply for an ITA.

New regulatory agilities over the life cycle of the clinical trial

Health Canada is proposing to introduce several regulatory tools to manage risk over the life-cycle of the trial. These regulatory tools are similar to flexibilities introduced by Health Canada under the Interim Orders.

Terms and conditions

One regulatory tool includes the ability to impose terms and conditions on a clinical trial authorization before or during the clinical trial. This regulatory flexibility draws on the authority introduced under the Interim Orders, which permits the Minister of Health to impose terms and conditions on a COVID-19 drug or medical device authorization, or to amend those terms and conditions, at any time.

Under the modernized clinical trial regulatory framework, Health Canada would similarly have the authority to impose terms and conditions on a case-by-case basis to address uncertainties or to mitigate risks related to the product being tested or the conduct of the trial. Potential terms and conditions could include:

- establishment of a data monitoring committee (DMC);
- more frequent safety monitoring and reporting;
- monitoring of specific populations due to potential increased risk (*e.g.*, children);
- requiring additional information to characterize newly identified risks during the course of the trial; and
- long-term safety monitoring and reporting beyond the period of study treatment.

Increased authority to cancel or suspend a clinical trial authorization in whole or in part

The Interim Orders provide the Minister of Health with the authority to suspend, in whole or in part, a COVID-19 drug or medical device authorization. Health Canada is also proposing to amend its authority under the new regulatory framework to cancel or suspend a clinical trial authorization to allow for the suspension or cancellation of a trial "in whole or in part".

This regulatory flexibility will provide Health Canada with the authority to cancel or suspend only an arm of a trial, a site, study enrolment, or the use of a particular product. Health Canada will be able to react more precisely if an aspect of the trial has demonstrated a lack of efficacy or poses a safety concern without compromising the trial as a whole, allowing the rest of the trial to remain open to participants.

Decentralized clinical trials

While decentralized clinical trials (DCTs) are not currently prohibited under Canada's regulatory regime, Health Canada is proposing several regulatory amendments to encourage their use. DCTs are clinical trials executed through telemedicine and mobile/local healthcare providers, using processes and technologies differing from the traditional trial model. In a DCT, the study takes place remotely, without a physical site by participants to the trial site. Potential amendments to the clinical trial regulations include:

- changing the wording of “written informed consent” to “documented informed consent” (which would be described in guidance as including an electronic signature or a video or audio recording of the informed consent process);
- defining “trial site” in regulation as “the location where trial-related activities are actually conducted” (where “trial related activities” could include recruitment, informed consent, monitoring and visits completed in a virtual manner);
- allowing a witness to attest that informed consent was given in exceptional circumstances; and
- allowing greater flexibility for the types of health professionals that can be a qualified investigator (currently, only a physician or a dentist may conduct a clinical trial under the pre-existing pathways set out in the *Food and Drug Regulations* and the *Natural Health Products Regulations*).

The proposed regulatory amendments are similar to flexibilities introduced under the Interim Orders. The Interim Orders expanded the definition of “qualified investigator” for clinical trials involving drugs to include additional regulated health care professionals, such as nurse practitioners. In addition, other means of obtaining informed consent were enabled to include remote, written informed consent and non-written informed consent when prospective participants are unable to consent in person or in writing. Incorporating these regulatory flexibilities into the modernized clinical trial framework would expand clinical trial recruitment eligibility, enable multi-site clinical trials and increase clinical trial access in remote locations, where fewer physicians are available to act as qualified investigators.

Transparency

Health Canada is also exploring policy and regulatory options to increase transparency of clinical trial information. While compliance with voluntary registration and reporting has been high among sponsors for drug trials, there remains a need to increase transparency for trials involving medical devices and NHPs, and to provide greater access to clinical trial information.

Under the proposal, Health Canada is considering introducing policy and/or regulatory requirements for sponsors to register their trials in an existing international registry, such as the ISRCTN. Registry eligibility would be determined based on criteria that aligns with the International Committee of Medical Journal Editors (ICMJE) requirements and the World Health Organization (WHO) criteria for a primary registry. Sponsors would also be required to publicly disclose their trial results. Health Canada could also require that the sponsor provide proof of their registration or public disclosure of the results within a prescribed time frame.

Modernization of compliance and enforcement

Health Canada is also considering several approaches to modernize its compliance and enforcement activities for clinical trials.

Expanded oversight for medical devices and NHPs

Health Canada’s oversight activities for clinical trials has been limited to drug trials. Under the proposed framework, Health Canada would extend clinical trial oversight to

medical devices and NHPs. When identifying which trials to inspect, Health Canada would apply a risk-based, proactive approach that considers the trial design and other factors, such as the target population, medical condition under study or associated risks of the trial. Health Canada would also implement a cyclical risk-based inspection approach when deciding which sponsors, contract research organizations (CROs), or Site Management Organizations (SMOs) to inspect.

Compliance and enforcement of third parties

Health Canada is also proposing to amend the regulations so that any third party, such as a qualified investigator, CRO, or SMO, who conducts all or part of a clinical trial on behalf of a sponsor would be legally responsible for those activities, and therefore subject to regulatory action in the event of non-compliance.

Record retention requirements

Health Canada is proposing to amend the *Food and Drug Regulations* and the *Natural Health Products Regulations* to reduce the current record retention requirements from a minimum of 25 years to a minimum of 15 years, with certain exceptions, for all clinical trials of drugs involving human subjects. The regulatory amendments would not limit any provincial or territorial laws or regulations that require longer record retention timeframes.

This proposal would improve alignment of Canadian records retention requirements for clinical trials with international standards prescribed by other global health regulators. It would also reduce the regulatory burden on Canadian clinical trial stakeholders.

Implications for clinical trial stakeholders

Health Canada's proposal for a modernized clinical trial framework would enable the regulator to oversee the broad range of innovative trial types increasingly being used by clinical trial stakeholders. It will also benefit stakeholders by providing clear, coherent, and streamlined regulatory requirements across product lines.

The introduction of proportional, risk-based oversight would lower the regulatory burden for low risk clinical trials. In addition, the introduction of regulatory agilities, such as the ability to impose terms and conditions on a clinical trial authorization, would allow Health Canada to better regulate trials with greater risk. Qualified investigators and institutions would need to ensure when negotiating clinical trial agreements that any additional regulatory requirements imposed by Health Canada, and the associated costs, are the responsibility of the sponsor.

Health Canada's proposal to amend the regulations to enable sponsors to transfer part of their legal responsibility to third parties has the potential to increase liability for CROs, SMOs, qualified investigators, and institutions. To mitigate this risk, qualified investigators and institutions would need to ensure that they do not take on any responsibilities of the sponsor, and that the parties' responsibilities are clearly delineated in any clinical trial agreements.

By

Holly Ryan, Lydia Wakulowsky

Expertise

Corporate Commercial, Health Care, Health Care & Life Sciences

---

BLG | Canada's Law Firm

As the largest, truly full-service Canadian law firm, Borden Ladner Gervais LLP (BLG) delivers practical legal advice for domestic and international clients across more practices and industries than any Canadian firm. With over 725 lawyers, intellectual property agents and other professionals, BLG serves the legal needs of businesses and institutions across Canada and beyond – from M&A and capital markets, to disputes, financing, and trademark & patent registration.

blg.com

BLG Offices

Calgary

Centennial Place, East Tower
520 3rd Avenue S.W.
Calgary, AB, Canada
T2P 0R3

T 403.232.9500
F 403.266.1395

Ottawa

World Exchange Plaza
100 Queen Street
Ottawa, ON, Canada
K1P 1J9

T 613.237.5160
F 613.230.8842

Vancouver

1200 Waterfront Centre
200 Burrard Street
Vancouver, BC, Canada
V7X 1T2

T 604.687.5744
F 604.687.1415

Montréal

1000 De La Gauchetière Street West
Suite 900
Montréal, QC, Canada
H3B 5H4

T 514.954.2555
F 514.879.9015

Toronto

Bay Adelaide Centre, East Tower
22 Adelaide Street West
Toronto, ON, Canada
M5H 4E3

T 416.367.6000
F 416.367.6749