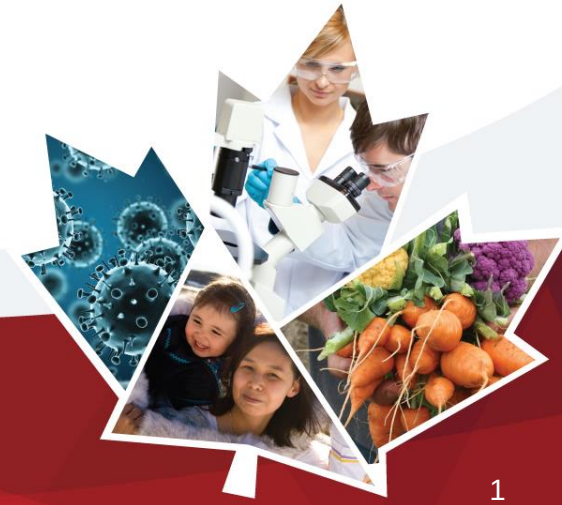
Modernizing Clinical Trial Regulations



Outline

- Modernizing clinical trial regulations
- Risk-based regulations
- OECD framework for clinical trial regulations

MODERNIZING CLINICAL TRIAL REGULATIONS

Modernizing clinical trial regulations

to encourage clinical trials in Canada by creating an environment that supports more innovative trials

The current state of clinical trials in Canada:

Three overarching objectives to the regulation of clinical trials:

1. **Continue to ensure protections for research participant;**
2. **Increase R&D investment in clinical trials in Canada; and,**
3. **Increase confidence in the integrity of Canadian clinical trial data.**

- Current **authority related to authorizing the sale of product** for the purposes of a clinical trial.
  - Authority related to oversight of trial conduct and design not as clearly defined.
- Publication of clinical trial information reliant on voluntary measures.
- Some **requirements vary across product lines** and internationally, and food trials are not enabled.
- Regulatory inflexibilities may be limiting innovation.

Evolving science in the clinical trial environment

- **Innovations** in clinical trial design (e.g., basket trials, umbrella trials, platform trials) **warrant new agility over the lifecycle of a trial.**
- Increasingly complex and personalized **products shift how the regulatory framework might best manage risk**.
- New uses of **technology and data could change how trials are conducted and reviewed** (e.g., reliance on modelling, virtual and remote trials).
- **Global nature of trials is a pressure for** international collaboration in **compliance and enforcement**.
- **New approaches needed** to address regulatory and health system challenges.

Push for agile regulations included in COVID-19 response

Government calls for more agile regulations to support innovation

Stakeholders respond with request for greater trial agility and alignment

COVID-19 further necessitates agile approaches which uphold patient safety

- Economic Strategy Tables recommended more **agile regulations**.
- In 2018-19, **Health Canada's** Review **of the Health and Bio-Sciences Sector** found **oversight for clinical trials may be constraining growth; committed to modernizing clinical trial regulations** across product lines.
- **In consultations to date**, stakeholders have asked for agility in enabling trials and patient participation, reducing unnecessary administrative burden and advancing greater domestic and international coordination.
- In May 2020, **Health Canada introduced some of the "agile" concepts envisioned as part of clinical trial modernization** through an Interim Order (IO) to facilitate COVID-19 medical device and drug trials.
- We also introduced guidance on **clinical trials during a pandemic**, and regularly share information on authorized COVID-19 trials.

Modernized clinical trial framework: Key proposed changes

New risk-based approach	Streamlined across product lines	Lifecycle authorization for the conduct of clinical trials	New registration and disclosure of results	International alignment	Decentralized trials and health system efficiencies

Legislative changes to *Food and Drugs Act* in 2019 enable us to make future regulations to:

- **Authorize and oversee clinical trials, as well as product(s) within the trial,** throughout the lifecycle (e.g., enabling a single authorization for trials involving different product lines, and ability to cancel or suspend part of a trial).
- **Tailor authorization and oversight to the risk of the trial/product(s) by:**
  - Lightening labelling and record keeping requirements for studies involving new uses for approved products supported by evidence; or,
  - Adding Terms and Conditions to manage risks/uncertainties across the lifecycle of a trial.
- Require the **registering of trial information** in a publicly accessible registry and disclose results.
- **Alignment across product lines of drugs, devices and Natural Health Products**, as well as internationally, where appropriate.

Proposed steps forward for product lines

FROM	TO
HUMAN DRUGS Unnecessary requirements for certain low-risk trials, not well suited to more complex trials.	***Increase regulatory agility to address different types of clinical trial applications received.***
MEDICAL DEVICES Requirements for medical device investigational trials out of step with international counterparts.	***Enable investigational testing of medical devices by independent researchers and healthcare professionals, greater alignment.***
NATURAL HEALTH PRODUCTS Approach to clinical trials for non-prescriptions drugs, Natural Health Products misaligned (e.g., timelines).	***Natural Health Product investigators will benefit from faster approval timelines for trials.***
FOOD Cannot conduct clinical trials on infant formula to generate safety and nutrition data for authorization.	***Enable agri-food industry to conduct clinical trials for foods for special dietary purposes (e.g., new infant formula) within Canada.***

Supported by risk-based compliance and enforcement

Unique opportunity to leverage COVID-19 experience

New risk-based approach | **Streamlined across product lines** | **Lifecycle authorization for the conduct of clinical trials** | **New registration and disclosure of results** | **International alignment** | **Decentralized trials and health system efficiencies**

- COVID-19 Interim Order pathway has **enabled some key concepts** envisioned within broader clinical trial modernization, such as:
  - Risk-based approach for already marketed drugs;
  - Ability to add Terms and Conditions to authorization for drugs and devices;
  - Shifting from default “no objection” scheme to new authorization for drug clinical trials;
  - Broadening who can sponsor a medical device trial as well as who can conduct a drug trial as qualified investigator; and,
  - Ability to suspend or cancel part of a trial.
- **Some flexibilities were specific to the pandemic**, such as enabling alternate means of informed consent.
- COVID-19 risk-based **agilities and lessons learned will be assessed for broader applicability under clinical trial modernization** to ensure regulations are responsive to a changing health environment.

Next steps: Ongoing consultations to inform trial modernization

2019-2020	2020-2021	2021-2022 and beyond*
Budget 2019 legislative amendments received to modernize clinical trial framework	**Regulations to transition the IO for COVID-19 trials**	Propose amendments to the *Food and Drug Regulations*, the *Medical Devices Regulations* and the *Natural Health Products Regulations*
Interim Order introduced agilities for COVID-19 trials	**Leverage IO lessons learned and policy development for overall clinical trial modernization**	Publish final regulatory amendments, implement modern approaches
	Targeted engagement and publish Consultation Paper	

Ongoing stakeholder consultations

* Subject to confirmation

RISK-BASED REGULATIONS

Regulation

- Identifiable and discrete mode of government activity
- Specific set of commands binding set of rules to be applied by government

Uncertainty and Risk

- Identification of risk not easy task
- Risk is multi-dimensional concept that cannot be easily reduced to probability of occurrence and consequence
- Inherently about the control of risk caused by exposure
- Widely defined as the probability that a particular event will occur during a stated period time and subsequent severity of impact of event
  - Predictable risk- assessment of probability based on available statistics about past events
  - Unpredictable risk- based on evidence of a causal connection between event which may be weak or unquantifiable (maybe one off)
  - Voluntary/societal imposed

Factors considered in the analysis of uncertainty and risk

- **Technical**
  - Relative frequency of events
  - Assess probabilities by extrapolating from statistics of past events
  - Seeks to anticipate physical harm
  - Does not account for what person perceives as undesirable
- **Psychological**
  - How an individual understands, estimates and evaluates risk based on:
    - Catastrophic potential of risk
    - Degree of personal control over risk
    - Familiarity with the risk
    - Degree of perceived equality in sharing risk and benefit
    - Visibility of the benefit of taking the risk
    - Potential to impose blame on risk creator
    - Delay in the manifestations of harm
- **Cultural**
  - Risk acceptance varies according to cultural biases
  - Risk can be attenuated or intensified through social interactions, which have further secondary consequences

Risk-based approach

- Two levels:

Overall Framework

- Must be transparent and easy to understand and apply
- Each category associated with a specific set of regulatory requirements proportionate to risk

Trial-specific

- Tailored approach to manage risks of specific trial still required

Central elements of a regulatory framework

- Regulator defines the objectives of the regulation
- Regulator identifies the uncertainties/risk that the regulated organization may have in achieving objectives
- Regulator develops a system for evaluating risks (probability of harm)
- The allocation of resources to manage uncertainty/risk is depend on degree of risk

Trial-specific uncertainties/risks

Investigational drug	• Safety profile of drug • Need risk mitigation measures and Pharmacovigilance Plan
Protocol	• Trial design, population, mandated procedures, etc. • Need risk mitigation measures
Trial conduct	• SOPs, training, etc. • Need monitoring plan, quality assurance, follow ICH E6

OECD FRAMEWORK FOR CLINICAL TRIAL REGULATION

OECD risk-based framework for clinical trials

- **Stratified approach** reflective of the marketing authorisation status of the medical product

- **Trial-specific approach** considers issues such as additional diagnostic procedures, specific populations concerned, or whether informed consent is still required

OECD stratified framework

- **Category A**
  - Authorised medicinal products tested in accordance with their marketing authorisation
- **Category B**
  - Authorised medicinal products tested according to treatment regimens outside their marketing authorisation (in terms of population, condition, route of administration, formulation or dosage):
    1. Supported by published evidence or guidance or established medical practice
    2. Not supported by published evidence or guidance or established medical practice
- **Category C**
  - Clinical trials on medicinal products without any marketing authorisation

Examples of regulatory requirements that could vary according to category

- Labelling
- Record keeping
- Safety reporting
- Other?

Key takeaways for clinical trial modernization

- **Clinical trial modernization supports research and innovation** as a first step in developing new health products for Canadians.
- **Enabling more flexible, risk-based regulations could allow for more trials and greater representation of patients** in national and global trials.
    - e.g., greater alignment with international risk-based approaches and enabling novel clinical trial designs could increase treatment options and product access for consumers.
- **Consideration as to how the revised framework can reflect the evolving health product environment continues**, including learning from the COVID-19 experience and enabling broader patient participation.
    - e.g., use of virtual/decentralized clinical trials, where satellite sites are linked by technology to an established trial site.
- **Stakeholders have been and will continue to be engaged in progress on clinical trial modernization** at key stages, from development to implementation of a modern clinical trial framework.

Points for discussion

A. Do you agree with the use of the OECD approach?

- If so, how would you define “Supported by published evidence or guidance or established medical practice” in order to distinguish between category B1 and B2?
- If not, what would you propose instead?

B. Which regulatory requirements should be removed or relaxed in categories B1 and B2 and why?