PRACTIcE

Pediatric Routinely Administered Clinical Therapeutics In Everyday practice Trials: Regulatory Reform to Advance Evidence-Based Pediatric Care

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RareKids CAN | SickKids Child Health Policy Accelerator

Regulatory Reform to Advance Evidence-Based pediatric Care

Prepared by:

Lori Anderson
Regulatory Affairs Specialist, Maternal Infant Child and Youth Research Network

Gwendolyn Moncrieff-Gould, BA, MPM
Policy Lead, SickKids Child Health Policy Accelerator

Charlotte Moore Hepburn, MD, FRCPC, FAAP
Associate Professor, Department of pediatrics, University of Toronto Faculty Pediatrician, The Hospital for Sick Children Director, SickKids Child Health Policy Accelerator

Reviewed by

(in alphabetical order):

Jason Arsenault
Family Partner, RareKids-CAN: Pediatric Rare Disease Clinical Trials and Treatment Network

Lauren E. Kelly, PhD, MSc, BMedSci, CCRP
Associate Professor, Department of Pharmacology and Therapeutics, University of Manitoba Clinical Trials Director and Scientist, Children's Hospital Research Institute of Manitoba Clinical Trialist, George & Fay Yee Centre for Healthcare Innovation

Thierry Lacaze-Masmonteil, MD, PhD
Scientific Director, Maternal Infant Child Youth Research Network Clinical Professor, Department of Pediatrics, Cumming School of Medicine Child Health & Wellness Researcher, Alberta Children's Hospital Research Institute

Souvik Mitra, MD, MSc, PhD, FRCPC
Neonatologist, BC Women's Hospital Associate Professor of Pediatrics, University of British Columbia Research Director, Division of Neonatology, Michael Smith Health Research BC Chair, Fetus and Newborn Committee, Canadian pediatric Society

Georg M. Schmölzer, MD. PhD
Clinical Scientist and Professor, Department of Pediatrics, University of Alberta

Breanne Stewart
Network Director, RareKids-CAN: Pediatric Rare Disease Clinical Trials and Treatment Network
Network Director, Maternal Infant Child and Youth Research Network

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Endorsements

Regulatory Reform to Advance Evidence-Based pediatric Care

Executive Summary

Canadian children deserve access to the full benefits of modern medicine. Unfortunately, pediatric-specific regulatory barriers to clinical trials undermine Canada's pediatric clinical trial ecosystem and ultimately compromise health outcomes for our youngest citizens.

Challenges associated with pediatric epidemiology, limited funding, and deficiencies in drug labelling have left many routine therapies for children with critical gaps in evidence to guide everyday care. Sadly, outdated clinical trial regulations at Health Canada further hinder the generation of pediatric evidence, burdening the Canadian pediatric clinical trial community with unnecessary regulations and leaving this vulnerable population understudied.

With an aim to decrease costly, unproductive, and outdated regulations, expand domestic and international clinical trial opportunities, and attract top clinical trial talent, **Health Canada should immediately establish a full exemption pathway for low-risk pediatric clinical trials involving drugs routinely used in clinical practice.** This reform would eliminate financial and other administrative burdens on federally regulated clinical trials that do not benefit from federal oversight, aligning Canada with international regulatory best practice. Recognizing the robust safeguards already in place in pediatric research centres across Canada, this exemption would accelerate evidence generation while maintaining the highest standards of safety, quality, and transparency.

By implementing a risk-based regulatory framework—including a full exemption pathway for clinical trials evaluating drugs routinely used in clinical practice—Canada will join with global regulatory leaders by ensuring that federal oversight is proportionate to trial risk and complexity. This reform will expedite trial timelines, enhance trial feasibility, improve patient recruitment, and reduce costs, all while maintaining stringent safety standards. By streamlining regulatory policies, Canada will maximize the impact of federal health research funding, drive innovation, and deliver timely, evidence-based advancements in pediatric care.

Optimizing Clinical Care for Children:

Investigating evidence-based pediatric care practices without unnecessary regulatory burdens

Pediatric patients have long been considered "therapeutic orphans,"[1] a term used to highlight the lack of clinical studies investigating the safety, dosing, and efficacy of drugs used in children. Bourgeois et al. examined drug trials for conditions with a high pediatric prevalence (e.g., asthma) and reported that, although almost 60% of people affected were children, only 12% of the studies focused on pediatric patients.[2] Similarly, Groff et al. examined the publication of randomized controlled clinical trials in high-impact medical journals, and noted that 67% enrolled exclusively adults, while only 14% enrolled exclusively pediatric patients.[3] This lack of rigorously generated, high-quality pediatric clinical trial data compromises the care and outcomes of children and youth with a variety of both common and less common medical conditions.

In addition to being "therapeutic orphans," Canada's pediatric population has also been subject to significant, longstanding regulatory neglect. By failing to mandate the submission of pediatric data in all New Drug Submissions—a globally recognized regulatory best practice[4,5]—Health Canada routinely reviews and approves medications without assessing their use in children and youth.[6] This structural shortcoming has resulted in Canada having one of the highest rates of "off-label" prescribing for children among comparable jurisdictions,[7,8] with certain sub-populations, including preterm infants, neonates, and those with critical illness or mental illness, particularly affected.

Off-label drug use refers to the use of a medication for an indication (i.e., reason for clinical use), population, route of administration, or dosage not specified in the Health Canada-approved product monograph. In clinical practice, drugs may be used off label at the discretion of the treating physician. While risks do exist when providing off-label care,[9] and efforts to improve pediatric drug labelling remain vital to optimizing child and youth health outcomes, it important to recognize that off-label care is often evidence based.[10] Many off-label care practices are supported by longstanding clinical practice, robust comparative and non-comparative research, as well as consensus-based expert opinions.[11] This is especially true in pediatrics. In fact, with studies confirming that up to 80% of all medications currently prescribed in Canadian pediatric hospitals are for off-label uses,[12] it is fair to characterize off-label care as a mainstay of pediatric practice.

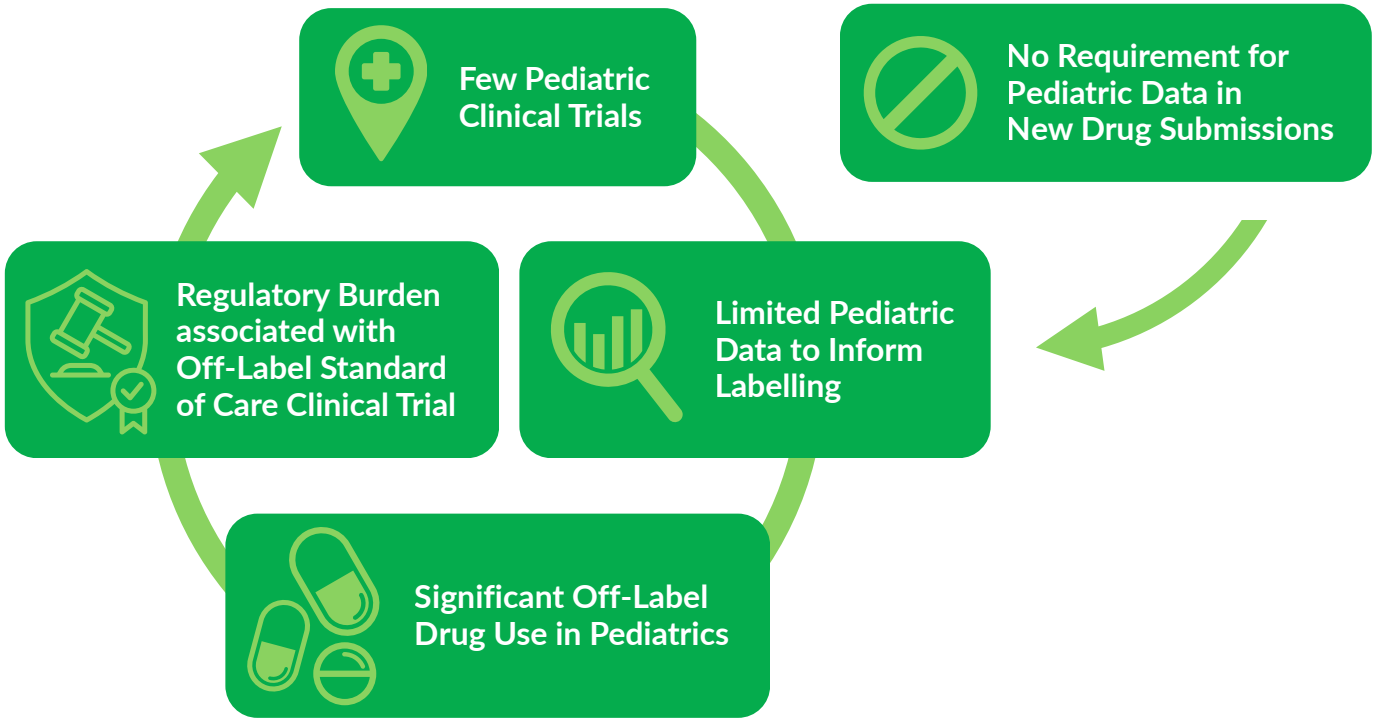
Unfortunately, Health Canada classifies any off-label drug use in a clinical trial as "investigational," regardless of the strength and durability of the evidence supporting its use. More specifically, under the Food and Drugs Act[13] and the Food and Drug Regulations,[14] clinical trial sponsors must submit a Clinical Trial Application (CTA) to Health Canada for any trial involving a marketed drug used outside of the approved labelling.[15] Once approved, these trials remain under Health Canada's regulatory oversight for their entire duration.

Optimizing Clinical Care for Children:

Unlike regulatory agencies in other jurisdictions, Health Canada provides no exemption pathway for clinical trials investigating the off-label use of drugs routinely used in practice—even when supported by extensive experience and robust clinical data. This rigid one-size-fits-all approach delays trial initiation while increasing the financial and administrative burdens associated with running a clinical trial. In fact, a recent survey of Canadian pediatric research institutes found that regulatory compliance costs for federally regulated clinical trials average 20% of the total trial budget,[16] with some trials exceeding that figure significantly. Moreover, many trials are abandoned entirely when investigators are faced with the overwhelming regulatory requirements. These challenges discourage early-career researchers from launching clinical trials in Canada, deter experienced clinician investigators and scientists from conducting trials in Canada, and reduce international interest in engaging with Canadian sites. In 2010, 6% of all global clinical trials included Canadian sites; by 2022, that figure had dropped to just 3%.[17]

These cumbersome regulatory requirements not only impede efforts to optimize routine pediatric care but also threaten the broader viability of Canada's pediatric clinical trial ecosystem. Moreover, they undermine Canada's ability to recruit, train, and retain skilled pediatric researchers, attract international talent, strengthen national scientific communities, and ultimately deliver high-quality, evidence-based care to children.

Figure 1. Challenges associated with Canada's pediatric trial ecosystem



Optimizing Clinical Care for Children:

"Requiring a Health Canada–regulated clinical trial for a routinely used pediatric drug administered off-label places a substantial burden on academic investigators. Increased regulatory requirements demand additional time, funding, and specialized expertise throughout the trial duration, further straining researchers and institutions already working with limited resources. Over the years, I've witnessed many researchers become discouraged and ultimately abandon their trials, which only widens the gap in the generation of high-quality pediatric evidence."

- Regulatory Consultant

Protecting participants through institutional best practices

While Health Canada plays a vital role in regulating clinical trials investigating novel therapies and novel applications of standard therapies, it is important to recognize that Canada's research and clinical institutions have robust, well-established mechanisms to optimize safety and ensure adherence to scientific, ethical, and operational best practice across all trials. These longstanding safeguards ensure the safety of participants, the integrity of trial data, and compliance with ethical and other standards for both federally regulated clinical trials adhering to Division 5 of the Food and Drug Regulations,[18] and those not requiring Health Canada oversight. These safeguards include those listed in Table 1.

Table 1. Clinical trial safeguards

Guiding principles for study conduct	• Nuremburg Code[19] • Declaration of Helsinki[20] • International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH-GCP)[21]
Research ethics boards (REBs)	• Provide study approval and oversight throughout the trial • Ensure ethical conduct and compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)[22] • Require informed consent to be obtained from participants before and throughout the duration of the trial • Ensure study risks are clearly communicated to participants • Maintain authority to audit trials to ensure adherence to ethical standards and accepted research practices
Scientific protocol reviews	• Conducted to ensure that trials have scientific validity and will generate meaningful outcomes, and to foster public trust in research • Shared responsibility by multiple stakeholders, including REBs, institutional/departmental scientific committees, as well as funding agencies and peer review panels (e.g., Canadian Institutes of Health Research, private foundations/endowments)

Clinical trial oversight committees	• Steering committees
	  ◦ Oversee study progress
	  ◦ Ensure alignment with study objectives and scientific rigor
	• Data safety monitoring boards (DSMBs)
	  ◦ Regularly review and evaluate study data to assess participant safety and study progress
	  ◦ Make recommendations regarding the continuation, adaptation, or termination of a trial

Safety reporting and oversight requirements of investigators	• Maintain documentation of all adverse events, assessing for severity, expectedness, and causality • Report all adverse events to the REB, the DSMB (if applicable), and/or trial steering committee in accordance with established standard operating procedures (SOPs) and institutional policies
Examples of additional institutional safeguards	• Institutional SOPs (e.g., record-keeping, auditing and monitoring, storage, and handling of investigational product) • Site-specific operational approvals • Site-specific requirements for legal agreement(s) • Trial registration in an approved registry • Local, provincial, and federal data privacy and security regulations • TCPS 2, ICH-GCP, privacy and security training for investigators and research staff

These well-established oversight systems provide comprehensive safeguards to ensure participant safety, data integrity, and compliance with ethical and other care standards. In the context of low-risk pediatric clinical trials involving drugs routinely used in clinical care, these mechanisms effectively fulfill the majority of the core objectives of trial oversight as outlined in Division 5 of the Food and Drug Regulations.

Moreover, the strict Division 5 requirements that govern trial conduct post-authorization, including investigational product labelling, record keeping, validated data systems, and federal reporting, also largely duplicate existing institutional systems. These added administrative burdens do not enhance patient safety or trial integrity, particularly when the drugs under study are already in routine clinical use.

Regulatory Reform to Advance Evidence-Based pediatric Care

The strengths and limitations of the Investigational Status Assessment pathway

In an effort to reduce a portion of the regulatory burden associated with clinical trials, Health Canada introduced the Investigational Status Assessment (ISA) pathway[23] in 2019. The ISA pathway allows CTA applicants to request that an off-label drug used in a clinical trial be classified as "non-investigational." To qualify, applicants must justify how the use of the drug in the study population aligns with Canadian "best medical practices" and poses "low risk" to the study participants. If Health Canada accepts the justification, labelling and record keeping regulatory obligations are waived for that specific drug(s); however, the broader regulatory requirements under Division 5 of the *Food and Drug Regulations* continue to apply to the study as a whole.[8,14]

While the ISA pathway offers some regulatory relief in select trial settings, it does not allow for a full exemption from Health Canada's oversight. Under current requirements, at least one drug in a trial must be designated as investigational—even if all drugs under study would independently qualify for ISA consideration. This requirement applies even when only a single off-label drug routinely used in clinical practice is being investigated. In multi-drug trials where each drug would otherwise independently meet ISA criteria, researchers are instructed to arbitrarily select one drug to list as the investigational product in the CTA submission. As a result, the full suite of post-authorization regulatory obligations remains in place, even for drugs that Health Canada itself would otherwise consider low-risk and non-investigational. This undermines the intent of the ISA pathway and highlights the rigidity of the current regulatory framework.

The ISA pathway reflects Health Canada's recognition that off-label drugs routinely used in clinical practice, when supported by evidence and clinical consensus, are "low risk." By adjudicating and approving these uses as "non-investigational" within the ISA framework, Health Canada has acknowledged that trials employing such drugs do not warrant the same level of regulatory scrutiny as those involving novel or high-risk interventions. This important precedent lays the foundation for a complete exemption pathway. Building on the ISA, Health Canada is well positioned to implement a more coherent, risk-based approach that fully exempts low-risk trials involving drugs already in routine clinical use. This exemption would strengthen Canada's alignment with international best practices while upholding patient safety and scientific integrity.

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Cross-Jurisdictional Scan/Best Practices

The Food and Drug Administration (FDA) in the United States, the Therapeutic Goods Administration (TGA) in Australia, and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom are examples of regulators that have implemented significant risk-based reductions and/or full exemption pathways for clinical trials involving the use of off-label medicines routinely used in clinical practice. Many of these regulatory pathways have been in place for decades, allowing pediatric clinical trial ecosystems to flourish in these countries. While each model possesses slight differences, all are designed to limit the time and cost associated with regulatory oversight, while simultaneously maintaining the integrity and safety of patients participating in clinical trials.

United States

The FDA allows full regulatory Investigational New Drug submission exemptions for trials involving modifications to product dosage, population, or formulation—so long as these changes do not increase risk to the participant beyond that outlined in the approved labelling.

Specifically, a clinical trial investigating off-label use of a marketed drug is exempt from Investigational New Drug requirements if the following apply to the trial:

a. the study does not involve a route of administration, dosage level, patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug;
b. the study is not intended to support a new indication or any other significant labelling change;
c. the study is not intended to support a significant change in advertising;
d. the study has complied with the requirements of an institutional review board,[24] including the requirement for informed consent;[25] and
e. the study adheres to the requirements of 21CFR312.7[26] regarding the promotion and sale of investigational drugs.

Implemented in the 1980s,[27] this pathway has demonstrated no harm to the United States population over several decades. Sponsors determine whether a trial qualifies for an exemption, with the option to consult the FDA if uncertain. If an institutional review board disputes a trial's eligibility, the FDA provides a final decision.

Australia

The TGA offers two regulatory pathways for clinical trials involving the off-label use of marketed health products: the Clinical Trial Notification scheme and the Clinical Trial Approval scheme.[28]

The Clinical Trial Notification scheme is generally limited to clinical trials involving drugs considered to be low to moderate risk. Prior to applying under this scheme, a human research ethics committee (HREC) must first assess the scientific validity, risk-benefit balance, and ethical acceptability of the trial. If approved by the HREC, the study sponsor is responsible for notifying the TGA of the study plans. The TGA does not review or evaluate data related to the clinical trial but may request information, as necessary, to ensure requirements of the scheme are met. If the submission requirements are satisfied, the exemption comes into effect, allowing the sponsor to supply drugs for the study under the HREC approval and any applicable institutional requirements.

Sponsors must follow the Clinical Trial Approval scheme for trials involving novel or any higher-risk products (e.g., those with limited safety data). This pathway involves TGA evaluation of preliminary scientific data following receipt of a formal application. The TGA review is focused on the safety and quality of the unapproved therapeutic good, while the HREC reviews the scientific and ethical aspects of the trial. Both bodies must provide approval prior to trial initiation.

The decision as to whether a Clinical Trial Notification or Clinical Trial Approval is required is the responsibility of the trial sponsor.

United Kingdom

The MHRA provides for a risk-based approach to the initiation, management, and monitoring of certain clinical trials.[29] Through a sponsor-driven risk-assessment,[30] the potential risks associated with the investigational medical product are considered, and assignment into one of three risk categories is made: category A (no higher than that of standard medical care), category B (somewhat higher than that of standard medical care), or category C (markedly higher than that of standard medical care).

The MHRA may allow risk adaptations for category A trials involving products licensed in any European Union member state if:

- the trial involves the licensed indications, dosage, and formulation of the product, or;
- the trial involves off-label use (such as in pediatrics and oncology) that is established practice and is supported by published evidence and/or guidelines.

These adaptations may include modifications to the MHRA's approval role ("notification" versus "approval"), content required in the regulatory application, investigational medical product labelling and management, safety surveillance, documentation and record keeping, and good clinical practice inspections.[29]

Case Studies

This series of case studies illustrates the disconnect between the real-world use of commonly prescribed therapies and the disproportionate regulatory burden placed on researchers seeking to formally evaluate these treatments in pediatric populations. Each case describes a recent trial subjected to Health Canada's full regulatory requirements. Taken together, these examples underscore how Canada's current approach may inadvertently discourage investigator-initiated research, delay evidence generation, inflate trial costs, and ultimately limit progress toward safe and effective pediatric drug use.

Case 1: "HiLo" trial on oxygen concentration to improve neurodevelopmental outcomes in preterm infants (NCT03825835)

Oxygen is an essential drug for preterm babies whose lungs are underdeveloped at the time of birth. While widely endorsed by national[31] and international practice guidelines,[32] the optimal oxygen concentration for resuscitation remains unclear.[33] The international HiLo trial aims to fill this knowledge gap by comparing the effects of a low (30%) versus high (60%) oxygen concentration. Importantly, both 60% and 30% concentrations of oxygen are within the parameters of current practice.

Health Canada's position: Despite robust evidence supporting safety and efficacy, as well as extensive clinical experience with oxygen in the study age group, Health Canada's approved product labelling does not support its use in this protocol. The trial must be regulated by Health Canada.
Positions of comparable regulators: A concurrent trial investigating the same research question in Australia was exempt from oversight by the TGA.

Case Studies

Case 2: Acetaminophen and ibuprofen for patent ductus arteriosus closure (NCT05011149)

A patent ductus arteriosus (PDA), an open connection between two blood vessels leading from the heart, is a common cardiac condition experienced by preterm newborns. The use of ibuprofen and acetaminophen to close a PDA is standard pharmacological practice in neonatal intensive care units across North America. While clinical practice guidelines support the safety and efficacy of these medications in this population for this purpose,[34] variation in the timing of therapy exists. This trial was designed to determine the optimal therapeutic window (early versus delayed) when prescribing these medications for this condition.

Health Canada's position: The trial must be regulated by Health Canada, with either ibuprofen or acetaminophen designated as the investigational product. Given the available safety and efficacy data supporting use in this population, both drugs would be eligible for the ISA pathway; the assignment was left to the investigator in terms of which drug to choose. No pathway allowed both drugs to be considered non-investigational, despite justification being possible for each.

Positions of comparable regulators: This trial included sites in both Canada and the United States. No FDA oversight was required for clinical trial sites in the United States as this trial qualified for an Investigational New Drug exemption.[35]

Case Studies

Case 3: Hypertonic nebulized saline (salt water) in bronchiolitis

Bronchiolitis is a common lung infection in children that is primarily caused by the respiratory syncytial virus. Despite existing treatment protocols, infants with bronchiolitis often experience severe respiratory distress and prolonged hospital stays. This trial was designed to evaluate the effectiveness of nebulized hypertonic saline[36] (3% salt water) as compared to normal saline (0.9% salt water) on hospital length of stay and clinical outcomes in infants with bronchiolitis. Despite longstanding evidence of safety and efficacy, as well as extensive clinical experience in the study age group, the indications for use were outside of labelling parameters.

Health Canada's position: The proposed use of the study drugs is off label. The trial must be Health Canada regulated.

The early-career investigator trial lead ultimately abandoned the research due to the regulatory burden and associated costs.

"I came to Canada with my family to further advance my training. I am establishing myself as an applied researcher was excited to launch my first clinical trial. When I heard that my trial was going to be regulated, I had to cancel it. The funding I had wasn't going to be enough. It's made it hard to gain the experience I need."

- Early Career Researcher

Unleashing the Potential of Canada's Pediatric Clinical Trial Ecosystem

Policy recommendations for Health Canada

To enhance access to high-quality, evidence-based care for children, develop and retain scientific talent, attract international pediatric clinical trials, and reduce unnecessary, costly, and cumbersome regulatory requirements, Health Canada should immediately develop and implement a full regulatory exemption pathway for pediatric clinical trials investigating off-label therapies routinely used in pediatric clinical practice.

Eligibility criteria for exemption

To ensure the highest standards of safety, scientific integrity, and transparency, a full exemption pathway should be based on fulfillment of the following criteria:

- Therapeutic criteria: The drugs under investigation must be routinely used in pediatric clinical care and be known to be both safe and effective in the intended study population.
- Evidence criteria: The indication, intended population, dose, and route of administration for the study drug(s) must be supported by evidence equivalent to that required to qualify for the ISA pathway.[23] Acceptable sources include the following:
  - Canadian and/or international medical organization guidelines, federal and/or provincial government consensus treatment guidelines, health technology assessment reports, Cochrane reviews, or a systematic review of the existing literature based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest of the authors; and/or
  - Information confirming that the drug has been used in the population under study for a sufficient period of time and has an established safety profile in the population under study.
- Ethics and consent criteria: The trial must be approved by an REB and include appropriate informed consent of the participants (or surrogate decision-makers).
- Trial intent criteria: The trial must not be intended to generate data in support of a labelling change, or for promotional, advertising, or marketing-related purposes.

Trials that do not meet these criteria should continue to follow the standard CTA pathway.

Unleashing the Potential of Canada's Pediatric Clinical Trial Ecosystem

Oversight and implementation

Recognizing the valuable role Health Canada plays in clinical trial oversight, Health Canada should adjudicate the appropriateness of each clinical trial seeking regulatory exemption. A study proposal, along with justification and supporting evidence, should be provided to ensure transparency and allow appropriate adjudication of the study to ensure the above criteria are met.

As this pathway is intended to address, in part, longstanding pediatric-specific regulatory deficiencies related to drug labelling, to preserve the integrity of this pathway:

- Only investigator-initiated trials—sponsored by academic institutions or investigators—should be eligible.
- This pathway should be made available for the recruitment and enrollment of patients up to their 18th birthday.
- Trials approved under this exemption must retain oversight through established institutional mechanisms, including REBs, DSMBs, and scientific steering committees, as appropriate.

> "The application appears to still be in process, and we doubt it will be fully reviewed in time for us to meaningfully launch our study activities. As a consequence, we won't be enrolling subjects or conducting any testing in Canada. Our team's key takeaway from this project is that approval process with Health Canada need to commence significantly earlier than we're accustomed to in the US and Europe."
>
> - Clinical Trial Sponsor

Unleashing the Potential of Canada's Pediatric Clinical Trial Ecosystem

Conclusion

Implementing a full exemption pathway for low-risk pediatric clinical trials is a critical step toward unlocking Canada's potential as a global leader in pediatric research. By reducing unnecessary regulatory burdens while maintaining rigorous safety and ethical standards, Health Canada can foster innovation, improve health outcomes for children, and strengthen Canada's position in the international clinical research community. Swift action will ensure that Canadian children benefit from advances in medical science without delay.

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