CCCTG
Canadian Critical Care Trials Group

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Response to Health Canada's Clinical Trials Regulatory Modernization Initiative

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Background / Who We Are

The Canadian Critical Care Trials Group is a long-standing collaborative research network focused on acute care and critical care trials. We have:

- 32 years of successful research excellence and knowledge translation (since 1989).
- 350 members across the country including clinicians, scientists, allied health professionals, research coordinators, trainees, patient and family partners.
- Been at the forefront of pandemic-related research since Canada's 2003 SARS experience.
- Collaborated internationally with critical care consortia to complete large-scale generalizable randomized controlled trials.
- Championed scalable, context-responsive research approaches, including the parallel evaluation of multiple therapies using adaptive platform clinical trials into which we have now incorporated COVID-19 pandemic-relevant treatment arms and enrolled COVID-19 infected patients in Canada around the world.
- Already enrolled **>6000 patients** with COVID-19 in trials and studies across Canada and **>20,000 patients** in other countries through international partnerships.
- Generated **>350 peer-reviewed publications** that have helped to change clinical practice and improve the care of patients with critical illness including COVID-19.

In January 2021, Dr. Robert Fowler as the nominated PI representing the CCCTG was awarded $6 million from CIHR to create the **COVID-19 Network of Clinical Trials Networks**.

Response to the Consultation

First, we applaud the speed and agility with which Health Canada has responded to the COVID-19 pandemic. We support the directions taken with the Interim Orders, and Health Canada's stated intention with this consultation to implement those key directions more broadly for clinical trials.

We strongly support Health Canada's intention and efforts to modernize the regulatory framework for clinical trials in Canada.

We believe there is an opportunity for Canada to build robust capacity to support ongoing clinical trials research in a more efficient and effective way. **Integrating research into clinical care, targeting health research investments and reducing duplication, start-up time and costs will create the "health emergency readiness" needed for rapid responses in the future.**

Approaches like the Network of Networks can create capacity for rapid, efficient trials, enabling research infrastructure and programs of research that are flexible, can pivot, and facilitate trials in diverse sites and hospitals with existing research ethics, data sharing and contracts. This will provide the foundation for a long-term approach that will not only ensure pandemic readiness but will make Canada a leader globally in clinical trials research.

Success will require that the infrastructure, research expertise, and innovative research design all promote a culture of integrating research into routine clinical care. And it must be enabled by a supportive policy, funding and regulatory environment that recognizes the fundamental importance of randomized trials in improving the outcomes of patients.

Some of these issues are beyond the scope of the current consultation, but are nonetheless relevant and should be addressed in a broader modernization process.

This consultation is focused on health products. We strongly support the approach of this proposal "as the foundation for the new regulatory regime that would provide proportional risk-based oversight, new regulatory agilities over the lifecycle of the trial, greater transparency through registration and public disclosure of results, and a modernized compliance and enforcement regime" for health products.

As clinicians and researchers, we feel that a similar approach to creating a single clinical trials framework for acute care and critical care trials is a tremendous opportunity for Canada to maintain its reputation as a leader in international clinical trials research.

We recommend that Health Canada commit to applying the innovative and progressive concepts proposed to clinical trials more broadly. Below, we describe some particular recommendations to support that.

Canada endorsed the G7 Health Ministers' Declaration, Oxford, 4 June 2021 that endorsed the G7 Therapeutics and Vaccines Clinical Trials Charter. The commitment in the Charter to "work with G7 regulators, ethics institutions and committees to achieve greater harmonisation and to streamline regulatory process to act more proportionately to risk" supports our recommendations below, and should drive Health Canada's modernization effort.

We would welcome the opportunity to work closely with Health Canada to advance these important directions.

Comments on Health Canada's Key Proposals for Consideration

1. **Agile Life Cycle Approach**

We **strongly support** the ability by Health Canada to better regulate new types of innovative trial designs such as those studying multiple therapies within a single clinical trial (i.e., master protocols) and novel adaptive trial designs which allow for planned changes to the study protocol to occur at pre-specified times during the life cycle of a trial (i.e. adaptive trials). Proposed modifications that allow for suspending only an arm of a trial, a site, study enrolment, or the use of a particular product, not a whole platform trial **are welcome**. We note that innovative trial methods currently in practice go beyond platform and adaptive trials, to include cluster designs, which should also be considered in Health Canada's approach. A standardized approach to innovative trials will be important as various components are integrated and suspended, and ensuring that ethics boards and Health Canada are aligned in their processes to ensure efficiency will be crucial. An expedited review for previously approved trials that are brought onto a platform trial would also align with these principles.

2. Proposed **Risk Based Approach**

We **strongly support** using a common risk-based approach for trials involving any type of health product with proportional oversight based on the level of risk to study participants.

The introduction of Decentralized Clinical Trials (DCT) allowing the potential for patients residing in a remote rural location to be enrolled in a clinical trial that is being overseen centrally from a major urban center, allowing for a more patient-centered approach to trials **is excellent**, and changing the wording of the requirements in the regulations from "written informed consent" to "documented informed consent" **is welcome**.

We note that the proposed risk categorization is focused on the product or drug being tested. As researchers with a particular focus on critical care, we would encourage a focus on incremental risk to the patient, and caution that the classification of "low risk to study participants" *not exclude* research involving critically ill patients, particularly given the importance of ensuring that these vulnerable patients can participate in clinical trials.

The requirement for a single QI at each site should be clarified to ensure that one individual may be the QI responsible for a number of trial sites over which they have jurisdiction, either across a health authority or common ethics review.

The proposed risk-based approach to allow greater flexibility for the types of health professionals that can be a Qualified Investigator is a very important direction. The consultation paper states that "the type of qualification required for the Qualified Investigator would be determined on a case-by-case basis through the review of a trial protocol at the approval stage and/or by the REB prior to the start of the trial, or alternatively be defined in regulation." We note that in Annex 2, Health Canada is "also assessing the ability to apply several concepts introduced through the CT-IOs more broadly, such as enabling alternate means of obtaining informed consent, and enabling a broader range of health care professionals who are permitted conduct a trial." Such an approach, designating health professionals that can be QIs is preferable to the case-by-case approach and more aligned with international practice.

3. **Transparency**, particularly public registry, and public reporting of results.

We would emphasize the importance of transparency in the conduct of clinical trials in Canada. This would include publicly available trial tracking activities, such as participating sites, trial recruitment, and updated information on results reporting during trial conduct. Additionally, we would emphasize the need for transparent tracking of important equity-based metrics for research participation to ensure that results are relevant for all Canadians, with stated goals during trial registration and mandatory reporting at time of results.

4. **Modernization of Compliance and Enforcement** including implementing a cyclical risk-based inspection approach

Having participated in numerous site-based audits, we acknowledge the complexity and burden this imposes on already busy hospitals. Taking a sponsor-focused approach is laudable.

Responses to some of the questions posed by the Consultation

[**survey Q5**] Based on your experience and knowledge, **would the proposals in the Consultation Paper meet Health Canada's goal of enabling innovative clinical trials in Canada**?

The key proposals are certainly welcome and an excellent advancement toward innovative clinical trials. Our submission outlines a number of specific recommendations to further apply the new policy direction that Health Canada has outlined.

[**survey Q6**] **Are there innovations or other future considerations that Health Canada should account for when modernizing the clinical trials framework?**

- Modified Consent: Decentralized Clinical Trials (DCT) and the proposed change to the wording of the requirements in the regulations from "written informed consent" to "documented informed consent" will lead to flexibility in consent language and timing. Health Canada should consider extending this to allowing for potential deferred and/or waived consent.

- Harmonization: Innovative trials often incorporate novel designs, including Bayesian statistics and response-adaptive randomization. Other jurisdictions globally are beginning to incorporate these processes in their clinical trial authorization and subsequent regulatory approval processes. Clear language from Health Canada to help guide clinical trial design as to minimum standards for quality of these innovative designs would be useful and should be harmonized with other regulators (i.e. the FDA or EMA, who have put out language in this respect).

- We also note, and strongly support the proposal to “allow for the **single authorization** of a clinical trial involving multiple health products from different categories, such as drugs, NHPs, and medical devices.” We agree that this will “significantly increase efficiencies for the application, amendment, and authorization processes for clinical trials involving multiple health

products" and in fact will be critical to clinical trials that may need to examine a drug and device intervention (for example).

[**survey Q7**] Are there **other factors Health Canada should consider** when implementing this proposal to **streamline regulatory requirements** across product lines to better enable a single authorization?

- Although possibly outside of jurisdiction, the need for a centralized REB process for multi-centre clinical trials, particularly for innovative and platform trial approaches, cannot be overstated. There are significant inconsistencies across ethics boards in requirements and language leading to long delays in starting, modifying and completing potentially practice changing trials.

[**survey Q8**] Are there factors Health Canada should take into consideration in the implementation of a **risk-based approach**?

- The proposed risk-based approach to regulatory requirements for the off-label use of marketed drugs in a clinical trial when these drugs are not the subject of the investigation in the trial is welcome. Drugs used in clinical trials that have been used in clinical practice with a long tradition of safety currently require onerous, local site-specific control that could be streamlined or ideally exempted from regulation. An opportunity for early and direct engagement by investigators with HC officials early in the research approvals process would also streamline this process.

- Specifically, we recommend the definition of studies under proposed "Category A" include some marketed products tested outside of their approved indication. Approval labels for many products used in routine clinical care are very narrowly defined, and there is a need for further study of repurposed medications in clinical care. Discretion to apply 'Category A' classifications which would be exempt from authorization should be allowed upon a standardized consultation with Health Canada. Many medications used in critical care, our area of specialty, are not formally approved for their currently used indications and would therefore fall under Class B for study. We recommend a 'typical clinical care' approach whereby a study would be classified Category A unless there is a deviation from standard care, and CCCTG would be pleased to help inform that 'typical clinical care' adjudication process

- Other components of using risk-based approach is in the current onerous requirement for Good Clinical Practice (GCP) Training for all individuals involved in Class A or Class B clinical trials, specifically as it relates to clinical staff who care for patients and deliver research interventions. Other jurisdictions have taken the approach that good clinical care is equivalent to GCP, abrogating the need for formal GCP training for clinical staff and mandating it only for qualified investigators, and we would support that approach.

- Incorporated into a risk-based approach is the option of alternate consent models for studies, including the possibility of integrated or waived consent, for studies that fall into 'Category B'. Currently, no language in Part C, Division 5 of the Food and Drug Regulations allows for this, and from our experience, incorporating risk-based approaches to clinical trial implementation that include modifications to traditional consent models, should be an option for future trials, according to TCPS guidance.

- Further, drugs that are well established for use in Pediatrics often do not specifically list children as an approved population in their product monograph. Thus, they must be treated as investigational drugs requiring application to Health Canada (an insurmountable challenge for some sites resulting in even less health product research being conducted in children). Similar to above, drugs that are an established part of typical clinical care and that have an established safety profile in pediatrics should be considered "lower-risk" and require less oversight, shifting towards Category A on a case-by-case basis through a standardized adjudication process. Emphasizing 'standard use and risk', rather than 'current label' as the determinant between Category A and Category B will enhance clinical trial conduct, particularly innovative pragmatic trial approaches in Canada in children.

[**survey Q9**] **Are there other areas where burden can be reduced that will better enable your organization to conduct clinical trials without compromising patient safety?**

- Labeling requirements for Category B trials, where products must be relabeled, bilingually, are burdensome and do not protect patients in appreciable ways. While the changes in the CT-IO are laudable, they likely do not go far enough in the requirements for re-labeling for Category B proposed trials.

- **As a stated goal of the G7 communique is to further embed randomization into clinical care, and there are similar goals about achieving equity in research across the health system**, the lack of research pharmacies in community hospitals to satisfy Health Canada requirements is a significant impediment to achieving those goals. Along those lines, **we would recommend Category A and Category B trials do not require added clinical trial labelling, clinical trial-specific temperature monitoring, and clinical trial-specific activity logs, which would not compromise patient safety and, similarly, would expand the reach of regulated clinical trials across the Canadian health system.**

[survey Q10] **Are there areas where Health Canada could go further in modernizing the Canadian clinical trials regulatory framework beyond what is proposed in the consultation paper?**

- Regarding retention of data, we would like to raise a different aspect that has not been addressed in the consultation, but is relevant for the modifications to consenting requirements: the need to be able to retain data of patients where informed consent is not obtained when study recruitment is conducted under a deferred consent model (substitute decision makers provide consent to continue the study intervention). For example, retention of all study data of participants who pass away early after enrollment (even those without a consent) is proposed to be allowed. This was frequently the process during the COVID pandemic due to families being unable to visit, and consent not being obtained from the patient in deferred consent models and subsequently kept under ethically-approved processes.

Thank you for the opportunity to contribute.

Sincerely,

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