CCCTG
Canadian Critical Care Trials Group

Network of Clinical Trials Networks

01 October, 2021

To: secretariat@srcr-scrr.gc.ca

CC: Tammy Clifford, VP, Research Programs (tammy.clifford@cihr-irsc.gc.ca)
Sarah Viehbeck, Associate VP, Research Programs – Strategy (sarah.viehbeck@cihr-irsc.gc.ca)
Susan Zimmerman, Executive Director, SRCR (susan.zimmerman@srcr-scrr.gc.ca)

Re: Response to TCPS2 Consultation

Respondent information: Canadian Critical Care Trials Group (CCCTG) is a national, not-for-profit research organization. Its members conduct research and clinical trials with a critical care focus and are affiliated with universities and hospitals across the country. The signatories are submitting this response on behalf of the CCCTG, as members of the executive.

Background / Who We Are

The CCCTG is a long-standing collaborative research network focused on trials involving critically ill children and adults. We have:

- 32 years of research excellence and successful 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.
- Already enrolled **>6000 patients** with COVID-19 in trials and studies across Canada and **>20,000 patients** with COVID-19 in other countries through international partnerships.
- Generated **>350 peer-reviewed publications** that have changed clinical practice and improved the care of patients of all ages with critical illness including COVID-19.

In January 2021, Dr. Robert Fowler, as the Nominated Principal Investigator 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 Panel on Research Ethics (PRE) and the Secretariat on Responsible Conduct of Research (SRCR) for bringing forward new proposed guidance to inform broad consent and enable multi-site ethics approvals. This is a timely and important clarification that will help to expedite approvals for clinical trials without compromising patient safety.

We would welcome the opportunity to work closely with the Panel on Research Ethics (PRE) and the SRCR to advance these important directions.

Comments on Proposed Guidance Regarding Broad Consent for the Storage and Use of Data and Human Biological Materials

As clinicians and researchers, we agree with the direction to enable study PIs to seek broad consent for the "use of stored data and human biological materials for less or un- specified research that may be conducted in different and unspecified contexts, now or in the future."

It is crucial to ensure that Canadian broad consent guidance reflects evolving global principles and allows for consistency across jurisdictions. Specifically, this should allow for broad use of de-identified clinical trial data by other researchers for any purpose after its initial publication, as specified according to the International Council of Medical Journal Editors. We encourage the SRCR to include this in TCPS guidance, and endorse this as a standard requirement across clinical trial consenting documents in Canada.

The draft guidance does not address the practical challenge in which researchers are required to seek assent from minor children at the time of research and may be required (this is applied inconsistently by local REBs) to subsequently obtain actual consent to retain samples or data when the child reaches an age of majority. This is often impracticable, given the global data sharing principles outlined above; sometimes impossible, as study ID logs may be deleted once analysis is complete and data and samples are anonymized. TCPS guidance on these processes should be put in place so that standards are consistently applied. As experienced pediatric acute care trialists, we would be happy to engage in that process.

Comments on Proposed Revised Guidance for Ethics Review of Multijurisdictional Research

As clinicians and researchers, we strongly support and appreciate the direction of the guidance to require harmonized ethics review of multi-jurisdictional minimal risk research. We share the confidence as articulated "that a single, comprehensive ethics review of minimal risk studies should, in the vast majority of cases, be sufficient to provide the appropriate protection to participants."

The proposed new guidance makes clear that a single approval for multi-site ethics approvals will be mandatory for minimal risk studies. This is a good start. We note that the TCPS guidance applies only to "eligible institutions" (those eligible to receive tri-agency funding) although we understand it is the

practice of most REBs to apply TCPS principles and requirements to all reviews. In practice this will apply to virtually all institutions participating in investigator-led clinical trials.

The comments below reflect our strong belief in the need for a process in Canada that applies a **clear single approval process for all studies**, as well as our appreciation for the need for a step-wise process to get there.

Minimal risk studies

We strongly support the direction of mandatory single approval for minimal risk studies. We would encourage clarity in the definition of "minimal risk" as this currently is not consistently applied in the context of applications receiving delegated vs. full board review.

We appreciate and support the clarification of a process for allowing a REB of record to be the REB of an institution that is different from the PI's institution where appropriate.

We note that harmonized REB of record approval processes are already in place in a number of jurisdictions and work well. It is important for federal guidance to recognize this and clarify the role of provincial/territorial harmonized review processes. An explicit statement that an approval from a REB of record in one province must be accepted as the single approval for other provinces and territories (with the local acknowledgement processes as outlined) is a necessary clarification.

Lines 130 – 135 place the onus on the researcher for multiple submissions to the local REBs, including receiving decisions of local REBs and working with them individually if there are any changes to the study. The onus for coordination across REBs should be on the REBs (particularly the REB of record or regional or provincial REB organizations (e.g. CTO in the Ontario example) to collaborate across REBs in the region/province AND increasingly with similar REBs/organizations across the country. With multi-jurisdictional studies, the existing alternative is untenable for researchers to manage if we hope for more efficient and effective research ethics vetting for multi-jurisdictional studies and trials. Again, leveraging the presence in most jurisdictions of a harmonized review process will be important.

REBs are encouraged to communicate with each other regarding local issues that need to be considered – we recognize that this is often important in working out issues and coordinating reviews. This also supports the onus being on REBs to coordinate submissions, allowing them to effectively share information and focus on more substantive issues. Standardization of approaches among REBs across the country is needed, this would be a step in that direction.

We support the approach of an acknowledgement by local REBs, and the imposition of a short time limitation for response. However, we have some concern that the requirement for local REB acknowledgement may continue to unnecessarily delay approvals. Clarification and awareness regarding expectations for response, and when acknowledgement is required, will be important. In particular, we encourage SRCR to clarify that a lack of response within the 3-week timeframe will be deemed as acknowledgement. Guidance should clarify that local REB consideration and acknowledgment would ideally be done by a single individual (not the full board).

Also, SRCR is encouraged to clarify what will be accepted as constituting "local circumstances or substantive issues requiring further review." It is our expectation that these would be narrowly defined, outside of Indigenous or other rare considerations. A list of examples of "substantive issues" would be helpful.

We have some concern that the mandatory single approval will not be uniformly applied. It has been our experience that even when there is a stated intent for single approval (e.g. in harmonized provincial processes in Ontario and Quebec), this is not applied in practice, with local approvals sometimes requiring changes in study conduct. Again, it is important that PRE and SRCR proceed as articulated in making this guidance mandatory (at least for minimal risk studies for now) and that REBs across the country are quickly made aware of the requirement and supported in complying with it.

The expected process for REB of record approval and local REB acknowledgement should be clearly defined. Can a researcher start the study after the REB of record issues clearance? Also, making the REB of record responsible for communicating decisions to local REBs would streamline the process and alleviate a burden on researchers.

The "process for researchers to follow" section (at line 122) makes clear that the local REBs will receive the package submitted to the REB of record. This is very important – the current requirement to submit packages in different formats and with different information to different REBs is unnecessary.

The guidance is a good start. However, given the varied REB submission processes and provincial mechanisms for harmonization, explicit direction for how to harmonize across provincial and territorial jurisdictions is needed.

For multi-jurisdictional work, there is inconsistency regarding the collection of race/ethnicity-based data within clinical trials. As race/ethnicity-based data becomes increasingly important in the conduct of scientifically valid trials and mandated by medical journals (for example, NEJM is now requiring authors to report on representativeness of study population: https://www.nejm.org/doi/full/10.1056/NEJMe2114651), it is important that updated TCPS2 guidance contain very clear language on the importance of including this data so that REBs provide approval for the collection of sensitive data, and multi-jurisdictional research can report this data in a rigorous and consistent way.

More than minimal risk studies

The approach of a single REB of record should apply equally to more than minimal risk studies. Although the sensitivities and level of scrutiny will be greater, however with clear guidance (and a nationally coordinated process) this should be possible irrespective of the risk level.

We are pleased to see that the single REB of record approach for more than minimal risk studies is enabled by the guidance and would like to see this direction further encouraged. We would be pleased to work with our national clinical trial membership to pilot this and clarify the application to non-minimal risk studies with real world examples.

We appreciate that **investigator-initiated** multi-site clinical trials that are **truly multi-jurisdictional** (including international) are a small subset of the applications reviewed by most REBs and we feel they

need special attention – in particular to create a process that is robust enough to manage the need for expedited approvals in a national health crisis.

We see two potential ultimate solutions to implementing a coordinated single REB of record approach that is truly multi-jurisdictional:

1. A national REB: which would include a common harmonized process and electronic portal, with "opt in" by local institutions, modelled on the existing harmonized processes. This would be applicable only for eligible institutions and projects that have substantive involvement of institutions in more than one province/territory. This may only be feasible if applicable to a specific discipline. This REB would require a different mandate from the existing Health Canada/Public Health Agency of Canada REB (which is limited to studies that are conducted by those agencies, or for federally funded studies where there is no local REB).
2. A national harmonization process: which would allow coordination across provincial/territorial review processes and REBs where they exist (and support their creation where they do not exist). We note that in most cases under the current provincial harmonized processes a local REB is designated the REB of record. Local REBs would require designated support to undertake the REB of record role for multi-jurisdictional studies under a nationally harmonized process.

We would like to note that the administration of inter-institutional contracts is an issue that also needs to be addressed to facilitate multi-jurisdictional clinical trials. Negotiating and finalizing these contracts often takes even longer than the REB approvals, and generally can't begin until the REB approval is granted. We recognize this is out of scope for the current consultation.

Conclusion and next steps

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 global leader in clinical trials research.

The Canadian Critical Care Trials Group, and the COVID-19 Network of Clinical Trials Networks, would be happy to work with the PRE and SRCR to convene the many CCCTG members, partners and networks with an interest in these important directions to consider how best to implement – and expand upon – the revised guidance for the investigator-led clinical trials context.

Thank you for the opportunity to contribute.

Sincerely,

Dr. Rob Fowler, Chair
Canadian Critical Care Trials Group

Dr. Kusum Menon, Vice-Chair
Canadian Critical Care Trials Group

Dr. Srinivas Murthy
Lead, Regulatory & Ethics Working Group
Canadian Critical Care Trials Group

Brenda Lucas
Executive Director
Canadian Critical Care Trials Group