ETHICS REVIEW OF MULTIJURISDICTIONAL RESEARCH – PROPOSED REVISED GUIDANCE

PURPOSE

The Tri-Agency Panel on Research Ethics proposes policy guidance to require harmonized ethics review of multijurisdictional minimal risk research. The goal of this proposed guidance is to promote the expeditious review of research while maintaining appropriate protections for research participants. This guidance may also apply to research of more than minimal risk.

BACKGROUND

The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS) requires researchers and REBs "to navigate a sometimes difficult course between the two main goals of providing the necessary protection of participants and serving the legitimate requirements of research." (Chapter 1, Section B, Conclusion). Striking that balance presents a particular challenge where more than one eligible institution[1] or REB has a connection to the research.

The 1998 TCPS did not have detailed guidance on the review of multi-jurisdictional research. The 2010 version added a chapter explicitly permitting multiple models for the ethics review of research involving multiple sites/multiple REBs. Canada now has a number of successful initiatives at the disciplinary, provincial, or regional level that provide harmonized ethics review for multi-site research. Some established examples include models organized by jurisdiction (health research in Quebec, health research in Newfoundland and Labrador), by discipline (the Ontario Cancer Research Ethics Board, Clinical Trials Ontario, pediatric oncology clinical trials between the IWK Health Centre, and the Nova Scotia Health Authority, the Prince Edward Island health authority and parts of New Brunswick) or by region (a harmonization agreement among three western universities: University of British Columbia, University of Alberta, and University of Saskatchewan). Others are in the planning stages (for example, the CHEER project for pediatric research across the country.)[2]

Nevertheless, many institutions have not established, or do not participate in mechanisms for multi-jurisdictional ethics review. Instead, they review all research conducted under their auspices, even when they are not the host institution or the main site for the research. One factor undoubtedly contributing to this approach is the statement in the TCPS that "Each

[1] An "eligible institution" refers to an institution that is eligible to receive and administer funding from any or all of the Agencies (CIHR, NSERC, or SSHRC), in accordance with the *Agreement on the Administration of Grants and Awards by Research Institutions* https://www.ic.gc.ca/eic/site/063.nsf/eng/h_56B87BE5.html

[2] These streamlined models have primarily addressed multi-jurisdictional ethics review of health research. The goal of streamlining ethics review is *not* limited to any one discipline, nor is it limited to minimal risk research.

institution is accountable for the research carried out in its own jurisdiction or under its auspices." (Art. 6.1, Application). Another factor is likely the broad interpretation from the Tri-Agency Panel on Research Ethics and Secretariat on Responsible Conduct of Research of what constitutes research carried out within an institution's auspices and jurisdiction.

We are unaware of evidence that multiple ethics reviews provide commensurately greater protection for research participants. They do cause significant burdens and delays for researchers and for prospective participants. Many researchers believe that they may unnecessarily hinder the progress of research. This can certainly be true of minimal risk research, but may also be true of research involving more than minimal risk.

It has become clear that the added guidance in TCPS 2 has not been sufficient to increase the use of more harmonized approaches to ethics review. With the benefit of a decade of experience with TCPS 2, the Tri-Agency Panel on Research Ethics believes it is time to establish new guidance that mandates a departure from the model of multiple single-site reviews of multi-jurisdictional studies toward a model of single review for multiple sites, unless local circumstances merit additional scrutiny.

This guidance is proposed as mandatory only for minimal risk research at this stage, and optional for research that is greater than minimal risk. The examples of harmonized ethics review noted above are not limited to minimal risk research. We note however that these examples are the result of formal agreements which took time to negotiate. Similar effort may be required to extend harmonized ethics review to other models involving more than minimal risk.

GUIDANCE

What is the policy basis for a single review of multi-jurisdictional research?

All institutions eligible to administer Agency funds must comply with the TCPS. Consequently, all researchers based at eligible institutions must apply a common set of ethical principles to the design and conduct of their research. Similarly, all REBs must review research based on those same common ethics principles and guidance. The driving force behind this guidance is the principle of a proportionate approach to research ethics review (Chap.1, Sec. C): "[T]he intention is to ensure adequate protection of participants…while reducing unnecessary impediments to, and facilitating the progress of, ethical research."

A single review of minimal risk research should not compromise participant protection. Researchers are the first to consider participant protection as they design their research. That consideration must include how the research will affect participants at all contemplated sites. Review by a single REB affords a second opportunity for consideration of the ethical impact of the research on all participants, at all sites. The proposed guidance is based on confidence 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.

Through the Tri-Agency Framework: Responsible Conduct of Research (the RCR Framework), there is also a shared accountability mechanism for the responsible conduct of researchers, and the appropriate oversight of research by institutions. Taken together, the shared principles and shared accountability framework provide a sound basis on which institutions may accept the review of REBs at other eligible institutions.

What is the scope of this guidance?

This guidance is mandatory for all minimal risk research conducted under the auspices of multiple institutions. This includes:

- research conducted by researchers from more than one eligible institution;
- research conducted using the resources of more than one eligible institution;
- research involving researchers from one eligible institution and resources from another.

The expectation is that a single REB of record will conduct the ethics review. Its decision and reasons, along with the final study materials, would then be available to the REBs of all sites, for acknowledgment. Ideally, that consideration and acknowledgment would be done by a single individual at the local REB. This could be a member, or a research ethics administrator "with the appropriate experience, expertise and knowledge" (Art. 6.4, application)[3]. Both the researcher (research team) and the REB of record should have considered local circumstances (i.e. circumstances unique to the particular site, such as a specific participant demographic, language, culture not necessarily present at other sites) as part of the study design and the review, respectively. If the local REB identifies a missed local circumstance, or a substantive missed issue, these should be flagged to the REB of record for consideration. The intention is to keep the REB of record as the sole REB that can make changes to the terms of the ethics approval.

This guidance may also be extended to research that is more than minimal risk, in accordance with the policies of the local institution, or where mandated through a formal agreement or by law (see discussion in the final section).

Who is responsible for ethics review of minimal risk research involving multiple institutions?

The REB of record is the research ethics board with authority to conduct the review. The REB of record has the responsibility for continuing ethics review. The REB of record must be from an eligible institution. The starting premise is that the REB of the (lead) principal investigator (PI) is usually the REB of record. However, it is possible for another REB to serve as the REB of record – for example, the one with the greatest expertise in the research topic, the one at the site closest to recruitment for the research, or with some similar important connection to the study. If the researcher(s) believe(s) that the REB of record should be from an institution other than

[3] Research administration staff with these qualifications may be appointed as non-voting members of REBs.

that of the PI's institution, the onus would be on the PI to justify to their home REB why another REB would be better suited. They would also have to demonstrate that the other REB is willing to serve as the REB of record.

Normally, local REBs will acknowledge the decision of the REB of record. Exceptionally, a local REB may advise the REB of record to reconsider its decision in light of local circumstances or a substantive issue that had not been addressed. Examples of local circumstances that might warrant flagging to the REB of record for reconsideration:

- Issues that only affect a locally recruited population (e.g. language, culture);
- Issues imposed by unique characteristics of the local site (e.g. remoteness, limited access to needed resources to support local participants, issues specific to the local investigator);
- Statutory requirements (federal, provincial, or those of the country where the research is being conducted) that would have an impact on how the study was conducted;
- Substantial differences in access to services or standards of care normally followed at the local site.

Process for researchers and local REBs to follow

Researchers should provide involved institutions with the complete study documentation, along with evidence of the ethics approval from the REB of record, and the final version of the study application, as approved by that REB. The designated individual at the local REB should consider these documents and determine whether there are local circumstances or substantive issues requiring further review by the REB of record. If there are not, the local REB should acknowledge the ethics approval by the host institution's REB.

If there are local issues, or substantive issues, the local REB must flag them for the REB of record. REBs are encouraged to communicate among themselves, as this may be a way to resolve informally some of the issues that may arise during the process of multijurisdictional assessment. If local REBs do raise substantive issues, even if only for participants at their site, the REB of record must address those in consultation with the REB that raised them.

Timelines should be established by the REB of record for researchers to provide the necessary documents, and for local REBs to provide their acknowledgement. In general, local REBs should complete their process and issue a letter or notice of acknowledgment within three weeks of receiving the complete package from the researcher, including the decision of the REB of record.[4]

[4] This is a general guideline. Formal multi-jurisdictional mechanisms, for example in Quebec and other provinces, may have established different timelines.

Once the REB of record has completed its ethics review and made a decision, it is the researcher's responsibility to send that decision and associated final approved materials to the local REBs from all institutions involved in the research. When the local REBs have provided their acknowledgment, the researcher is responsible for sending the local acknowledgments to the REB of record. In addition, any further decisions by the REB of record during the course of the research must be communicated to the local REBs, and it is the responsibility of the researcher to do so.

No formal agreement between institutions is required to implement the process described above.

How does this guidance apply to ethics review for more than minimal risk research involving multiple institutions?

While this guidance is mandatory for minimal risk research, institutions may also apply it to more than minimal risk research. The same policy basis that applies to a single review of minimal risk multi-jurisdictional studies applies to studies of more than minimal risk. The same procedures described above could therefore also apply to more than minimal risk multi-jurisdictional research. A single REB of record would carry out the main ethics review, in general intended to be the only ethics review. In the case of research involving more than minimal risk, however, there is a greater likelihood that a missed issue could have a substantive impact on participant welfare. For this reason, there should be an opportunity for local review. One way to address this is to allow a designated period for local review, following receipt of the main review – perhaps four to six weeks.

In situations where all local REBs have not completed their review, the research may begin at the other sites, if appropriate in the context of the specific study (for example, if the inclusion of the site is not essential in order to respond to the study question). Research may not begin at a local site until review is complete at that site.

Researchers and REBs should consider whether there is a preponderance of similarities among the sites, rather than features requiring local review. In this regard, it is useful to look at the examples given earlier of the factors that justify local review:

- Issues that only affect a locally recruited population (e.g. language, culture);
- Issues imposed by unique characteristics of the local site (e.g. remoteness, limited access to needed resources to support local participants, issues specific to the local investigator);
- Statutory requirements (federal, provincial, or those of the country where the research is being conducted) that would have an impact on how the study was conducted;
- Substantial differences in access to services or standards of care normally followed at the local site.