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From: Renaud Boulanger (CUSM)
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To: secretariat (SRCR/SCRR)
Subject: RE: TCPS 2 CONSULTATION
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Attachments:
MUHC Centre for Applied Ethics - Response to Oct 2021 TCPS2 consultations.pdf

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To Whom It May Concern:

As discussed below, please find attached written comments from representatives of the Centre for Applied Ethics of the McGill University Health Centre and members of the institution's REB regarding the proposed revisions to the Tri-Council Policy Statement.

We hope the perspective we bring, that of a Québec-based hospital, will help enrich the ongoing reflection about single-site review of multicentre research, the use of broad consent as part of banking initiatives, and ethics review of cell line research.

Please do not hesitate if you have any question about this submission.

Province or territory: Québec

Affiliation: Hospital

Capacity in which you are submitting the comments: REB members

Your main discipline: Health Sciences

Kind regards,

Renaud

Renaud Boulanger MSc\
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Centre universitaire de santé McGill
McGill University Health Centre

Centre d'éthique appliquée
Centre for Applied Ethics

Montréal, October 4, 2021

On June 15, 2021, the Panel on Research Ethics (PRE) announced that it was seeking feedback on proposed revisions to its guidelines pertaining to four areas:

- the review of multi-jurisdictional research;
- broad consent in research;
- the review of research involving cell lines; and
- research involving totipotent stem cells.

The Centre for Applied Ethics (CAE) at the McGill University Health Centre (MUHC) is pleased to respond to this call and submit for consideration feedback on three of the four areas of proposed revisions. The CAE provides ethics services to the MUHC community in situations where competing values raise important questions related to clinical and innovative care, research, and organisational decision-making. Professional ethicists at the CAE also provide research ethics expertise to the MUCH Research Ethics Board (REB), which oversees all human participant research conducted under the auspices of the MUHC.

For each of the areas on which we provide feedback, we have sought to separate more substantive issues from the operational ones and propose hints for potential solutions. Although the operationalisation of the Tri-Council Policy Statement is generally left to institutions, normative writing that does not anticipate issues of operationalisation can make it impossible to implement policy. An example of this is the issue of file management discussed in the context of the review of multi-jurisdictional research.

We have provided comments in English, but we note that the translated version of the proposed text will need to be proofread before it is finalised, as there are several passages where the French text is confusing. Similarly, we did not point out typographical errors found in the revised texts (in both languages).

We are grateful for the opportunity to contribute the following thoughts, and we are available to provide additional feedback once the proposed revisions have been redrafted following this consultation period.

Sincerely,

Renaud Boulanger, MSc
Marie Hirtle, LL.B., LL.M.
Brigitte Pâquet, LL.B.
Marie-Sol Poirier, PhD
On behalf of the Centre for Applied Ethics, McGill University Health Centre

Proposed guidance on the review of multi-jurisdictional research

ETHICAL/SUBSTANTIVE ISSUES

Issues flagged	Potential solutions
Insurability - It is unclear if the proposed modifications would leave some study participants uninsured in case of harm/injury as some insurance plans may have specific requirements regarding the type of review conducted locally (cf. experience of the Québec public healthcare sector). REB members' insurance coverage might also not extend to the review of projects in other jurisdictions.	• Explore the issue of insurability to ensure that the mechanism endorsed by the TCPS does not leave study participants unprotected in case of research-related harm.
Misaligned focus - The new text of the TCPS seeks to address a problem that, at least in part, seems to have come from the requirement for local review based solely on a researcher's affiliation (cf. Article 6.1).	• Revise passages of the TCPS that require review by an REB when there is no value added from a participant safety perspective, including in Article 6.1. • Explore a risk-based approach to requiring REB submission. ○ In some cases, simply requiring disclosure by researchers of participation in a research project, rather than requiring local REB review, might be sufficient.
Empirical data supporting the approach - The proposed mechanism resembles the mechanism previously used in Québec for multicentre review – a mechanism that was replaced due to unsatisfactory performance. Is there any existing data from elsewhere that speaks to the success of the approach put forth in the proposed revisions?	• Ground the proposal in available data on real-world attempts at implementing single ethics review for multicentre research. ○ For instance, investigate what lessons can be learned from the Québec experience.

OPERATIONAL ISSUES

Issues flagged	Potential solutions
Applicability in Québec - As presently formulated, the revised text will not be applicable to research taking place within Québec's *Réseau de la santé et des services sociaux* (RSSS). The text appears neither reconciliable with Section 2.4.2 of the new "*Cadre de référence ministériel pour la recherche avec des participants humains*" nor, more generally, with the "*Cadre de référence des établissements publics du réseau de la santé et des services sociaux pour l'autorisation d'une recherche menée dans plus d'un établissement*".	• Convene a workgroup from the various multicentre review initiatives across the country to identify ways to reconcile the proposed text of the TCPS with existing frameworks. Such a workgroup should include provincial authorities and hospital insurers.
Section 3.3 and 3.4 - To assess whether local circumstances have been adequately taken into consideration requires conducting a review of the project by the local REB ("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"). This requirement eliminates any potential gain promoted by the proposed revisions. Furthermore, there are "local circumstances" that might not require the involvement of a local REB. For instance, access to health records without consent in Québec requires special approval per law, but that approval is not granted by the local REB.	• The need for a second, local REB review could be eliminated by going "all in" and clarifying that the local REB is not accountable for ensuring that "local circumstances" have been adequately taken into consideration when an REB has agreed to review the project for participating sites; however, this approach is likely not reconcilable with different jurisdictional requirements. • Clarify that, in addition to single REB review, local feasibility assessments may be required before a project can be authorised locally. This feasibility assessment need not involve the local REB.
Communication tools and timelines - The proposed mechanism suggests restrictions on communication and timelines (for e.g., "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*"; "local REBs should complete their process and issue *a letter or notice of*	• Eliminate confusion about roles and responsibilities by clarifying that the local REB is <u>not</u> accountable for ensuring participant well-being if the project is reviewed externally.

acknowledgment within three weeks of receiving the complete package from the researcher, including the decision of the REB of record"), but these delays and timelines appear arbitrary and, in some cases, may be longer than what research teams generally expect when submitting to their respective REB. More fundamentally, the revised text does not establish clear accountability for what happens if no answer is provided (for e.g., who is ultimately responsible for the safety and well-being of study participants, is the research team allowed to implement a project at a site where the local REB has not yet issued a "notice of acknowledgement" after a given period?). Different jurisdictions (or sectors within a jurisdiction) may have already adopted technological solutions to inter-institutional communications for multicentre projects. What seems to be suggested in the proposed revision to TCPS2 would not only be a step back (e.g., to the use of email, which has been shown to be inefficient and to lead to 'lost files.'), but would also be possibly disruptive to sites already well networked.	• Consider the implications of the proposal on the management of communications between sites, and anticipate which mechanisms and tools could be used.
<u>File management</u> - Experience in Québec's RSSS has revealed the complexity of managing and exchanging approved study files, and keeping those files updated even when an almost-universally shared electronic platform is used (for a visual representation of the issue, consult for example: https://cusm.ca/sites/default/files/users/user181/Sch%C3%A9mas%20communication%20et%20D.O.%20-%20MP%20initial%20%28v.4%2C%2020-juin-2017%2C%20v.EN%204-d%C3%A9c-2017%29.pdf).	• Do not move forward with a multicentre review process before hashing out clear responsibilities for file management.

Requiring a shared REB review without a clear vision of responsibilities for the management of files is expected to lead to major deviations (use of outdated consent forms, etc.). This might jeopardise participants' well-being, and it is a serious risk in the case of audits from health authorities or funders.	
<u>Local circumstances</u> - Experience in the Québec's RSSS has revealed the complexity of assessing and responding to local circumstances, even when operating within a shared jurisdiction. The proposed TCPS revisions state that "Both the researcher (research team) and the REB of record should have considered local circumstances." It is unclear that a research team or REB has the resources to familiarise themselves with different legal and administrative frameworks.	• Consider encouraging the use of multicentre review mechanism within the same jurisdiction (e.g., Québec's RSSS) but not cross-jurisdiction at this time.
<u>Ongoing review</u> - The proposed revisions put emphasis on the initial approval process, but there is little guidance on ongoing follow-ups and monitoring. For instance, the process to review amendments and ensure their implementation is not adequately discussed. There is no clear mechanism either to allow an REB of record to conduct monitoring activities of research activities at external sites, particularly across jurisdictions. REBs across the country have different Standard Operating Procedures regarding the submission of notifications to the REB (not only in terms of timelines but also in terms of types of notifications required).	• Consider standardising processes for ongoing review, particularly in light of non-harmonised Standard Operating Procedures (for a visual representation of a process used in multicentre review, see: https://cusm.ca/sites/default/files/users/user181/Sch%C3%A9ma%20communication%20et%20D.O.%20-%20MP%20Suivi%20sans%20F1MP%20%28v.4%2C%2020-juin-2017%2C%20v.EN%204-d%C3%A9c-2017%29.pdf)
<u>Choice of REB of record</u> - It is problematic that the proposed text of the TCPS suggests that "The starting premise is that the REB of the (lead) principal investigator (PI) is usually the REB of record", as that REB may not have the type of direct	• Consider using the criteria laid out in the Québec's "*Cadre de référence des établissements publics du réseau de la santé et des services sociaux pour l'autorisation d'une recherche*

accountability to the participants recruited as does an REB from an institution where recruitment will occur.	*menée dans plus d'un établissement"* to determine which REB should be the REB of record. In particular, the REB selected should at a minimum be one from an institution where recruitment will occur.

Proposed guidance on broad consent in research

ETHICAL/SUBSTANTIVE ISSUES

Issues flagged	Potential solutions
Community engagement - The proposed wording (circa line 68) refers to Article 2.11 (community engagement). Insufficient guidance is provided to assess whether broad consent (for repositories) requires more in-depth community engagement than specific consent. Most biorepositories will have samples and data "Where the data or human biological materials are from a specific or unique community or group" (depending on the definition of "group"), suggesting that a community engagement process will be required for most biorepositories.	• Clarify expectations vis-à-vis community engagement.
Withdrawal - The revised text suggests that "Researchers must justify any limitations to the withdrawal of data or human biological materials to their REB." However, it is unclear *what* criteria the REB should use to determine whether the justification is adequate or not.	• Clarify what ethical criteria can be used to limit the withdrawal of data or human biological materials from collections.
Free of coercion - Although the revised text firmly re-establishes the principle of autonomy, it appears out of touch with the direction of several initiatives emphasising the importance of data sharing. For instance, the revised text states that "Participating in a specific and known research project must not be contingent on the participant consenting to unspecified research." It is not clear how this statement can be reconciled with a) the policy adopted by some medical journals that makes publication contingent on the project's dataset being made available to the research	• Reconcile the need to protect study participants with the changing requirements of scientific journals, funders, and private industry by encouraging full disclosure to study participants and setting robust standards for data management.

community, b) the requirements of an increasing number of funders toward open data, and c) the current practice of several private partners that conduct clinical trials and that make data available without explicit consent from study participants (cf. https://clinicalstudydatarequest.com/).	
Role of REB - The revised text puts the onus on research teams to assess things they may not be well-equipped to (for e.g., "The researcher should consider what information is meaningful to the participant's decision to participate at the time of consent, and what information might be more appropriate as an addendum, which may be of more interest to them later.").	• Clarify best practices for the development of consent forms. This will help harmonise REB review practices and facilitate the consenting process.
Governance - In the proposed text, the passage "the details of a repository's governance" suggest that all repositories must have the equivalent of a management framework in which details about its governance are laid out. The absence of a management framework would make it difficult to know whether the governance structure of a registry is adequate to protect study participants.	• Management frameworks for registries are essential and the need for them should be made more explicit in the revised text.
Confidentiality - The proposed text specifies that "the onus may be on the participant to provide the repository with any updates to their contact information, and to confirm their ongoing consent". However, in many cases (e.g., repository held by a private entity sponsoring a clinical trial from which samples are collected), the owner of the repository does not know the identity of participants to the repository. As written, the proposed text might increase risks to study participants, by multiplying the opportunities for breaches of confidentiality.	• Clarify best practices for the protection of participant's privacy, particularly in the context of registries managed by private industry stakeholders.

OPERATIONAL ISSUES

Issues flagged	Potential solutions
Applicability in Québec - In Québec's *Réseau de la santé et des services sociaux* (RSSS), the guidance from the *Ministère de la santé et des services sociaux* (MSSS) regarding the creation and management of registries/banks must be followed ("*Guide d'élaboration des cadres de gestion des banques de données et de matériel biologique constituées à des fins de recherche*").	• Convene a workgroup to reconcile the proposed text of the TCPS with existing frameworks.
Status of repositories The revised TCPS text is unclear whether the creation of a repository itself must be reviewed by an REB. If not, and taking into consideration all revisions put forth through the current consultation period, it seems that new cell lines could be created without REB approval for consent* and then used for research without REB approval. *There is a statement to the effect that "*Research involving the creation of a cell line requires REB review",* but this statement is not currently part of the text that was proposed for addition to the official text of the TCPS.	• Clarify in the revised text of the TCPS that registries are infrastructures used in research that fall within the oversight of REBs and that, consequently, all registries must have a management framework. • Require that the broad consent AND the management framework be reviewed by the REB.

Proposed guidance on the review of research involving cell lines

ETHICAL/SUBSTANTIVE ISSUES

Issues flagged	Potential solutions
Coherence - The proposed exemption creates a double standard between types of samples that is not adequately justified. It is not clear indeed what discerning criteria makes an exemption from REB review acceptable for research with cell lines but not for research with other types of samples (obtained from a registry) that meet all of the same criteria.	• Provide an explanation as to why research with cell lines should be reviewed differently than research with samples that meets the same criteria as listed in this section. o Alternatively, if the Panel on Research Ethics recognises that there are no conceptual distinction and that the reason to limit the applicability of this exemption to cell lines only is to use a "prudent"/incremental approach ("watch and see"), this should be disclosed transparently. A paragraph explaining the prudent /incremental approach could be added to rationalise the exemption for cell lines specifically.
Known identity - It is unclear why the criterion "the researcher does not know or have access to the identity of the participant" is ethically relevant. Such a criterion will create double standards between researchers who constitute registries and wish to use samples from their registries (REB review required) and those who do not participate to the effort of collecting samples but do use samples (exempted from REB review). The text "They should therefore consider at the outset whether they plan to re-use these cell lines, and if so, seek REB approval (and participant consent, where applicable) for re-use at the time of the initial	• Demonstrate the relevance of the criterion "the researcher does not know or have access to the identity of the participant" or use criteria widely endorsed (cf. Article 5.5A/B, TCPS2, 2018)

ethics review" does not provide useful clarification: consenting participants for re-use of their samples should be the norm regardless of whether researchers who will use the samples will know the identity of participants or not.	
<u>Post hoc approval</u> - The phrasing "The urgency of seeking REB review after it has been determined that a condition of Article X has changed is commensurate with the level of risk that the change presents to participant welfare", in conjunction with the passage "REBs should consider the issues relevant to participant protection such as how the participant identity **was revealed**, to whom" makes it sound as if the request will be for the REB to retrospectively provide review/approval of the project/incident.	• Revise the passage to be consistent with the consensus that an REB ought to never retrospectively provide review/approval of a project.
<u>Whole Genome Sequencing (WGS)</u> With rapidly changing technology and the increased availability of databases, it is increasingly likely that WGS of human samples could lead to re-identification of individuals.	• Clarify that whole genome sequencing (WGS) *de facto* means that the criteria for exemption from REB review are not met (specifically, criterion (d): "the research is unlikely to reveal the identity of the participant.) o Adding this clarification would have the advantage of taking care of the section in the revised text about WGS of HeLa cells (Article 8).
<u>Sensitive research</u> As drafted, the article does not exclude, from the exemption to receive REB review, research that may be sensitive or ethically dubious. As no REB will be tasked with ensuring that the core principles underpinning the TCPS2 are reflected in research projects involving cell lines, this task must be explicitly delegated to research teams.	• Add, in "Article X", a criterion (e) along the lines of: "the research is consistent with the principles of Respect for Persons, Concern for Welfare, and Justice as discussed in this Policy".
<u>New cell lines</u> No information is provided in the revised text about what criteria apply for the ethical	• The text should clearly allude to the fact that the creation of new

creation of new cell lines (e.g., type of consent required).	cell lines requires that consent from study participants be obtained and that the consent signed be consistent with requirements laid out in the section on broad consent. (Note that some of this information is presently available in italics, but it is our understanding that italicised text is *not* expected to be added to the revised TCPS).
<u>Identified cell lines</u> - The proposed text states that "The example to which this article applies is the HeLa cell line", but we anticipate that other cell lines will be identified in the future.	• Consider keeping the wording of the TCPS generic and move the text referring to the HeLa cell lines to one of the public interpretations of the TCPS.

OPERATIONAL ISSUES

N/A