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Dear members of the Secretariat on the Research Ethics

I am submitting the attached comments in consultation with and on behalf of my colleagues at the University of Calgary, the University of Alberta and Alberta Health Services.

The University of Calgary is a research intensive university with two REBs, one focused on health research, the other on human participant research that is not health related. Contributors from the University of Calgary include the Chair of the health REB and research administrators.

The University of Alberta is a research intensive university with four REBs, two focused on health research and the other two on human participant research that is not health related. The UA contributors are research ethics administrators.

Alberta Health Services is the single provincial health authority for the Province of Alberta. Contributors support health system access and related services for researchers.

Thank you for the opportunity to comment on the proposed changes to the application and interpretation of the TCPS2 2018.

Best wishes, Susan

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October 4, 2021

Secretariat on Responsible Conduct of Research
Canadian Institutes of Health Research
160 Elgin Street, 9th Floor
Ottawa ON K1A 0W9 Canada

VIA e-mail: secretariat@srcr-scrr.gc.ca

Dear Members of Panel on Research Ethics and the Secretariat on the Responsible Conduct of Research,

Re: TCPS2 Consultation 2021

In consultation with my colleagues Ms K Kordov (University of Alberta), Dr S Page, Dr. T Lier and Ms L Longpre (University of Calgary) and Ms B Wong, Ms C McLeod, Ms C Vos and Ms M Preziger (Alberta Health Services - Health System Access) and on behalf of our offices and the REBs and researchers we support, I am pleased to provide the following joint response on the documents related to interpretation and implementation of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 (2018)).*

Proposed revisions to the TCPS2 (2018)

1. Changes to the definition of human embryonic stem cell and the addition of a definition of totipotent cells.
   https://ethics.gc.ca/eng/consultations_2021_totipotent.html

(Note: UA staff member Ms. Susan Babcock is a member of the CIHR Stem Cell Oversight Committee, which drafted the proposed revisions.)

The proposed amendments are necessary technical changes to the TCPS2 and should be implemented.

2. Exemption from REB review for de-identified cell lines
   https://ethics.gc.ca/eng/consultations_2021_cell_exemptions-exemptions_cellulaires.html

(Note: UC faculty Drs. Stacey Page and Michael Hill were members of the PRE Subcommittee (CLAS), which drafted the proposed revisions.)

The principles underpinning these revisions are entirely sound and the operational implications should be welcomed by REBs and researchers alike.

In our experience, REB review of re-use of an existing de-identified cell line adds to the administrative burden for researchers and REBs and does not increase risks to privacy or improve protection for the participants. The exemption from REB review for research that relies exclusively on identified cell lines in the public domain (the HeLa cell line) offers similar benefits and is an explicit recognition that where review by an REB cannot offer additional protections to the research participants, the need for that review should be examined. Basic scientists who use de-identified cell lines for *in vitro* research and who would not otherwise conduct human participant research will be particularly grateful for these changes.

Proposed new guidance documents

1. Ethics review of **minimal risk** multi-jurisdictional research (research involving two or more TCPS2 compliant institutions)
   https://ethics.gc.ca/eng/consultations_2021_multi_research-recherche.html

We support the goal of this guidance, which is to promote expeditious review of research while maintaining protections for participants. As the guidance suggests, for minimal risk research where there are no substantive, local considerations, additional reviews add to the workload for researchers, ethics offices and reviewers, may delay research activities and appear to be unlikely to increase protections for the participants. Reducing redundant, equivalent REB reviews reduces burdens on researchers, research ethics units and REB members alike. The underlying assumption is that such reviews are of equivalent calibre, however evidence supporting or refuting that assumption is lacking. We are in favour of this move to reduce duplication of REB review by enabling institutions and their REBs to accept the review of other qualified REBs with less formal mechanisms (i.e. an agreement at the "highest level") in place to do so.

In principle, the REBs administered by the University of Alberta and the University of Calgary rely as much as possible on reviews and approvals by other REBs, for studies where we are involved as the participating site(s). Additionally, all health studies in Alberta benefit from our provincial Health Research Ethics Reciprocity Agreement which has been in place since 2011. Similarly, the University of Alberta - University of British Columbia - University of Saskatchewan Research Ethics Reciprocity Agreement has simplified review requirements for studies involving those institutions since 2010. Earlier this year, the University of Calgary and the University of Alberta, with funding from Alberta Innovates implemented REB Exchange (REBX) which provides an elegant, online technical solution to the complexities of ethics review and institutional oversight for multi-jurisdictional research in Alberta. It is important to note that harmonization efforts in Alberta rely on formal reciprocity agreements between the relevant institutions and are compliant with Alberta's *Health Information Act (HIA).* Among other things, HIA requires that any research involving health information be reviewed by an REB designated to review such research by the Minister of Health (see comments below).

Initial approval

In practice, however, there is a vast array of research conducted at Tri-Agency eligible institutions and the oversight and operational requirements of some of that research, particularly health research, militates against both a mandatory requirement for single REB review of minimal risk studies and a standard process for managing such studies. Multijurisdictional involvement in studies may take different forms as outlined in TCPS2 2018 Chapter 8, Section A. Importantly, the nature, sequence and obligations of multijurisdictional research are not uniform. For example, collaborators may be added at different points in a study (before, during and after data collection), the research activities and/or participant population may vary site to site and investigators may assume very different responsibilities (from research conceptualization, consultation, and data collection to commenting on relevant theory, data analysis and developing manuscripts). The proposed guidance appears largely intended for the situation where the same study is being undertaken in different jurisdictions and launched at more or less the same point in time. It would be good if the revised guidance could specifically address those cases where the only trigger for multi-institutional review is the affiliation of co-investigators (i.e., the study is only conducted at one site, but members of the researcher team have different affiliations). In such cases, where there is no impact on the institutions of the other involved investigators, no local context to consider and the study is minimal risk), could a single approval, that of the PI's REB, be sufficient?

Ethics review processes at many research intensive institutions interface with financial management systems, administrative approvals and, for health research, operational and other approvals related to patient, data and facility access. Ensuring ethics compliance on research funds held by investigators at the second institution is required by the *Tri-Agency Agreement on the Administration of Agency Grants and Awards by Research Institutions.* Where the research ethics approval review from the lead institution is accepted (i.e., BOR), operationally, it should be shifting the second institution's consideration of the application to focus on ancillary approvals. While a research ethics review won't be undertaken, researchers may still have to complete full, or close to full applications. It would be good to recognize this. Putting a time window on outputs (i.e., lines 136-137; "within three weeks," line 158) "perhaps four to six weeks") is not appropriate. It undermines the research ethics administrative offices/units' and REB's authority in triaging their workflows and fails to take into consideration the myriad other factors involved in the review process, not least of which is REB workload..

Lines 82 – 96 "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." Put another way, the local REB must at minimum receive or have knowledge of the single REB review in order to accept or rely on it. The distinction between what must be undertaken for "local consideration and acknowledgement" and a delegated review is not clear. Identifying a substantive, missed local circumstance, or in particular, a missed substantive issue, implies that a research ethics review is to be undertaken. Moreover, where local issues are identified, requiring the second site to circle back to the BOR (lines 90-93 and 132-133) adds a step not justified by increased participant protections broadly (i.e., across both sites), as well as undermining the competence of the second REB. This has the potential to add significant time to start up and create significant frustration for both REBs and researchers.

The guidance states "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." This presupposes that all participating sites and collaborations are known at the outset or at a single point in time. This is often not the case and sites are often added later on. In such circumstances, the REB of record could not have considered "local circumstances" upon initial review. Moreover, it is not reasonable to require the REB at one site (i.e., BOR) to have knowledge of local circumstances at other sites.

Additionally, the proposed guidance does not adequately address provincial legislative requirements in Alberta and possibly elsewhere, with respect to research involving patients/data in a healthcare environment. In Alberta, the Health Information Act, which governs the collection, use and disclosure of health information under the control and custody of a data custodian, requires that research involving said health information be reviewed by an REB designated under the Act's Designation Regulation. Currently only three REBs are designated, namely the University of Alberta HREB, University of Calgary CHREB and an REB established by Alberta Innovates. To simplify, any research which involves access to patients and/or their records within the health care system, regardless of the level of risk, can only be undertaken once reviewed and approved by one of the above REBs. As such the wording in this mandatory guidance related to "minimal risk research" is inconsequential to the requirements for local REB review under this legislation and this legislation would impose a standard higher than the TCPS2, to which local research would need to adhere. Detailed commentary from Alberta Health Services on this issue is attached to this letter.

Continuing review

Line 98 - 99 “The REB of record has the responsibility for continuing ethics review” Practical considerations include how the BOR manages post approval activities. For example, at our institutions we use online forms that researchers complete for their annual review/renewals that are tied to their anniversary date and compare information from the original applications to that found in the renewal. The PI on the application receives automated reminders. If a secondary site is approved six months later (and to be clear, because it was submitted five months later), what anniversary date is to be used? How can the BOR require reporting from the secondary sites? What are the implications for reporting where such reporting requires institutional access to an electronic platform? Even with access, the platforms may not support BOR and secondary site reporting. This would become even more complex for above minimal risk protocols, in particular clinical trials reporting including protocol deviations and adverse events. Ensuring ongoing compliance of research funding with REB approval, necessary for all participating institutions to meet their obligations under the Tri-Agency Institutional Agreement, requires that participating institutions be notified of a study’s change in status, particularly in the case of suspensions. Since suspensions may involve the sudden emergence of a higher risk to study participants, and may require suspending access to research funds, institutions should not be left to rely on notification by the study team (143-145).

Line 97. In order to avoid REB shopping and also to avoid adding extra burden onto REB/research ethics units by having them consider requests for exemptions and/or additional reviews, we suggest that the requirement should be for the BOR to be that of the lead PI. This will also help promote consistency in practices across Canada.

Lines 143-145. “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.” Any further decisions made by the REB of record would ordinarily be in response to a submission by the lead PI. Accordingly, the lead PI should be responsible for keeping all participating sites informed about submissions to the REB and to be responsible for communicating decisions about researcher requests.

In summary, the proposed guidance appears to add steps, complexity and possibly barriers to a multijurisdictional review. In addition, it would likely need to be buttressed by revisions to the TCPS2 (2018) itself, including Sections

Exploring other possibilities would be good. As one alternative, the Panel might wish to consider providing a stronger endorsement of an REB’s authority to “accept” the review undertaken by an external REB at its own discretion. That is, for minimal risk research, REBs/institutions could choose to accept the research ethics approval granted by an external (Canadian, TCPS compliant) REB on a case by case basis, in the absence of a formal agreement. Researchers would still be required to submit a local ethics application, outlining local site specific considerations, but allowing the REB to simply accept that the prior review of the other REB is valid would still greatly streamline the process.

The Panel might also wish to consider defining types of multijurisdictional research activities that would be exempt from REB review by the participating sites. Examples include collaborations where local researchers only have access to anonymized data, are contributing only to research design or manuscript preparation or local involvement is limited to distribution of approved recruitment materials.

2) The use of **broad consent** (consent for unspecified research, often related to biobanks and data repositories).

https://ethics.gc.ca/eng/consultations_2021_broad_consent-consentement_general.html

More and more REBs see such storage activities described within research protocols and providing standard guidance about it is valuable for both researchers and REBs. Tiered consent models permit participants to maintain some choice over what will be done with their data, could this be recognized as another option?

Some provincial privacy legislation will preclude the application of broad consent for some types of data, for example Alberta's Health information Act. Moreover, the sharing and storage provisions and custodial arrangements for data and biological specimens may be distinct. Detailed commentary from Alberta Health Services on this issue is attached to this letter.

While the definition of data repository is accurate, it would be valuable to indicate that not all repositories are created equally. By this definition, a repository might range from an archive on an individual's computer to an institutional repository capable of storing huge amounts of data and having a defined governance structure in place. Given the exemption criterion "publicly available," it would be good to define what criteria need to be met for a repository to be considered "publicly available." Does this mean open access with no limits, data can be pulled down by anyone at any time? Does it mean that anyone can access the data, but must go through an application process and be approved by the repository stewards? Does this mean that only certain people/people with certain credentials can apply?

The guidance appears to recognize a shift in ownership of the data; from the original researcher/donor to the repository to the secondary researcher/user and therefore a concomitant shift in stewardship responsibilities. If ownership transfers, is it the case that the researcher can make assurances that in essence would be the responsibility of the third party to uphold? It might be more accurate to state that the data will be shared with repository X and future use of the data (including the possibility of withdrawal) governed by the policies of that repository.

Detailed description of elements to possibly include in a broad consent – Lines 126-190. All of these are important considerations and ideally, they should all be addressed at the point that broad consent is sought. However, this is rarely apt to be the case. It would be good to prioritize what information must be provided vs. what can be considered as optional/unknown. For example, a description of what data and biological materials will be shared, the state of the data to be shared (identifiable or de-identified) , and the choice to take part or not should be non-negotiable. The consent content required for broad consent should not overwhelm the consent for the larger project within which it is embedded.
Lines 72, 193, 207-208, 215 – Duties and responsibilities of repositories are described or implied. It is unclear how their accountability can be enforced. Once the data are transferred, to what extent, if any, is the original researcher responsible for ensuring processes or "mechanisms" are in place or upheld?

In conclusion, we would like to applaud the Panel for taking the initiative to develop concrete guidance to support the existing national dialogue on streamlining multi-site ethical reviews. The Province of Alberta and its Institutional REBs wholeheartedly support the departure from multiple single site reviews of multi-jurisdictional studies and moving toward a model encouraging a single comprehensive review where the research activities, institutional obligations and legislative framework allows such reviews.

The University of Calgary-University of Alberta REB Exchange (REBX) solution is an exemplar of this intent, where we have been able to truly streamline ethics reviews, whilst maintaining full integration with existing Institutional compliance and operational systems. It is our intent to broaden its use outside of Alberta in the upcoming months/years.

We believe that the proposed revisions will create unintended negative consequences for our already developed system of harmonized review in Alberta and within the Western Provinces. We believe the brunt of these consequences will be borne by Alberta researchers, academic institutions and our health authority alike, and will undeniably place additional burdens on each of these stakeholders, all within an environment with increasing scarcity of Institutional human resources.

We hope that the Panel finds our comments helpful and trust that our concerns, particularly those pertaining to the mandate of single REB review by a single REB in the context of the Alberta landscape will be helpful in further revisions to this guidance. If we can lend any assistance or advice to the Panel as it considers the myriad ways in which this goal can be facilitated, we would be happy to be consulted.

Yours truly,

Susan Babcock

Susan Babcock, MA, MBA
Director - Research Ethics Office
University of Alberta

Attachment

cc: Dr S Page, Chair - Conjoint Health REB, University of Calgary
Dr T Lier, Director - Grants, Awards and Ethics, University of Calgary
Ms L Longpre, Research Ethics and Compliance Manager, University of Calgary
Ms K Kordov, Associate Director, Research Ethics Office, University Alberta
Ms B Wong, Director - Health System Access, Alberta Health Services
Ms C McLeod, Senior Advisor - Health System Access, Alberta Health Services
Ms C Vos, Research Advisor - Health System Access, Alberta Health Services
Ms M Preziger, Privacy Business Advisor, Alberta Health Services

Attachment

Comments from Alberta Health Services Health System Access on the Proposed Guidance for Multi-jurisdictional Research and Broad Consent

AHS Health Systems Access has reviewed the new guidance proposed for multijurisdictional research and broad consent. We do not have any comment on the two proposed revisions to the TCPS2 at this time. Our responses to the new guidance is detailed below, first with respect to multijurisdictional research and REB review and second with respect to informed broad consent.

ISSUE #1: The Secretariat has proposed new guidance on the Ethics review of minimal risk multi-jurisdictional research where that research involves two or more TCPS2 compliant institutions. The guidance says that there should only be a single REB at the lead site and refers to this as the REB of record. "The intention is to keep the REB of record as the sole REB that can make changes to the terms of the ethics approval." Local REBs are expected to acknowledge the decision of the REB of record, but can flag local issues or substantive issues that were not addressed to them for reconsideration. This guidance is "mandatory" for minimal risk research but could be applied to more than minimal risk research.

Definition of "minimal risk research" in TCPS2:

> For the purposes of this Policy, "minimal risk" research is defined as research in which the probability and magnitude of possible harms implied by participation in the research are no greater than those encountered by participants in those aspects of their everyday life that relate to the research - (Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2 (2018) – Chapter 2: Scope and Approach (ethics.gc.ca))

AHS HEALTH SYSTEM ACCESS RESPONSE: AHS concerns with this mandatory guidance centre around the fact that minimal risk research could include research where patient health information would need to be accessed or collected for the purposes of the research. As custodians of patient health information in the Province of Alberta AHS is bound by the Health Information Act (HIA) of Alberta. The research division of the Act opens with section 49 which states "A person who intends to conduct research using health information in the custody or under the control of a custodian or health information repository must submit a proposed research protocol to a research ethics board for review by that board". Furthermore, the 'board' referred to in the Act are those designated in the HIA Regulations – the local Alberta CHREB, HREB and the HREBA boards.

In the Act, health information is "i) diagnostic, treatment and care information and ii) registration information." Individually identifying, when used to describe health information, means that the "identity of the individual who is the subject of the information can be readily ascertained from the information." And "'non-identifying', when used to describe health information, means that the identity of the individual who is the subject of the information cannot be readily ascertained from the information." While health information defined under the act includes both identifying

and non-identifying, research defined in the HIA "means academic, applied or scientific research that necessitates the use of individually identifying health information." Therefore, even if the research is deemed to be of minimal risk, if it concerns the collection, use or disclosure of any identifiable health information we must have a local REB review as required under the HIA.

Even though the HIA definition of research specifies identifiable health information, AHS' Research Information Management policy has no such specification. Instead research here is defined as "an activity whose purpose is to contribute to the growing body of knowledge regarding health and/or health systems that is generally accessible through standard search procedures of academic literature" and it stipulates that "all research studies must be reviewed and approved by a Research Ethics Board" as defined in the HIA Regulations.

Taking the HIA requirements only, as long as research of 'minimal risk' only involved non-identifying health information (meaning that the information was extracted by our internal analysts and released to the research team in a fully de-identified fashion that meets the AHS Non-Identifying Health Information Standard) or didn't involve patient information at all, then it may be possible to consider this new guidance. However, AHS policy as currently written would not allow it. At present research involving only non-identifying health information or not requiring health information is still required by AHS to have been reviewed by one of our local HIA-designated boards. It is also important to note that AHS has a non-identifying information standard and the definition of non-identifying would need to comply with it. The AHS Non-Identifying Health Information Standard details data elements that must be stripped or converted to non-identifying information including contextual information. AHS would apply our standard to each research study requesting information.

To summarize, if multijurisdictional research is approved by an REB of record in another province, Alberta could still be required under the HIA or AHS Policy to have one of our local REBs review it. In order for AHS to comply with our policies and/or the HIA, our local REBs may need to have alternate procedures to consider the REB review from another jurisdiction as suggested in this guidance, but still issue an approval. AHS is hopeful that our local REBs can help to educate and manage the expectations of our researchers so they understand that even though CIHR has issued this guidance, AHS and Alberta may still need to have local REB approvals to meet our policy and legislative requirements.

ISSUE #2: The Secretariat has proposed guidance on broad consent, meaning consent for unspecified future research purposes, and how this may be acceptable. The guidance highlights that free, informed and ongoing consent are still the key parts of broad consent, as they are for specific consent. The proposal is that research teams can still inform participants about specifics such as what is being collected and stored for future use, the risks associated with it, information surrounding the repository and its governance and options regarding withdrawal. This is to create an "informed broad consent".

AHS HEALTH SYSTEM ACCESS RESPONSE: This response is limited to data only (samples/biological materials are not governed by the HIA and in most cases are not under the custody of AHS).

The HIA discusses what must be included in patient consent. Section 34(2)(b) indicates that when consent is required there is the requirement that the consent contains “the purpose for which the health information may be disclosed”. Specific to research disclosures, Section 54(1)(b) requires health information may be used “only for the purpose of conducting the research in accordance with the research protocol”. The research protocol details specific activities that a study will undertake to answer the research questions being asked. As the custodian of the health information and to remain compliant with the HIA, AHS will only disclose health information to be used for the specific purposes in the current research protocol, not a general purpose of unspecified future research.

While the idea of ‘informed’ broad consent does sound possible, it may be operationally more difficult to implement an informed consenting process. Different studies/repositories have different amounts of information known about the possibilities or directions for future research, governance and possible risks. These all are evolving issues and an individual who is among the first to consent may not receive the same information as one several years later when a study or repository is more established. The onus is on research teams to adequately understand all of the possible future risks and potential uses for patient information in order to communicate them to participants and answer their questions satisfactorily as part of obtaining truly informed consent. This is a risk. There are also additional operational risks regarding the management of consent for a long term repository as any change in purpose would require contacting and re-consenting patients or establishing procedures for how to handle data in accordance with the original purpose for those who do not re-consent. There is also the possibility that information considered non-identifying today may not be with future technologies.

Additionally, given that a future research study must have its own REB approval which would stipulate either explicit patient consent for that specific study or a waiver of patient consent for it. In either case a ‘broad consent’ under the original REB approved study would hold no significance to the future study. It must be clear to researchers that future uses of data still require new REB approvals and must follow the consent requirements for those new approvals, rather than relying on a broad consent collected as part of the study under which the data was collected.

AHS must limit use of data to the requirements of the specific REB-approved study. AHS limits the uses for data when transferred to only what is contained within the REB approved protocol, thereby remaining compliant with the HIA. We would continue to expect that all future research studies, regardless of jurisdiction, would either require patient consent for information to be used or have a waiver of patient consent, thereby minimizing any value in obtaining ‘informed broad consent’.