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From: Ma'n H. Zawati, Prof.
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To: secretariat (SRCR/SCRR)
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Subject: TCPS 2 CONSULTATION
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Attachments:
Commentary on the Proposed Guidance to TCPS 2 (October 4).pdf

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Dear Colleagues,

Please find attached our comments to the proposed revisions to the TCPS2 (2018). These comments reflect feedback from the Centre of Genomics and Policy and ThéCell (cc'd).

Affiliations: university and government-funded organization (QC)
Capacity in which the comments are being submitted: researchers, representatives of several organizations
Main disciplines: Law, policy and bioethics, regenerative medicine, cell therapies

Do not hesitate to contact us should you have any questions.

Best regards,

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Commentary on the Proposed Guidance to TCPS 2 (2018)
October 2021

Theme 1: Review of Multi-Jurisdictional Research

The proposed revised guidance is well conceived and has the promise to do much in facilitating review of research while ensuring participant protection. Our comments here are limited to constructive critique. We want to nevertheless emphasize that the proposal holds great promise and that we hope its final form will maintain its core proposition, viz. that single-site review is presumed for minimal risk research unless other conditions obtain.

The general norm the guidance proposes should be indicated at the very beginning. Consider including a simple infographic to express the pathways introduced by the guidance.

The system of mutual recognition of single-site reviews must be built on a foundation of trust. To this end, the inclusion of the REB of record's reasons (82-83) can do much to establish trust that relevant aspects of the research were examined. We do, however, believe that these reasons should be more robust than the reasons REBs typically give to researchers. The reasons should assist local REBs in understanding the review process undertaken by the REB of record (90-93). These reasons should also form the basis of any additional discussions between REBs.[1]

The proposal relies upon agreement among REBs about whether or not the proposed research poses minimal risk. This determination may vary.[2] To this end, we highlight the very general guidance in the TCPS 2 for the determination of minimal risk.[3] The adoption of this proposal adds to a large number of pathways that are contingent upon a determination of minimal risk (e.g., waivers, delegated review). In the future, guidance for determining what constitutes minimal risk, especially for data-intensive research, would be most welcome. Moreover, the choice to begin the mandatory policy with minimal risk research is reasonable. Consider, however, a set timeframe for considering the extension of the policy to other research types (e.g., after five years).

For procedures to follow, we believe that it should be clearer as to how the REB of record and local REB(s) are to engage with one another when there are substantive issues to reconsider (129-133) and this should include clear time limits for responses. No single procedure will cover everything. Consequently, consider the use of instructive case studies to better build out what that engagement looks like. Consider also articulating what the relationship this engagement has to the Responsible Conduct for Research (RCR) Framework (70-74).

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1 Public reason is integral to much of liberal political thought, including liberal bioethics. See, e.g., Gerald Gaus, The Order of Public Reason: A Theory of Freedom and Morality in a Diverse and Bounded World (Cambridge: Cambridge University Press, 2010), https://doi.org/10.1017/CBO9780511780844; Hon-Lam Li, "Public Reason as the Way for Dialogue," The American Journal of Bioethics 20, no. 12 (December 1, 2020): 29–31, https://doi.org/10.1080/15265161.2020.1832618.

2 See, e.g., Brigitte Lemyre et al., "A Call for a Streamlined Ethics Review Process for Multijurisdictional, Child Health Research Studies," Paediatrics & Child Health 25, no. 7 (November 2, 2020): 406–8, https://doi.org/10.1093/pch/pxz160.

3 See article 2.8 (p 22) in the TCPS 2.

Finally, further consideration should be given to how single-site review affects communication with participants. For example, consent materials would likely want to include a contact person at the participant's local REB rather than the REB of record.

Theme 2: Broad Consent in Research

Beginning at line 16, and reiterated at line 235, the proposed guidelines adopt a sweeping definition of broad consent consisting of "consent for unspecified research." This interpretation may not align with prominent scholarly interpretations of the concept. Two specific elements are not included in the present formulation and may generate confusion. First, most scholars view broad consent as future-regarding, that is, broad consent seeks a participant's permission to have samples or data used in unspecified research sometime in the future.[4] Second, broad consent is usually understood to necessarily refer to consent provided subject to certain limitations/conditions. Though the future research for which consent is provided is indeed unspecified, it is generally limited in scope by the terms of the participant's consent itself or by the relevant repository's sharing policies[5]. That future unspecified research is delineated in some measure is a necessary feature of the definition because it is, in part, what distinguishes the concept of broad consent from blanket consent.[6] The Panel might consider clarifying its definition of broad consent to avoid guideline misinterpretation.

In the same measure, at lines 32–38, the proposed guidelines suggest that research participants may be less interested in the details of unspecified future sample and data use. This may be true, but is not the principal normative motivation for developing broad consent systems. Instead, broad consent is supported by the impracticability of continuously sharing research details with participants in repository-based initiatives. It will generally be impossible for repositories, such as population biobanks, to imagine all possible future data uses, and to require continuous reconsent would be infeasible for most repository-based research initiatives. Broad consent balances participant autonomy with the promotion of scientifically valuable research.[7] It also crystallizes a crucial characteristic of consent: that it be continuous.

The proposed guidelines do not offer a clear definition of 'data custodian' (43), nor do they explain how biobanks and researchers fit within the data custodian concept. The Panel should consider defining this term.

Lines 48–51 appear to imply that researchers using repository data take on obligations with respect to participant consent. This view requires some nuance, for external researchers generally enter contractual agreements with the repository. External researchers rarely have the capacity to access or communicate with participants, and indeed are usually obliged not to re-identify them. They cannot, as

[4] Garrison NA, et al., "A systematic literature review of individuals' perspectives on broad consent and data sharing in the United States" (2016) Genetics in Medicine, 18:7; Hansson G, et al., "Should donors be allowed to give broad consent to futurebiobank research?" (2006) Lancet Oncology,7:266.
[5] *Id*.; Barnes R, et al., "Biobanking for Genomic and Personalized Health Research: Participant Perceptions and Preferences" (2020) Biopreservation and Biobanking 18:3.
[6] Grady C, et al., "Broad Consent for Research with Biological Samples: Workshop Conclusions" (2015) American Journal of Bioethics, 15:9.
[7] Zawati M, "There will be Sharing: Population Biobanks, the Duty to Inform and the Limitations of the Individualistic Conception of Autonomy" (2014) Health Law Journal 21:97.

a result, be expected to discharge the same obligations as the repository (unless these are stipulated in the access agreement). The Panel might consider clarifying this section of the guidelines.

Line 76 indicates that the withdrawal of data may be difficult where contributions have been widely disseminated. This is also the case if the data/samples have been accessed by a researcher. The removal of data accessed by researchers may harm the scientific validity of the concerned research. Line 125 should be modified to remove the qualifier 'if known.' There should be no situation in which information about repository governance is unknown.

The proposed guidelines appear to imply at lines 133–135 that techniques such as whole genome sequencing are inherently compromising of participant privacy. The Panel should avoid singling out whole genome sequencing. Other data can be collected, but if the safeguards in place are not state of the art, privacy can be compromised. This is why information about the governance of the repository is essential.

Line 142 should be amended to make clear that in some cases, not agreeing to the storage of samples or data for future research will preclude participating in a project. Line 175 should be modified to add the line 'or shared with participants.'

The proposed guidelines suggest that there may be instances in which participants will not have access to information about research conducted with repository data (149). These cases should be limited and the sharing of research details should be encouraged. The Panel ought to amend this section accordingly.[8]

<u>Theme 3</u>: Review of Research Involving Cell Lines

i) *The re-use of de-identified human somatic cell lines*:

The proposed revised guidance provides an important shift in ethics review processes for de-identified somatic cell lines; an ethics review exemption that is much anticipated by the research community. There are extensive debates surrounding the identifiability of cell lines, and the associated privacy risks, as some risk of re-identification of genetic or genomic data derived from cell lines will always remain, regardless of whether cell lines are de-identified or anonymized. Although, re-identification attacks would require highly sophisticated techniques and have not yet shown to be a significant threat.[9] This new exemption recognizes the unique nature of cell lines and accepts a binary view of "identifiability," balancing the actual risk to participant privacy with the overall public benefit to society from cell-based research. We agree with the Panel of Research Ethics ("Panel") that REB review for the re-use of existing de-identified cell lines may not increase protection for participants, as REB members may lack expertise in privacy and security risks. We recognize and support efforts to streamline the REB review process because this would indeed ease the paperwork burden for researchers and REBs while creating a more efficient ethics review process. This new exemption would also align

[8] Rothstein MA, et al. "Broad Consent for Future Research: International Perspectives" (2018) IRB 40:6.
[9] Ogbogu U, et al., "Policy recommendations for addressing privacy challenges associated with cell-based research and interventions" (2014) BMC Medical Ethics, 15:7.

Canadian policies with positions adopted by other jurisdictions (e.g. US,[10] UK, [11] Australia[12]) which would ultimately facilitate the sharing and transfer of cell lines across borders.

However, if research involving the re-use of de-identified human somatic cell lines are exempt from ethics review, we would like to see an emphasis on ensuring that other robust mechanisms to protect privacy are in place (i.e. proper broad consent policies). The proposed exemption places the onus on researchers to determine whether the exemption requirements are met throughout the duration of the research study. This is a significant responsibility that should be combined with other measures. The proposed revision to the TCPS 2 (2018) should include a clear statement requiring researchers, and institutions seeking to use and share somatic cell lines, to have in place a comprehensive governance framework (at the institutional level or between institutions) outlining access procedures and security practices to monitor and respond to re-identification risks. This should go conjointly with access agreements. Furthermore, the Panel should commit to continuous monitoring of technological developments that would tip the balance towards putting participant privacy at risk. The definition of "identifiability" must remain fluid, and policies should be altered and adapted accordingly.

i) *The re-use of identified somatic cell lines in the public domain*:

Cell lines in the public domain (i.e. cell lines from commercial banks) are widely available and publicly accessible, posing very minimal risk to the individual from whom the cell lines were derived. We agree with this exemption. However, when considering possible harm to participants (162-165), researchers should not limit their assessment to the negative effects for the cell line donors, but should take into consideration implications for the donor's relatives and community.

Lines 162-164 should be modified accordingly: "When considering whether research may harm participants, researchers must consider whether anything about the research will have a negative effect on participants' welfare, broadly construed. **This should also include taking into consideration the welfare of the participant's relatives and community**."

[**Quebec context: The proposed REB exemption for the re-use of somatic cell lines would cause discordance with ethical governance and procedures in Quebec. Our discussions with Quebec researchers in the field of regenerative medicine/cell therapy revealed that REB exemptions for cell lines (whether anonymized, de-identified, etc.) would likely not be acceptable, as most REBs in Quebec have interpreted the Civil Code of Quebec as having the mandate to oversee *all* human research conducted in Quebec. From a practical point, there would be difficulties applying the exemption in Quebec, ultimately creating complications for Quebec researchers.]

[10] US Department of Health and Human Services 45 CFR 46. Code of Federal Regulations. Title 45. .http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subparta

[11] Human Tissue Act 2004. https://www.legislation.gov.uk/ukpga/2004/30/data.pdf

[12] National Statement for Ethical Conduct in Human Research (2007). https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018

<u>Theme 4</u>: Research Involving Totipotent Stem Cells

We agree with the proposed changes. The revised definition of "embryonic stem cell" and the inclusion of "human totipotent stem cells" under the purview of the TCPS 2 and the SCOC is appropriate given the scientific developments in the field of stem cell research.

To be noted, however, the application of Article 12.18 (191-194) should be modified to:

"This article seeks to minimize the risk that, for the purposes of stem cell research, **individuals** will feel pressured to create more embryos than needed for reproductive purposes…"

Changing "women" to "individuals" would allow more gender inclusive language and reflect a respect for gender diversity. There may be individuals who do not identify as "women" yet physiologically can produce embryos.