Cell Line Exemptions

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Exemption from REB review for de-identified cell lines

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Research involving human cell lines falls within the TCPS 2 (2018) definition of "research involving humans." As such, it is subject to review by an REB (Article 2.1). Current TCPS guidance is intended to protect the privacy of the donor (the "participant") from whose tissue the cell line was derived and to respect the terms they consented to, if any, for the use of their human biological materials.

Research involving the creation of a cell line requires REB review. However, REB review of research involving the re-use of an existing de-identified (see Glossary below) cell line may not increase protection for participants and may unnecessarily burden researchers and REBs. Risks to privacy are low if the researcher does not know or have access to the identity of the participant (b). Risks are even lower if the research is unlikely to reveal the identity of the participant (d) and the researcher will not take any steps to identify the participant (c).

If consent terms are known to the researcher, they must comply with them to ensure respect for participant autonomy (a). However, this is rarely the case with the re-use of de-identified cell lines. In the case of anonymized cell lines, the participant identity and the terms of their consent are unknown. In the case of coded cell lines, the source of the cell lines, typically a biobank, is responsible for ensuring the researcher's re-use of its cell lines are consistent with the terms of participant consent.

The Panel on Research Ethics proposes the following exemption from REB review, which balances the benefits to society of cell line research with low risks for participants.

The following article exempts from REB review research involving the re-use of somatic cell lines where privacy concerns are low and where REB review would not add any further protections for research participants beyond those already provided by the source of the cell lines.

Article X

REB review is not required for research that relies exclusively on the re-use of de-identified human somatic cell lines where:

a) the researcher will comply with known consent terms;
b) the researcher does not know or have access to the identity of the participant;
c) the researcher will not take any steps to identify the participant; and
d) the research is unlikely to reveal the identity of the participant.

Application

All members of the research team must comply with the conditions in Article X for the exemption to apply. Researchers must consider all stages of the research when determining whether it meets the conditions of the exemption, including, for example, analysis and results dissemination. When in doubt about the applicability of this exemption, researchers should consult their REBs. Explanations of the terms used in the exemption can be found in the Glossary section below.

Should any of the conditions described in Article X change during the conduct of the research, the researcher must seek REB review in a timely manner, because the risks to the participant will have increased if the terms of the exemption are not fulfilled. 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. REBs should consider the issues relevant to participant protection such as how the participant identity was revealed, to whom, and how participant privacy will be protected going forward. Consideration should be given as to whether consent can and should be sought from the participant for the research to continue.

The exemption in Article X does not invalidate other TCPS articles that may apply to the research being considered. The following are two examples. Research involving the derivation of induced pluripotent stem cells that will be transferred into humans or animals requires REB review (Article 12.10). Research involving the re-use of human biological materials, identifiable as originating from an Indigenous community, within Canada or internationally, requires REB review (Article 9.20). Note that the TCPS definition of human biological materials includes cell lines (Article 2.1).

Researchers who create cell lines, and who know the identity of the participant, will not meet the terms of the exemption for the re-use of those cell lines because they will not meet condition (b) of Article X. 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 ethics review.

Researchers are also responsible for ascertaining and complying with all applicable legal and regulatory requirements with respect to consent and the protection of privacy of participants (Chapter 5). [1]

Glossary

The following are more detailed explanations of terms used in the exemption:

Cell line

[1] These legal and regulatory requirements may vary depending on the jurisdiction in Canada in which the research is being conducted, and who is funding and/or conducting the research. They may comprise constitutional, statutory, regulatory, common law, and/or international or legal requirements of jurisdictions outside of Canada (Chapter 1, Section C).

Cells may be obtained from tissue and placed into culture in order to proliferate. When these cells can no longer proliferate because they have taken up all the nutrients in the primary culture, they can be transferred to a new culture to allow for continued growth, a process called subculturing. A cell line is the progeny of a primary culture when it is subcultured (Geraghty, et al., *Guidelines for the use of cell lines in biomedical research*).

De-identified (anonymized or coded)

De-identified cell lines are those from which direct identifiers of specific individuals have been removed. They include anonymized cell lines and coded cell lines where the researcher does not have access to the key code.

Anonymized cell lines are cell lines that have been irrevocably stripped of direct identifiers. Coded cell lines have had direct identifiers removed and replaced with a code (Chapter 12, Section A).

Relies exclusively

"Relies exclusively" means that, from a human participation perspective, the research only involves the human cell line. Research that involves the donor or other human research participants in conjunction with the cell line requires REB review.

Re-use

The exemption applies to research that involves the re-use of cell lines that already exist, for example, research involving a cell line that has been purchased from a commercial biobank. For those familiar with TCPS terminology, "re-use" means the same as "secondary use" in this context. "Re-use" is thought to be more generally understood by those unfamiliar with TCPS terms and therefore less open to interpretation.

Somatic

A somatic cell is any body cell other than gametes (egg or sperm). Sometimes referred to as "adult" cells (TCPS Glossary).

Exemption from REB review for identified cell lines in the public domain

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In general, REB review is required for research involving the re-use of identified cell lines (Article 12.3A). However, if the cell line and the participant's identity are already in the public domain, REB review would not address provenance or privacy issues in any meaningful way. If it is impossible or impracticable to seek consent, there is no consent process that can be reviewed by an REB. If the research is unlikely to cause new harm to the participant, the research-attributable risk is minimal. If the research complies with consent terms, then REB review offers them little additional protection.

The example to which this article applies is the HeLa cell line. The HeLa cell line was derived in the early 1950s, in Baltimore, from tissue that was obtained without consent from Henrietta Lacks, who later died. In addition, her privacy was not protected. This is not consistent with contemporary ethics requirements, both in the U.S. (under the Common Rule) and in Canada (under the TCPS). Because of its ability to replicate itself, the HeLa cell line was and is widely used in research. The scientific knowledge it helped acquire became the basis for many health-related products that proved to be lucrative to the companies that developed them. However, the Lacks family did not directly receive any of the benefits generated by its use.

Research using the HeLa cell line has resulted in benefits to society and the manner in which the cells were initially collected has stimulated many thoughtful discussions about ethical provenance. It is reported that the Lacks family is proud of what the cells have helped accomplish (Arnst, Sharing the Whole HeLa Genome, accessed July 14, 2020).

The following article exempts from REB review research involving the re-use of identified somatic cell lines that are already available and identified in the public domain, such as the HeLa cell line.

Article Z

REB review is not required for research that relies exclusively on the re-use of identified human somatic cell lines where:

a) the cell line is already available and identified in the public domain;
b) it is impossible or impracticable to seek consent;
c) the researcher will comply with known consent terms; and
d) the research is unlikely to harm the participant.

Application

Identified cell lines are those labelled with a direct identifier such as a name (Chapter 12, Section A). Cell lines in the public domain are those available from public catalogues such as one would find at a commercial biobank. Availability can range from freely available with no barrier at all, to accessible if a researcher formally requests and is granted access in accordance with established criteria, e.g., a materials transfer agreement.

Impracticable means incapable of being put into practice due to a degree of hardship or onerousness that jeopardizes the conduct of the research; it does not mean mere inconvenience (TCPS Glossary).

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. The nature of the harm may be social, behavioural, psychological, physical or economic (TCPS Glossary).

When in doubt about the applicability of this exemption, researchers should consult their REBs.

HeLa cell lines

The example to which this article applies is the HeLa cell line, which has been in the public domain for decades. The HeLa cell line was derived from tissue obtained without consent from Henrietta Lacks in 1951. It is impossible to seek consent for its use for research because the participant is deceased. The scientific community generally acknowledges that Ms Lacks' contribution to research has been significant. Permitting research involving HeLa cells benefits society while presenting little to no additional research-attributable risk to Ms. Lacks.

In the absence of knowing Ms. Lacks' wishes one can look to what is publicly known about the wishes of her relatives. In 2013, the Lacks family entered into an agreement with the U.S. National Institutes of Health (NIH) which lays out the family's expectation that researchers sequencing the whole HeLa genome adhere to the NIH agreement to protect the family's privacy. To respect the Lacks family's wishes, compliance with the NIH agreement should be considered when conducting research involving whole genome sequencing of the HeLa cell line.