Research on Human Embryos and Reproductive Materials: Revisiting Canadian Law and Policy

Recherche sur l'embryon et le matériel reproductif humains : examen des lois et politiques canadiennes

UBAKA OGBOGU, SJD
Assistant Professor
Faculties of Law and Pharmacy & Pharmaceutical Sciences
University of Alberta
Edmonton, AB

AMY ZARZECZNY, LLM
Associate Professor
Johnson-Shoyama Graduate School of Public Policy
University of Regina
Regina, SK

JAY BALTZ, PHD
Senior Scientist and Professor
Ottawa Hospital Research Institute
Faculty of Medicine, University of Ottawa
Ottawa, ON

PATRICK BEDFORD, MBHL
Manager of Clinical Translation and Regulatory Affairs
Centre for Commercialization of Regenerative Medicine (CCRM)
Toronto, ON

JENNY DU, BSC
Research Trainee, Faculty of Law
University of Alberta
Edmonton, AB

INSOO HYUN, PHD
Associate Professor, Department of Bioethics
Case Western Reserve University
Cleveland, OH

YASMEEN JAAFAR, BA
Research Trainee, Faculty of Law
University of Alberta
Edmonton, AB

ANDREA JURISICOVA, PHD
Associate Professor
Department of Obstetrics and Gynecology
University of Toronto
Investigator, Lunenfeld-Tanenbaum Research Institute
Mount Sinai Hospital
Toronto, ON

ERIKA KLEIDERMAN, LLB
Academic Associate, Centre of Genomics and Policy
Faculty of Medicine, Human Genetics
McGill University
Montreal, QC

YONIDA KOUKIO
LLM Candidate
Osgoode Hall Law School
Toronto, ON

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BARTHA MARIA KNOPPERS, PhD
Professor and Director, Centre of Genomics and Policy
Faculty of Medicine, Human Genetics, McGill University
Montreal, QC

FOROUGH NOOHI, MSc
PhD Candidate, Centre of Genomics and Policy
Faculty of Medicine, Human Genetics, McGill University
Montreal, QC

ARTHUR LEADER, MD
Professor of Reproductive Medicine
Department of Obstetrics and Gynecology
University of Ottawa
Ottawa, ON

VARDIT RAVITSKY, PhD
Associate Professor, Bioethics Programs
School of Public Health
University of Montreal
Montreal, QC

ZUBIN MASTER, PhD
Associate Consultant II, Biomedical Ethics Research Program
Mayo Clinic
Rochester, MN

MAEGHAN TOEWS, LLM
Lecturer, Faculty of Law
University of Adelaide
Adelaide, AU

MINH THU NGUYEN, LLM
Academic Associate, Centre of Genomics and Policy
Faculty of Medicine, Human Genetics, McGill University
Montreal, QC

Abstract

Research involving human embryos and reproductive materials, including certain forms of stem cell and genetic research, is a fast-moving area of science with demonstrated clinical relevance. Canada's current governance framework for this field of research urgently requires review and reconsideration in view of emerging applications. Based on a workshop involving ethics, legal, policy, scientific and clinical experts, we present a series of recommendations with the goal of informing and supporting health policy and decision-making regarding the governance of the field. With a pragmatic and principled governance approach, Canada can continue its global leadership in this field, as well as advance the long-term health and well-being of Canadians.

Résumé

La recherche utilisant des embryons et du matériel reproductif humains, notamment la recherche sur certaines formes de cellules souches ainsi que la recherche génétique, constitue un secteur qui progresse rapidement et dont la pertinence clinique est démontrée. Face à l'émergence de nouvelles applications dans ce domaine, il est urgent d'examiner le cadre politique actuellement en vigueur au Canada. En s'appuyant sur les fruits d'un atelier qui réunissait des spécialistes en éthique, en droit, en politiques, en science et en recherche clinique, nous présentons une série de recommandations dont l'objectif est d'éclairer et de soutenir les politiques de santé et la prise de décisions liées à la gouvernance dans ce domaine. Avec une approche pragmatique et basée sur des principes, le Canada peut continuer d'assurer un leadership à l'échelle mondiale dans ce domaine de même que faire progresser, à long terme, la santé et le bien-être des Canadiens.

In Canada, research involving human embryos and reproductive materials, including certain forms of stem cell and genetic research, is governed primarily by the *Assisted Human Reproduction Act* (AHRA) and the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS) (Government of Canada 2014). The AHRA, enacted in 2004 following considerable debate (Cattapan and Snow 2017), criminally prohibits several assisted reproductive activities and related research, including the creation of embryos for purposes other than reproductive use or improving or providing instruction in assisted reproduction procedures, the creation of human clones or chimeras and maintaining a human embryo *in vitro* for more than 14 days. Health Canada is charged with implementing and enforcing the AHRA. The TCPS lays out rules for the ethical conduct of permitted research involving human reproductive materials. These rules include consent to research involving such materials, privacy and confidentiality protections for identifiable materials and guidance on managing conflicts of interest. The TCPS applies to research supported by or conducted in institutions supported by federal funds and thus has a broad reach. The Stem Cell Oversight Committee (SCOC) oversees compliance with TCPS rules governing research involving human pluripotent stem cells. Together, this governance framework maintains prohibitions and funding restrictions against various research activities, including the creation of embryos for research, somatic cell nuclear transfer and the creation and use of non-human chimeras for research.

Canada, having deep expertise in this field of research, is also a global leader of research involving human reproductive materials (KPMG 2015). However, these prohibitions affect current basic research activities and will impact emerging areas of research aimed at developing novel reproductive technologies and improving our knowledge of human developmental biology, such as studies investigating *in vitro* derivation of gametes from human pluripotent stem cells (Yang et al. 2012), or the creation of embryo-like entities from stem cell cultures (Harrison et al. 2017; Pera et al. 2015; Warmflash et al. 2014). Recognizing the need to ensure continued relevance, the AHRA mandated a Parliamentary Review within three years of the establishment of its regulatory agency. However, this review never occurred. While the reasons why the review never took place are unclear, we speculate it may be because of a lack of a stable framework for implementation and enforcement and a legal challenge to the constitutionality of the Act initiated by the Province of Quebec in the period following enactment. As such, it is unclear whether the concerns that triggered the prohibitions remain current, especially in relation to basic research activities. The AHRA has also been criticized for its lack of clarity regarding its application to novel and emerging research activities (Rugg-Gunn et al. 2009), and these concerns remain.

With the goal of informing and supporting health policy and decision-making regarding the governance of embryo and reproductive materials research in Canada, we convened a workshop of ethics, legal, policy, scientific and clinical experts to consider reform options. The workshop was a principal activity under a Public Policy Impact Research Grant funded by the Stem Cell Network and part of a larger workshop series aimed at revisiting the AHRA (Knoppers et al. 2017a). Participants were identified and selected through

consultations with Canadian and international collaborators on the grant, including leading scientific, legal and public policy research experts, and with the health law and science policy research teams at the Health Law Institute, University of Alberta and the Centre of Genomics and Policy (CGP) at McGill University. Participants completed an anonymized questionnaire prior to the workshop, which was used to structure the workshop deliberations and ensuing recommendations. The questionnaire was based on a format prepared by the CGP and used in the other workshops in the series. This paper presents key areas of consensus at the workshop and builds on earlier workshops and recommendations (Knoppers et al. 2017a, 2017b). A draft of the recommendations presented in the paper was developed at the workshop and refined through a process of e-mail consultation with and feedback from the workshop participants. We argue it is time for the federal government to revisit the regulation of this field of research in Canada. We further propose that when considering reforms, it is appropriate to take a principled and pragmatic approach that relies less on overly rigid (and often shifting) lines in the sand and more on clear legal and ethical principles to guide governance of biomedical research.

Reasons for Action

There are several reasons to reform the current governance framework. Scientific developments are pushing legislative boundaries and highlighting problematic ambiguities and uncertainties that are particularly concerning when criminal liability is at stake. For example, in addition to the uncertainty noted above regarding the legal status of embryo-like entities, there is confusion regarding whether the ban on human germline editing in the AHRA extends to non-clinical research. Clarity in this area is important, especially given the research possibilities enabled by CRISPR/Cas9 (Knoppers et al. 2017a). There are also clinical demands where currently prohibited research activities, such as creation of human embryos, clones and chimeras for research purposes, have the long-term potential to improve the health and well-being of Canadians. The ban on human germline editing also appears to foreclose scientific exploration of clinical research studies of innovative fertility treatments, such as mitochondrial replacement therapy (Knoppers et al. 2017b). Though difficult to quantify, limits to promising fields of research may also constrain associated economic opportunities and result in loss of research talent and commercial prospects to other jurisdictions (Longstaff et al. 2013). Further, in Canada's growing, pluralistic society, public interests and priorities cannot be assumed to be static. Shifts in public understanding of science and its clinical potential underscore the need to regularly engage with Canadians to ensure policy is responsive to public interests and values.

Guiding Principles for Reform

Limitations on scientific and clinical progress should be justified. Where linked to ethical or other socially based arguments (as has so often been the case with this area of research), the goal should be to achieve an appropriate balance that reflects Canada's diverse society

in which a plurality of perspectives exists on key issues such as the point at which life begins, obligations to use science and medicine to ease human suffering and the sanctity (or lack thereof) of the human genome, among others. A principled approach to decision-making can be of immense value when striving for a balance between such diverse and sometimes conflicting priorities and perspectives. Recognizing that democratic engagement and appropriate consultation are vital when identifying guiding principles, we do not propose a definitive framework here. As a starting point, we suggest drawing on existing and tested guiding principles, including those of the International Society for Stem Cell Research (ISSCR), which focus on integrity of the research enterprise, primacy of patient welfare, respect for research subjects, transparency and social justice (ISSCR 2016). We also propose the following complementary principles for consideration.

Research policy limits should be proportional, with appropriate balancing of risks and benefits, as well as of possible penalties for harm. They should be guided by evidence, rather than speculation about hypothetical risks. They should be consistent, so that like activities are treated similarly and exceptionalism is avoided. They should be responsive rather than static, and amenable to flexible interpretation as circumstances change. They should be clear and supported by substantive criteria guiding how to interpret and apply them. Finally, they should be grounded in recognition of the value of scientific discovery and the interests of citizens in benefiting from science and its applications.

Recommendations

The recommendations that follow are not exhaustive. Rather, our focus is on identifying governance approaches and priority areas for a revised policy framework. The priority areas include clarifying the definition of embryo and restrictions on creation and use of embryos for research, the 14-day limit on the use of embryos for research, and rules governing creation and use of chimeras and human embryos created by cloning techniques for research purposes.

Governance approaches

> A distributed governance model involving research ethics and professional regulation should be implemented. The mandate and representation of SCOC should be expanded to provide oversight in the interim.

As some of us and others have argued elsewhere, criminal prohibitions are generally not an appropriate tool for governance of biomedical research activities (Knoppers et al. 2017a, 2017b). They lack the flexibility required to respond to dynamic and evolving fields of research and are problematic for both principled and practical reasons. As such, the criminal prohibitions should be replaced with a more flexible oversight system.

In the absence of federal responsibility exercised via the criminal law powers, there would be space for provinces and territories to exercise jurisdiction in this area. However, to avoid

a patchwork of policies and/or provincial/territorial inaction, we recommend a continued system of federal oversight via a distributed governance model involving both research ethics oversight and professional regulation. A national, independent review body could be charged with the mandate of reviewing and approving applications for research involving human reproductive materials, using the framework of a continually updated TCPS.

The credibility of such a body would be enhanced by requirements for diverse representation and a transparent appointment process as well as policies addressing conflicts of interest and review criteria. With appropriate consultation and partnering with the Colleges of Physicians and Surgeons, this oversight could be supplemented by professional regulation to ensure compliance from clinician-researchers who conduct research in private settings. Though perhaps ideal in the long-term, it would not be immediately necessary to establish a new body. The structure and mandate of SCOC, which is tasked with reviewing human pluripotent stem cell research where cells have been derived from an embryonic source and/or will be transplanted in humans or animals for compliance with the TCPS, could be updated to fill this role.

The definition of embryo and related restrictions on creation and use for research

> The current definition of embryo should be maintained. However, restrictions on the creation and use of embryos for research purposes should not extend to embryo-like structures patterned or derived from pluripotent stem cells, and which are not intended to create a human being.

The AHRA defines an embryo as "a human organism during the first 56 days of its development following fertilization or creation, excluding any time during which its development has been suspended, and includes any cell derived from an organism that is used for … creating a human being" (s. 3). It is illegal under the AHRA to "create an *in vitro* embryo for any purpose other than creating a human being or improving or providing instruction in assisted reproduction procedures" (s. 5[1][b]). Anyone who contravenes this provision is guilty of an offence and liable for a fine of up to $500,000 and/or imprisonment for up to 10 years (s. 60).

One new promising area of stem cell research involves the creation of structures that resemble embryos (Harrison et al. 2017; Warmflash et al. 2014). Commonly referred to as synthetic human entities with embryo-like features (SHEEFs) (Aach et al. 2017), these structures are not only a valuable research tool for understanding early embryo development and developmental disorders, but also raise ethical concerns (Pera et al. 2015). It is presently unclear whether (or at what point of development) these structures might be considered embryos under the AHRA and therefore illegal to create.

It seems unlikely that the harms the prohibition on creating embryos for research were originally intended to address, including concerns about exploitation of egg donors and the moral status of the embryo (Standing Committee on Health 2001), extend to synthetic

forms not requiring human eggs and likely incapable of developing into a human being. We recommend therefore that such synthetic forms be explicitly excluded from prohibitions in the AHRA. We further recommend that any limits on the creation and use of embryos or SHEEFs for research purposes be determined through an oversight process and based on criteria established through appropriate, transparent consultation. Meanwhile, Health Canada should issue public guidance regarding how the AHRA applies to SHEEFs to avoid an unnecessary chill on promising avenues of research while ensuring scientists are not risking criminal liability for work in currently ambiguous areas.

The 14-day limit on embryo research

> The 14-day limit on embryo research should be maintained, with amendments to vest authority in the Minister or her delegate to grant exceptions.

Per the AHRA, it is illegal to "maintain an embryo outside the body of a female person after the fourteenth day of its development following fertilization or creation, excluding any time during which its development has been suspended" (s. 5[1][b]). Doing so risks the same criminal liability outlined above. The 14-day rule reflects considerable international consistency and was confirmed again in the latest ISSCR Guidelines for Stem Cell Research and Clinical Translation (ISSCR 2016, s. 2.1.3.3.a.). Until lately, it was relatively uncontroversial because the longest anyone could keep an embryo alive in culture was nine days. However, recent advances extending that time frame (Deglincerti et al. 2016) have led to debates about whether and how to reconsider this limit (Chan 2017; Hyun et al. 2016) which may be impeding research that could elucidate how early human embryos and bodily organs develop, provide models to study the etiology of birth defects and chronic disease, and allow the study of developmental stages not ethically accessible in developing human embryos *in vivo*.

Canada has an opportunity here to demonstrate policy innovation in a measured fashion. The 14-day limit on embryo research should be maintained, but with the addition of a possibility for exceptions in appropriate circumstances (e.g., depending on scientific rationale and proposed limits). If the current regulatory framework is maintained, an amendment to the AHRA could vest authority to grant exceptions to the Minister, with potential for delegation to an appropriate body.

Creation and use of chimeras and human clones for research

> Restrictions on research uses of chimeras and human embryos created by cloning techniques (such as by somatic cell nuclear transfer) should be reconsidered and a more nuanced approach adopted. The ban on reproductive uses of clones and chimeras should be maintained.

The AHRA prohibits creation or transplantation of a human clone (s. 5[1][a]), defined as "an embryo that, [due to] the manipulation of human reproductive material or an *in vitro* embryo, contains a diploid set of chromosomes obtained from a single – living or deceased – human being, foetus or embryo" (s. 3). The AHRA defines a chimera as "(a) an embryo into which a cell of any non-human life form has been introduced; or (b) an embryo that consists of cells of more than one embryo, foetus or human being" (s. 3), and prohibits creation of a chimera and transplant of a chimera into a human or animal (s. 5[1][i]). Given that the definition of embryo in the AHRA captures only human organisms, the AHRA's prohibitions regarding chimeras do not extend to transplantation of human cells into non-human embryos and animals. The TCPS permits grafting of human stem cells into non-human animals after birth (with conditions) but does not allow pluripotent human stem cells to be combined with non-human embryos or fetuses (Article 12.10). These prohibitions limit research into the development of human organs and the developmental origins of human disease.

Ascertaining what degree of chimerism, if any, may be acceptable to Canadians is complex and requires both education and consultation. The Interagency Advisory Panel on Research Ethics (PRE), which is responsible for developing, interpreting and implementing the TCPS, has relevant expertise in this regard. PRE could lead such an engagement exercise and consider afresh the TCPS policy on research involving the introduction of human pluripotent cells into non-human embryos or fetuses, in line with the guiding principles outlined above.

We suggest it is appropriate to separate basic research activities from clinical research and practice involving human reproduction, as they raise different issues and would benefit from separate governance schemes. Such a separation would allow for strict restrictions to remain with respect to clinical reproductive use while leaving room for broader allowances for research uses, and would be consistent with similar international approaches (ISSCR 2016). In line with this recommendation, the use for research purposes of human embryos created by cloning techniques, such as by somatic cell nuclear transfer, should be permitted, subject to strict monitoring and ethical oversight.

Conclusion

Regulating continually evolving and socially controversial fields of science such as stem cell research can be challenging. Hard law approaches are often ill-suited to the task given their inflexible and entrenched nature. Law and policy instruments that leave greater room for public collaboration, engagement and regular evaluation and updating offer considerable advantages for emerging areas of bioscience (Nichol et al. 2017). Criminal law is the most coercive instrument available to the state and should be reserved for the gravest of harms. It is not, we suggest, a suitable tool for regulating the avenues of research currently captured by the AHRA. We recognize that revising, amending and repealing the AHRA in whole or in part will require considerable time, effort and resources, as well as both public and political support. However, we suggest this task cannot be avoided any longer.

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Correspondence may be directed to: Ubaka Ogbogu, Assistant Professor, Katz Research Fellow, Faculty of Law, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, 4th Floor Law Centre, Edmonton, AB T6G 2H5; e-mail: uogbogu@ualberta.ca; tel.: 780-492-9055; fax: 780-492-4924.

References

Aach, J., J. Lunshof, E. Iyer and G. Church. 2017. "Addressing the Ethical Issues Raised by Synthetic Human Entities with Embryo-Like Features." *eLife* 6: e20674. doi:10.7554/eLife.20674.

Assisted Human Reproduction Act, S.C. 2004, c. 2.

Cattapan, A. and D. Snow. 2017. "Everything and Nothing: Regulating Embryo Research in Canada." *New Genetics and Society* 36(1): 43–65. doi:10.1080/14636778.2017.1289469.

Chan, S. 2017. "How to Rethink the Fourteen-Day Rule." *Hastings Center Report* 47(3): 5–6. doi:10.1002/hast.698.

Deglincerti, A., G.F. Croft, L.N. Pietila, M. Zemicka-Goertz, E.D. Siggia and A.H. Brivanlou. 2016. "Self-Organization of the *In Vitro* Attached Human Embryo." *Nature* 533(7602): 251–54. doi:10.1038/nature17948.

Government of Canada. 2014. "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans." Retrieved February 14, 2018. <http://www.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/>.

Harrison, S.E., B. Sozen, N. Christodoulou, C. Kyprianou and M. Zernicka-Goetz. 2017. "Assembly of Embryonic and Extraembryonic Stem Cells to Mimic Embryogenesis *In Vitro*." *Science* 356(6334): eaal1810. doi:10.1126/science.aal1810.

Hyun, I., A. Wilkerson and J. Johnston. 2016. "Embryology Policy: Revisit the 14-Day Rule." *Nature* 533(7602): 169–71. doi:10.1038/533169a.

International Society for Stem Cell Research (ISSCR). 2016. "Guidelines for Stem Cell Research and Clinical Translation." Retrieved January 8, 2018. <http://www.isscr.org/docs/default-source/guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=2>.

Knoppers, B.M., R. Isasi, T. Caulfield, E. Kleiderman, P. Bedford, J. Illes et al. 2017a. "Human Gene Editing: Revisiting Canadian Policy." *Regenerative Medicine* 2(3): 1–2. doi:10.1038/s41536-017-0007-2.

Knoppers, B.M., A. Leader, S. Hume, E. Shoubridge, R. Isasi, F. Noohi et al. 2017b. "Mitochondrial Replacement Therapy: The Road to the Clinic in Canada." *Journal of Obstetrics and Gynaecology Canada*. doi:10.1016/j.jogc.2017.05.007.

KPMG. 2015. "Following Through: Realizing the Promise of Stem Cells, A Canadian Stem Cell Strategy and Action Plan 2015-2025." Retrieved January 8, 2018. <http://stemcellfoundation.ca/wp-content/uploads/2014/07/Following-Through-Realizing-The-Promise-of-Stem-Cells.pdf>.

Longstaff, H., V. Khramova, M. Eijkholt, A. Mizgalewicz and J. Illes. 2013. "Hopes and Fears for Professional Movement in the Stem Cell Community." *Cell Stem Cell* 12(5): 517–19. doi:10.1016/j.stem.2013.04.016.

Nichol, D., R. McWhirter and J. Dickinson. 2017. "Implementing Values-Based Governance for a New Bioresource Model." *Journal of Law and the Biosciences* 4(2): 401–11. doi:10.1093/jlb/lsx007.

Pera, M.F., G. de Wert, W. Dundorp, R. Lovell-Badge, C. Mummery, M. Munsie and P. Tam. 2015. "What if Stem Cells Turn into Embryos in a Dish?" *Nature Methods* 12(10): 917–19. doi:10.1038/nmeth.3586.

Rugg-Gunn, P., U. Ogbogu, J. Rossant and T. Caulfield. 2009. "The Challenge of Regulating Rapidly Changing Science: Stem Cell Legislation in Canada." *Cell Stem Cell* 4(4): 285–88. doi:10.1016/j.stem.2009.03.004.

Standing Committee on Health. 2001. *Assisted Human Reproduction: Building Families*. Ottawa, ON: House of Commons. Retrieved January 8, 2018. <http://www.ourcommons.ca/DocumentViewer/en/37-1/HEAL/report-2/page-5>.

Warmflash, A., B. Sorre, F. Etoc, E.D. Siggia and A.H. Brivanlou. 2014. "A Method to Recapitulate Early Embryonic Spatial Patterning in Human Embryonic Stem Cells." *Nature Methods* 11(8): 847–54. doi:10.1038/nmeth.3016.

Yang, S., J. Bo, H. Hu, X. Guo, R. Tian, C. Sun et al. 2012. "Derivation of Male Germ Cells from Induced Pluripotent Stem Cells *In Vitro* and in Reconstituted Seminiferous Tubules." *Cell Proliferation* 45(2): 91–100.