

An Investigation of Embryo Donation, Informed Consent, and Research Oversight in Canadian Human Embryonic Stem Cell Research

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Abstract

Objectives: To investigate compliance with applicable regulations by Canadian human embryonic stem cell (hESC) researchers and fertility clinics involved in providing embryos for their research, and to ascertain actual consent practices in the hESC research context.

Method: Telephone interviews were conducted with all hESC researchers, and email interviews were conducted with fertility clinics that provide embryos to these researchers. Consent forms currently used for donation of embryos to hESC research were reviewed. Separate questionnaires were used for the researchers and clinics.

Results: Three of four clinics responded. Of the clinics that responded, each had provided embryos for hESC research to at least one of the researchers. Despite considerable policy attention given to hESC research, very few researchers and clinics are actually involved in the research in Canada. Only cryopreserved embryos are currently being used in hESC research, but one researcher has applied to use fresh embryos. Fertility clinics play a primary role in the consent process, and researchers have no contact with patients/donors. Although representations have been made in academic literature and the popular press suggesting a lack of compliance by Canadian hESC researchers, researchers and clinics report that they are in substantial compliance with applicable regulations. The researchers appear to be very conscious of the ethics of hESC research. In addition, they state that they are willing to follow the rules, but they are frustrated by the lack of regulatory clarity and by delays in the research oversight process.

Conclusion: Empirical research on perceptions other stakeholders (donors, research ethics boards etc.) have of the hESC research process appears essential.

Key Words: Human embryonic stem cells, research, fertility, ethics, consent

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Résumé

Objectifs : Explorer l'observance, par les chercheurs du domaine des cellules souches embryonnaires humaines (CSEH) et les cliniques de fertilité qui fournissent des embryons à des fins de recherche au Canada, des règlements applicables et évaluer les pratiques actuelles en matière de consentement dans le domaine de la recherche sur les CSEH.

Méthode : Des entrevues téléphoniques ont été menées auprès de tous les chercheurs du domaine des CSEH et des entrevues par courriel ont été menées auprès des cliniques de fertilité qui fournissent des embryons à ces chercheurs. Les formulaires de consentement actuellement utilisés pour le don d'embryons aux fins de la recherche sur les CSEH ont été analysés. Les chercheurs et les cliniques se sont vu administrer des questionnaires distincts.

Résultats : Trois des quatre cliniques ont répondu à notre demande. Chacune des cliniques qui nous ont répondu avait fourni des embryons aux fins de la recherche sur les CSEH à au moins un des chercheurs. Malgré l'attention considérable qui est accordée aux politiques réglementant la recherche sur les CSEH, très peu de chercheurs et de cliniques travaillent en fait dans ce domaine au Canada. Seuls les embryons cryoconservés sont actuellement utilisés aux fins de la recherche sur les CSEH; cependant, un des chercheurs a déposé une demande d'utilisation d'embryons frais. Les cliniques de fertilité jouent un rôle de premier plan dans le processus de consentement; les chercheurs, quant à eux, n'ont pas de contacts avec les patientes / donneurs. Bien que certains intervenants des domaines de la littérature universitaire et de la presse populaire aient fait des allégations laissant croire que les chercheurs canadiens s'intéressant aux CSEH ne se pliaient pas aux règles en vigueur, les chercheurs et les cliniques indiquent qu'ils font preuve d'un respect non négligeable envers les règlements applicables. Les chercheurs semblent être très sensibilisés aux questions éthiques entourant la recherche sur les CSEH. De plus, bien qu'ils mentionnent être disposés à respecter les règles, ils ressentent de la frustration face au manque de clarté réglementaire et aux délais imposés par le processus de surveillance de la recherche.

Conclusion : La tenue de recherches empiriques sur les perceptions qu'ont d'autres intervenants (donneurs, comités d'éthique de la recherche, etc.) au sujet du processus de la recherche sur les CSEH semble essentielle.

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INTRODUCTION

As embryonic stem cell research progresses, the need for research ethics policies becomes more pressing. In particular, the process of informed consent for donation of embryos to hESC research has come under scrutiny.^{1,2} In Canada, issues associated with the consent process have been relatively high profile, emerging in legislation and policy documents,^{3–5} academic literature,^{1,6–10} and in the popular press. One commentator has gone so far as to suggest that current consent practices among fertility clinics involved in hESC research in Canada are so lacking that they involve “breaches of laws and ethical requirements” and the “public trust.”^{11,12}

Given these developments, and the ongoing policy activity and controversy related to informed consent and stem cell research, it is important to explore actual consent practices among hESC researchers and fertility clinics. Past studies have analyzed aspects of the consent process, including consent documents used by fertility clinics for assisted reproductive technologies.⁸ In addition, research has been done on policies and procedures for cryopreservation and for donation of surplus IVF embryos to research.^{7,10} To date, however, there has been no investigation into the consent process as a whole, particularly with respect to actual consent practices among researchers and fertility clinics conducting hESC research and the associated ethics review process. This study attempted to fill that gap through interviews with Canadian hESC researchers and fertility clinics to determine their understanding of and compliance with existing regulations. The purpose of this study was twofold: (1) to investigate compliance with existing Canadian regulations by Canadian hESC researchers and fertility clinics that provide embryos for hESC research, and (2) to ascertain actual consent practices.

Background

Canadian consent law governing research on human embryos is complex and evolving.¹ Aspects of consent are governed by legislation, ethics policy, and the common law. In the spring of 2004, the Parliament of Canada passed the

Assisted Human Reproduction Act.³ The legislation governs clinical and research activity involving human reproductive material, including gametes and embryos. Although the AHR Act received Royal Assent in March 2004, very few of its provisions have yet come into force, as many of the provisions require the creation of regulations. However, following considerable policy activity,^{13,14} regulations relating to informed consent requirements under section 8 of the AHR Act were recently released.¹⁵

Prior to the enactment of the AHR Act, the Canadian Institutes of Health Research crafted guidelines to be followed by all hESC researchers associated with an institution receiving CIHR funding.⁵ Since their introduction in 2002, the CIHR Guidelines have been revised three times. The AHR Act incorporates the CIHR Guidelines into its definition of consent and explicitly mentions the 2002 version of the Guidelines. This has led to some uncertainty about the definition of consent for the purposes of the AHR Act and associated Regulations, particularly because there were amendments to the consent process in the 2005 iteration of the Guidelines.

The CIHR also established a specialized ethics review committee, the Stem Cell Oversight Committee, to consider all applications to the CIHR for funding of research projects requiring the derivation and use of stem cells. The SCOC is not a substitute for local ethics review by the appropriate research ethics board, but adds an additional layer of oversight specifically concerned with the ethical issues that are or might be unique in the context of stem cell research.

Informed Consent to Participation in hESC Research

CIHR guidelines

According to the CIHR Guidelines, informed consent must be obtained from gamete donors and individuals or couples pursuing fertility treatment that involves the creation of embryos. The Guidelines state that these parties should be informed of the options for disposition of their unwanted embryos and should make a decision about the eventual disposition of these embryos prior to the collection of gametes and the creation of embryos. In addition, the consent of embryo providers must be “reiterated” when researchers seek to use donated embryos in stem cell research. When the embryos were created using gametes donated by third parties, there is no need for re-consent by gamete donors provided that at the time of gamete donation the donor(s) consented to the unrestricted research use of any embryos no longer required for reproductive purposes.⁵

The foregoing rules are incorporated by reference in the AHR Act and are therefore legally binding with respect to

ABBREVIATIONS

AHR	assisted human reproduction
ART	assisted reproductive technologies
CIHR	Canadian Institutes of Health Research
hESC	human embryonic stem cell
IVF	in vitro fertilization
REB	research ethics board
SCOC	Stem Cell Oversight Committee

all hESC research conducted in Canada. All such research must also be reviewed by the SCOC.

The 2005 version of the Guidelines introduced a new restriction to the informed consent process. Article 8.3.2 of the Guidelines now stipulates that “members of the health team treating and/or counselling the client should not be the persons to obtain consent from the embryo provider at the time of re-consent.”⁵

METHODS

The survey group consisted of all Canadian researchers engaged in hESC research before and at the time of this study, and fertility clinics that provide embryos to those researchers. The three researchers belonging to this group were identified through consultation with colleagues and funding agencies, including the Stem Cell Network. Only two of the three are currently conducting hESC research. The interviews were conducted via telephone.

During the interviews, the researchers identified four clinics that provided embryos for their hESC research. We then contacted the clinics to request telephone or email interviews. All clinics preferred to receive the questionnaires via email. Each of the three clinics that returned completed questionnaires had provided embryos for hESC research to at least one of the researchers.

Two separate questionnaires were used: one for researchers, and one for fertility clinics. Both questionnaires consisted of open-ended questions. The questionnaires used for the researcher interviews consisted of 26 questions covering the following: the fertility clinics involved in their research, the process of obtaining embryos from the clinics, involvement of the researchers in the informed consent process for gamete donation to fertility treatment and embryo donation to research, consent documentation and donor counselling, the REB/SCOC approval process, and knowledge of and opinions about the regulatory process. The interview questionnaires used for the clinics consisted of 13 questions focusing on general information about the clinics; the number of embryos in cryostorage; involvement in the gamete/embryo donation, informed consent process, and the REB/SCOC process; consent documentation; and opinions about the regulatory process.

We also requested and obtained copies of the consent forms used by the researchers for consent to donation of embryos for research. We received two forms: one for consent to donation of excess or damaged fresh embryos for research, and another for consent to donation of excess or damaged thawed embryos. Both forms had been approved by the relevant REB and by the SCOC.

RESULTS

General Information

Information gathered from the researchers during the interviews revealed that Canadian hESC research began in 1997 with only one researcher. Since then, only the three researchers interviewed have been conducting hESC research, and one is no longer involved.

Two researchers reported that they use only cryopreserved embryos in their research. The third researcher had used fresh and frozen embryos and at the time of the interview had a protocol pending before the SCOC for approval to use fresh embryos in research. This researcher understood from discussions with fertility clinics that over 100 fresh embryos are discarded each year when patients decide not to cryopreserve. In this researcher’s view, this poses an ethical problem since “us[ing] these embryos for hESC research . . . would be better than discarding them.”

Of the three fertility clinics that responded, only one specifically mentioned the number of embryos in cryostorage at the clinic. That clinic had 2008 embryos in storage at the time of responding, 503 of which have been designated for donation to research. The remainder are stored for patient use. The other clinics simply stated that they have cryopreserved embryos donated to research and stored for future patient use.

Consent Process

The researchers all agreed that within the context of hESC research, informed consent is absolutely essential. According to one researcher, “the [embryo] owners are the parents, and they have the right to decide what’s happening to their property.” This researcher also noted that SCOC review is “very important as it assures researchers they are in compliance.” Another stated that Canadian researchers “are very cooperative and are abiding by the rules.” One researcher noted there were disagreements between fertility clinics and researchers on the length of time embryos should remain in cryostorage before it is appropriate to seek reiterated consent for donation to research.

None of the researchers are personally responsible for obtaining consent to donation of embryos for use in hESC research. One clinic’s practice has been to have the medical director of the IVF program send patients the consent form for embryo donation to hESC research. In another clinic, a nurse or laboratory technician oversees the consent process.

Fertility clinics deal with both stages of the consent process. At the outset of IVF treatment, fertility clinics obtain initial consent to treatment and a decision from patients regarding

eventual disposition of embryos. The fertility clinics also obtain consent for embryo donation to hESC research.

Researchers have no contact with the donors during either stage of the consent process. The researchers stated that fertility clinics deal with the patients/donors at both stages. This was confirmed by the clinics, with one clinic stating that the researcher they work with recruited one of the clinic's embryologists to obtain consent for embryo donation to hESC research.

Once clinics receive documentation indicating that consent requirements have been satisfied, embryos are thawed by the clinic and delivered to the researcher without identifying information. The embryos are coded, and only the fertility clinic knows the identity of the donors.

Consent Documentation

The clinics stated that their consent documentation consisted of two forms, one for gamete collection or donation for purposes of IVF treatment, and the other for donation of embryos to hESC research.

Each clinic developed its own consent form for gamete collection or donation for IVF treatment in consultation with lawyers and ethicists. One clinic also consulted with the affiliate hospital's health records and risk management department. In all clinics, the affiliate hospital's REB generally reviews the forms and subsequent amendments. In the case of one clinic, the affiliate hospital's reproductive care advisory committee provides additional review.

All three clinics stated that their consent form for gamete donation lists a number of eventual disposition options for embryos resulting from the IVF treatment process, including donation for use in research (and specifically, hESC research), freezing, donation to another couple, and being discarded.

Consent forms for donation of embryos to hESC research were originally developed separately by each researcher with guidance from local REBs and the SCOC. All forms are designed as templates and are not protocol specific. The forms and any subsequent modifications are presented to and approved by local REBs and the SCOC. Only one researcher stated that the local REB made changes to his or her original consent form during the ethics review process.

One researcher developed a consent form before the 2002 CIHR Guidelines were made available. Another relied on the guidelines in crafting a consent form but noted that they were not very helpful; in developing the form, this researcher relied on "a mixture of common sense and guidance about hESC research—by questioning what you can and cannot do." The two researchers currently involved in

hESC research now use common documentation approved by the local REBs and the SCOC.

In addition to information about consent documentation collected during the interviews, we reviewed the REB and SCOC approved consent forms currently used by the researchers. There are two forms: one for creating hESCs from thawed embryos (Form 1) and one for creating hESCs from fresh embryos (Form 2). The stated purpose of both forms is to obtain donors' consent to participate in a study designed to create hESCs. However, both forms make it clear that participation in the study is limited to donation of embryos. The forms are similarly worded; the main difference is that in Form 1, donor(s) provide consent to forgo continued freezing of excess embryos, and in Form 2, they provide consent for their excess embryos not to be frozen. The word "excess" is also defined differently: in Form 1, excess refers to "the number of embryos . . . in frozen storage because [the donor] had more embryos available at the time of . . . previous IVF round(s) than what could be safely transferred back to [the] uterus," and in Form 2, it refers to "the number of embryos . . . higher than what can be safely transferred back to [the] uterus."

The forms state that the decision to donate embryos to research must be made by the donor couple. Both consent forms reiterate the disposition options made available to donors at the time of IVF treatment.

Other information provided on the forms relates to the destruction of donated embryos that fail to reach the blastocyst stage (2–3 days); worldwide distribution for research use of stem cell lines created from donated embryos; risks and benefits, including the risk that donating embryos as opposed to freezing (or continued freezing) for future use will reduce the options available to the donor(s) for future pregnancy attempts; confidentiality of donor information and anonymization of resulting stem cell lines; and the right to withdraw consent to use of donated embryos prior to the time of creation of an embryonic stem cell line.

The data on consent processes presented here conflict with existing literature on the legality of consent documentation used by Canadian fertility clinics. Another Canadian study has concluded that consent forms used for gamete donation to fertility treatment and embryo donation to hESC research do not conform to the CIHR Guidelines.⁸ The information gathered from our investigation, by contrast, reveals that consent processes employed by fertility clinics involved in hESC research do appear to comply with existing regulations. The source of the distinct findings may lie in the difference in focus of the two investigations. The previous study gathered data from a large number of fertility clinics, but may not have included data from the clinics that

are actually involved in hESC research, while these clinics were our focal point.

Ethics Review Process

The researchers informed us that ethics review of hESC research protocols, including review of consent documentation, is done by both local REBs and the SCOC. In the researchers' experience, both review boards suggest changes only to the consent forms, not to the research protocols themselves. All researchers stated that the SCOC approval process is fraught with delays. According to one of the researchers, delays in the SCOC approval process "compromises research in a very competitive field."

Although fertility clinics do not participate in the ethics review process, one clinic indicated that they request a copy of the ethics approval certificate from the researcher before providing donated embryos to researchers.

Regulatory Process

Two researchers reported that they had little or no knowledge of the regulatory process for hESC research, including informed consent, prior to contacting or working with fertility clinics for the first time. The other was aware of the consent requirements and had developed a consent form during a pilot project. All researchers expressed the view that the regulatory process lacks clarity. However, the tone of the answers varied. One felt the process could not be clear because it is still evolving. Another was frustrated by the delays in the ethics review process.

Two of the researchers were frustrated that their research practices have been misrepresented as unethical, particularly with respect to their compliance with current regulations, when in fact their practices comply with applicable guidelines.

Clinic specific

All fertility clinics included in this investigation are affiliated with academic research hospitals, and all became involved in the process of donation of cryopreserved embryos to research about three to four years ago. We noted that this date was not consistent with the date hESC research commenced in Canada (1997). At the time of the interviews, the clinics were providing only cryopreserved embryos to researchers.

Two clinics stated that the regulatory process governing donation of embryos to stem cell research is clear. A representative of the third clinic disagreed, stating that there is a need to clarify the technical and scientific contribution of physicians and ART laboratory scientists in stem cell research.

DISCUSSION

This study builds on existing studies assessing the level of regulatory compliance among Canadian fertility clinics and hESC researchers with current regulations on embryo donation for stem cell research,^{8,10} and on developing a free and informed consent process for hESC research.⁷ The study reveals a very low level of hESC research activity in Canada as only two researchers and three or four fertility clinics have actually been participating in research. This fact seems in marked contrast to the level of attention hESC research has received in both academic literature and media reports. In addition, the limited scope of hESC research in Canada provides an important context for understanding the extent to which researchers and fertility clinics are in compliance with regulatory processes. It also suggests that while there is a need for fertility clinics to create consent processes that will allow for the use of human embryos in research in the future, there may not be much cause for immediate concern about what appear to be "inadequate" consent processes in some fertility clinics, since most clinics have no role in hESC research. To date, the consent processes used by fertility clinics involved in hESC research appear to conform to existing law and policy.

The investigation also reveals that Canadian hESC researchers are highly engaged with the issues associated with informed consent and embryo donation for research, although they do express concerns about lack of clarity in applicable legal, ethical, and procedural requirements. Canadian hESC researchers are sensitive to ensuring that their research is built on ethical practice and seem hesitant to become involved in areas that remain unsettled in Canadian law and policy. The researchers would benefit from a clear set of consistent rules, rather than the existing patchwork of regulatory rules, policies, and procedures. These concerns may be alleviated as the Canadian regulatory process matures.

Researchers also expressed concerns about the significant delays inherent in the oversight process; all would like to see this process streamlined. The researchers did not suggest that the rules are too stringent or that oversight is unnecessary. They simply articulated the view that the rules need to be clear and the process needs to be efficient.

The link between policy and practice remains unclear in determining who should obtain consent to embryo donation for research. Our study reveals that fertility clinic personnel, including the medical director of the IVF program in one clinic, are generally responsible for obtaining consent. Existing Canadian regulations do not dictate who should obtain consent, except to state that it should not be the treating clinician.^{5,16} The mischief that these regulations seek to avoid is the potential for undue influence by treating

clinicians, given the level of trust and dependence patients have in their caregivers.² However, it has been argued that there is sufficient legal and ethical justification for vesting the responsibility of obtaining consent in the treating clinician who is not involved in the hESC research protocol.⁶ The clinics we interviewed appear to be complying with the regulations by excluding treating clinicians from the consent process.

With respect to consent documentation, although the dual system of ethics review leads to delays in the research process, it ensures that consent documentation is carefully scrutinized to assess conformity with existing regulations. The review process, together with the changes made to the consent forms by REBs and the SCOC, therefore has a direct impact on the patients/donors' experiences and perceptions of the informed consent process.

The main limitation of this study is the subjectivity of the interview data. Having undertaken this initial research, the next step is to seek to audit regulated activities in fertility clinics, including observing the consent process. A number of additional factors arise in the context of such observational research, including patient confidentiality and research funding. Also, future policy action with respect to compliance monitoring in this area of research appears essential.

This study underscores the importance of empirical research in providing much-needed evidence on the ethical, legal, and social issues relevant to stem cell research.¹⁷ By clarifying some of the existing informed consent practices in hESC research, this investigation should provide policymakers with more accurate information on the state of compliance with existing regulations, and regulatory gaps that need to be addressed.

CONCLUSION

Much research still needs to be done to provide a complete picture of the impact of informed consent rules and practices on all participants in the hESC research process. In particular, we recommend that empirical research be undertaken to determine what patients think about the consent process and the rules, and to evaluate how well the process works from the perspectives of REBs and the SCOC.

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