

# Oversight of Stem Cell Research in Canada: Protecting the Rights, Health, and Safety of Embryo Donors

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## Introduction

Stem cell research has come to the fore of scientific and public interest in the past decade, bearing the promise of providing treatments for many serious diseases and conditions.<sup>1</sup> Yet the pursuit of this research has raised significant issues of public policy and ethics in Canada and elsewhere. Recent policy discussion centers on developing ways of overseeing stem cell research that are consistent with the regulation of other forms of scientific research and yet take into account distinctive aspects of this research.<sup>2</sup> Ethical issues revolve around the derivation, study and research use of human pluripotent stem cells within the bounds of the ethical requirements of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)*.<sup>3</sup>

In 2002, the Canadian Institutes of Health Research (CIHR) developed guidelines to address the oversight and associated ethical issues raised by stem cell research, the *Human Pluripotent Stem Cell Research Guidelines* (the Guidelines).<sup>4</sup> It also established the Stem Cell Oversight Committee (SCOC) to ensure that all pluripotent stem cell research carried out at institutions receiving funding from the Tri-Council Agencies – and, on a voluntary basis, at other

public or private granting agencies in Canada or within the private sector – is in accordance with the Guidelines.<sup>5</sup>

The SCOC consists of a chair and a minimum of 11 additional members chosen by the CIHR Governing Council on advice from the Nominating Committee.<sup>6</sup> It is structured to be:

a heterogeneous group of individuals with a range of backgrounds and disciplines relevant to the mandate of the Committee. Technical experts will provide the Committee access to the latest scientific and ethical information, and representatives from the general public will represent the views and values of Canadians potentially affected by the new technologies.<sup>7</sup>

Members of the SCOC include professionals in stem cell biology and therapeutics; developmental biology or embryology; health care (*in vitro* fertilization [IVF] specialist); ethics; law; international stem cell research policy; and the social sciences. Persons from the voluntary health sector, IVF patients, and members of the general public who have a general interest in health research<sup>8</sup> and who are not ad-



vocates for any specific interest group are also included.<sup>9</sup> Members of the SCOC are not employees of CIHR and do not receive an honorarium or remuneration of any kind from CIHR.

The SCOC was mandated to provide periodic updating and proposals for revision of the Guidelines to the CIHR Governing Council and has done so twice, once in 2005<sup>10</sup> and again in 2006.<sup>11</sup> Important questions have recently been raised by several commentators about modifications made in the Guidelines before and after their publication. Others have questioned certain requirements of the Guidelines that they believe are too restrictive. In this article, those who were members of the SCOC from 2003 to 2006 trace certain clarifications of the Guidelines made during that period and discuss the rationale for them in light of these concerns. They also address criticisms made of the substance of the Guidelines. The thrust of this article is to exhibit that the paramount consideration underlying the development of the Guidelines has been the need to protect the rights, health, and safety of those who donate embryos for human pluripotent stem cell research.

## **I. Major Provisions of the CIHR Guidelines for the Oversight of Stem Cell Research**

The Guidelines permit research to study human embryonic stem cell lines derived from human embryos created but no longer required for reproductive purposes, as well as pre-existing human embryonic stem cell lines.<sup>12</sup> They mandate that persons for whom the embryos were created, and third parties who have donated gametes for the development of embryos, must have given free and informed consent for the research use of such spare embryos. They also require that no commercial transactions be carried out in connection with the development and use of such embryos.<sup>13</sup>

The Guidelines also cover research to derive and study pluripotent cell lines from human fetal tissue or amniotic fluid, the umbilical cord and placenta, and from somatic tissues.<sup>14</sup> Research involving the grafting of human pluripotent cells into non-human animals from birth to adulthood and into legally competent humans is also considered.<sup>15</sup> They preclude research involving somatic cell nuclear transfer into human oocytes, transfer of human pluripotent cells to a human embryo or human fetus, and the merging of human pluripotent cells with a non-human embryo or non-human fetus.<sup>16</sup> Fi-

nally, the Guidelines provide additional detailed conditions regarding consent, privacy and confidentiality.<sup>17</sup>

In the course of the provision of IVF, more embryos frequently result from each cycle of ovarian stimulation than can safely be transferred to a woman's uterus for implantation.<sup>18</sup> Couples and individuals with spare embryos remaining after the completion of IVF treatment may choose to freeze them, donate them for research, donate them to others for their reproductive purposes, or discard them.<sup>19</sup> Some elect to donate such embryos for various forms of research, including stem cell research.<sup>20</sup> A basic principle underlying the Guidelines is that donors of spare embryos for stem cell research must give "[f]ree and informed consent, provided voluntarily and with full disclosure of all information relevant to the consent."<sup>21</sup> This means that those considering embryo donation should decide whether to proceed with it taking account of full information provided to them about the relevant medical, social, and psychological risks and benefits that such donation entails. Moreover, they should do so freely, without coercion or exploitation. Accordingly, the SCOC has reinforced strict and detailed requirements for the provision of voluntary and informed consent for the donation of embryos for stem cell research in Canada in the course of its clarifications of the Guidelines.

## **II. Adequacy of the Informed Consent Provisions of the Guidelines**

Two sets of updates to the Guidelines regarding the conditions for providing and obtaining informed consent are of concern to Françoise Baylis (who was a member of the CIHR *ad hoc* Working Group on Stem Cell Research (*ad hoc* Working Group), an advisory body that recommended the initial 2002 Guidelines<sup>22</sup>) and Caroline McInnes.<sup>23</sup> One set of updates was introduced between the acceptance of the final report of the *ad hoc* Working Group by the CIHR Governing Council on 16 January 2002<sup>24</sup> and the issuance of the Guidelines by the Governing Council at the beginning of March 2002.<sup>25</sup> The other set was recommended by the SCOC and approved by the CIHR Governing Council in 2005<sup>26</sup> and 2006.<sup>27</sup> These changes raise questions for Baylis and McInnes about the adequacy of the protection offered to women who donate embryos for stem cell research by the Guidelines. They believe that, in effect, these changes remove certain essential elements of informed consent.



## A. Putatively Missing Elements of Informed Consent

The report of the *ad hoc* Working Group included a series of articles that were intended to “help clarify how the ethical principles and articles of the *TCPS* apply to the derivation and use of human embryonic stem cell lines and other human cells or cell lines of a pluripotent nature.”<sup>28</sup> Baylis and McInnes note that the *ad hoc* Working Group detailed under article 5.4 of its report nine elements of information to be disclosed to prospective participants as part of the consent procedure for embryo donation.<sup>29</sup> Of these nine, four could be found in the 2002 Guidelines; five did not explicitly appear in them.

The four elements of information carried forward from the report of the *ad hoc* Working Group to the 2002 Guidelines are as follows:

1. An explanation that the research participants will not benefit directly financially from any future commercialization of cell lines . . . ;
2. An explanation that the cell line(s) will be anonymized, except if the research involves autologous donation . . . ;
3. An explanation that the research could result in the production of a cell line that could be maintained for many years and used for different research purposes;
4. An assurance that prospective research participants are free not to participate and have the right to withdraw at any time before an anonymized cell line is created.<sup>30</sup>

The five informed consent provisions of the report of the *ad hoc* Working Group that do not specifically appear in the 2002 Guidelines are as follows:

1. A description of the purpose of the research;
2. A description of the research procedures;
3. A description of reasonably foreseeable harms and benefits that may arise from research participation;
4. An explanation that consent to, or refusal of, research participation will not affect access to treatment;
5. An explanation of the potential uses of the stem cells including any commercial uses, and the presence of any apparent or actual or potential conflict of interest on the part of researchers, their institutions or sponsors.<sup>31</sup>

Although the version of the four requirements carried forward to the 2002 Guidelines differs somewhat in wording

from the report of the *ad hoc* Working Group,<sup>32</sup> Baylis and McInnes appear to accept that it is substantially the same. However, the absence of the remaining five requirements of the *ad hoc* Working Group report from the 2002 Guidelines, and their replacement with the general instruction to provide the “usual information” to potential embryo donors,<sup>33</sup> is of considerable concern to them. They observe:

As the 2002, 2005 and 2006 Guidelines are to be read in conjunction with the *TCPS*, which outlines information that researchers must disclose to prospective research participants, the *TCPS* is at least one potential source of the “usual information.” But will stem cell researchers know to consult the *TCPS*?<sup>34</sup>

Baylis and McInnes suggest that researchers would, if they happened to read the *TCPS*, find this information and be able to augment their informed consent procedures appropriately. However, they maintain that researchers might not do so, become confused or look to inappropriate sources for guidance about informed consent. The result, they conclude, is that the 2002, 2005 and 2006 Guidelines “thereby failed to effectively insulate women from potential coercion associated with uninformed consent.”<sup>35</sup>

There is good reason, however, to maintain that these five requirements are not in fact missing from the Guidelines. The five points at issue are exactly the same as those described in subsections b-e of *TCPS* article 2.4. These are as follows:

- (b) A comprehensible statement of the research purpose, the identity of the researchers, the expected duration and nature of participation, and a description of research procedures;
- (c) A comprehensible description of reasonably foreseeable harms and benefits that may arise from research participation, as well as the likely consequences of non-action, particularly in research related to treatment, or where invasive methodologies are involved, or where there is a potential for physical or psychological harm;
- (d) An assurance that prospective subjects are free not to participate, have the right to withdraw at any time without prejudice to pre-existing entitlements, and will be given continuing and meaningful opportunities for deciding whether or not to continue to participate; and



- (e) The possibility of commercialization of research findings, and the presence of any apparent or actual or potential conflict of interest on the part of researchers, their institutions or sponsors.<sup>36</sup>

(Point b of the *TCPS* includes two of the elements written into the report of the *ad hoc* Working Group.) These requirements for informed consent are not specific to human embryonic stem cell research but apply to *all* research involving human subjects, tissues, biological fluids, embryos, and fetuses. In contrast, the four points that were transferred from the final report of the *ad hoc* Working Group to the 2002 Guidelines are specific interpretations of the corresponding *TCPS* consent requirements in the context of stem cell research.

Further, finding these elements of informed consent is not a matter of mere chance for researchers but is essential to the pursuit of CIHR-funded scientific research in Canada. The *TCPS* is not just “one potential source” of the “usual information” but is *the* source of information about the requirements for the pursuit of such research in Canada, since observance of the *TCPS* is a legal precondition of eligibility for CIHR funding. The CIHR requires institutional recipients of its funds to undertake that all of their investigators will conform to the *TCPS*. In addition, all researchers who conduct human research with CIHR funds or at institutions receiving funding from one or more of the Councils must conform to the *TCPS*. Thus, all researchers falling under the aegis of the CIHR 2002, 2005 and 2006 Guidelines also come under the jurisdiction of the *TCPS*. They must demonstrate both to the SCOC and to their local institutional Research Ethics Board that they will include all nine requirements in their consent procedures. Consequently, no publicly funded stem cell investigator in Canada should receive approval of any CIHR-funded research proposal that does not meet the requirements of the *TCPS*.

The SCOC saw this plainly and created a checklist to help evaluate applications; this list includes a section on informed consent materials and procedures that is used during SCOC review of informed consent documents included in stem cell research proposals.<sup>37</sup> The items on it correspond to the

five putatively missing elements. No application may be approved by the SCOC unless these (and the other) elements are included in informed consent procedures. Members of the SCOC therefore disagree with Baylis and McInnes’s assertion that the absence of specific reference to the five elements set out in the report of the *ad hoc* Working Group from the Guidelines places women at risk. Their claim that investigators addressing the SCOC guidelines might overlook the *TCPS* is formalistic and improbable.

*Members of the SCOC therefore disagree with Baylis and McInnes’s assertion that the absence of specific reference to the five elements set out in the report of the ad hoc Working Group from the Guidelines places women at risk.*

## **B. Preliminary Consent versus Preliminary Information**

Baylis and McInnes argue further that a revision to the 2002 Guidelines made in 2005 negated a key consent provision that originated in the report of the *ad hoc* Working Group.<sup>38</sup> Section 5.1 of that report and section 7.2.1 of the 2002 Guidelines reads:

Embryos no longer wanted for reproductive purposes may be donated to another couple, used for research (including research to derive and study human ES cells), or discarded. These options should be discussed with the gamete providers (and the embryo providers if these are different individuals), and *a decision regarding the eventual disposition of unwanted embryos should be made prior to the collection of gametes and the creation of embryos for reproductive purposes.*<sup>39</sup>

Section 8.3.1 of the 2005 Guidelines reads:

Those who no longer require fresh or frozen embryos for their reproductive purposes may: 1) donate the embryos to others to use for reproductive purposes; 2) donate the embryos for research (including research to derive and study human ES cells); or 3) provide authorization for the embryos to be destroyed. The embryo provider(s) (and the third-party gamete provider(s), if applicable) *must be informed of these options prior to the collection of gametes*



and the creation of embryos for reproductive purposes.<sup>40</sup>

Baylis and McInnes point out that the revision transforms a requirement that embryo donors and third-party gamete providers make a *preliminary decision* about the disposition of spare embryos to a requirement that they *be informed about* the available disposition alternatives as they enter into treatment.

Baylis and McInnes detail several possible negative consequences of this change. For example, they maintain that the opportunity to make a pre-treatment decision about the disposition of spare embryos helps patients to “explicitly recognize and value the dispositional rights of individuals over their reproductive material”<sup>41</sup> and that the absence of such opportunity denigrates those rights. They conclude that for this and other reasons the failure of the 2005 Guidelines to provide for pre-treatment disclosure of disposition options offers insufficient protection for the rights and interests of women.

They also assert that the 2005 revision is inconsistent with the *Assisted Human Reproduction Act (AHR Act)*.<sup>42</sup> The essence of their claim is that because the *AHR Act* incorporates the consent provisions of the 2002 Guidelines,<sup>43</sup> those provisions can be changed only by Parliament, not by the CIHR.

### ***1. Creation of Embryos for Reproduction or for Research?***

The first issue, whether the Guidelines should require the provision for consent to the donation of spare embryos for research at the beginning of IVF treatment, requires a brief look at the history of the revision of the 2005 Guidelines.

In May 2005, representatives of Health Canada, which develops regulations to support the *AHR Act* and reports to the Minister of Health,<sup>44</sup> advised CIHR that, in their view, the preliminary consent provisions in Section 7.2.1 of the 2002 Guidelines were not consistent with the intent of the *AHR Act*. These Health Canada representatives reasoned that if couples or individuals were to decide to donate their spare embryos for research *before* the actual assisted reproduction procedures had begun, their decision could be seen as enabling the *deliberate production of embryos for research purposes*. This, they maintained would be a prohibited activity under Section 5 of the *AHR Act*, which specifies:

(1) No person shall knowingly...

(b) create an *in vitro* embryo for any purpose other than creating a human being or improving or providing instruction in assisted reproduction procedures.<sup>45</sup>

On this basis, Health Canada representatives asked that the 2002 Guidelines be revised to state that “the embryo provider(s) (and the third party gamete provider(s), if applicable) must be informed of these options prior to the collection of gametes and the creation of embryos for reproductive purposes,” rather than requiring a decision about disposition prior to the initiation of assisted reproduction procedures.<sup>46</sup>

The SCOC and CIHR, not wishing to counsel or approve illegal acts, agreed to this request on a provisional basis, with the understanding that the SCOC would examine the issue at its next meeting. Therefore, on June 7, 2005, updated Guidelines were posted on the CIHR website with the wording provided by Health Canada at section 8.3.1 and a proviso stating that the change was “currently being reviewed.”<sup>47</sup>

Subsequent discussion at the July 2005 SCOC meeting focussed on whether a preliminary decision to donate excess embryos could be construed as an act in the service of creating embryos for research purposes. The SCOC respectfully disagreed with Health Canada’s speculative interpretation of the *AHR Act*. The argument that those who indicated just before beginning of IVF treatment that they wished to donate any supernumerary embryos remaining at the completion of this treatment for research were creating embryos for research was viewed as insupportable by SCOC members, given that the prior and seemingly obvious intention of couples in obtaining assisted reproduction procedures is to have children. A decision regarding the disposition of such embryos would be just that – a decision about what to do should there be embryos in excess of those needed to develop a pregnancy. It was inconceivable to SCOC members that a couple would have as their primary intention the creation of embryos for research purposes and use IVF to initiate a pregnancy and bear a child in order to do so. It was just as inconceivable that some mixture of a desire for children and a desire to benefit stem cell research would lead couples to attempt to have children by means of IVF when they would not independently have done so in the absence of the opportunity to benefit stem cell research.



The SCOC relied in its discussion on an accepted legal and ethical distinction between *knowledge* and *intent*. A physician may *know* that a particular surgery will result in some degree of pain and suffering to a patient, and yet not *intend* that the patient experience such pain and suffering. The physician would avoid that pain and suffering, if that were possible, but recognizes in advance that it will ensue. Similarly, a couple seeking to have children by means of IVF *knows*, after discussions with the treating physician and counselors at the IVF centre, that this process may result in embryos in excess of their current reproductive needs – and yet that couple does not *intend* to produce such additional embryos. They *intend* to have children.

The view of this matter adopted by the SCOC is supported by a subsequent discussion in a 2006 paper by Elizabeth Kuruvila of the Law & Government Division of the Library of Parliament, which provides authoritative information for Committees and Members of the Senate and the House of Commons.<sup>48</sup> Kuruvila observes that the forthcoming Health Canada consent regulations, approved by the House of Commons Standing Committee on Health and awaiting Senate approval, define “donor” as “*the person/couple for whose reproductive use the embryo was created.*”<sup>49</sup> Clearly, this definition requires that the intention of those who donate spare embryos for stem cell research must be to create these embryos for reproductive purposes. Kuruvila goes on to explain that “if an *in vitro* embryo is to be used for a specific research project...the written consent of the donor of the human reproductive material is also necessary, *unless he or she has already consented to that use as the donor of the embryo.*”<sup>50</sup> This statement confirms that consent to embryo donation may lawfully be given before the embryo becomes surplus. It therefore supports the point made by the SCOC that to make a pre-treatment decision to donate spare embryos remaining at completion of an IVF process to research does not derogate from the intention to create embryos for reproductive purposes. It is to plan ahead for the disposition of any spare embryos that, as events may turn out, cannot be used for reproductive purposes.

## 2. The AHR Act and Amendments to the 2002 Guidelines

The SCOC returned to the issue of whether CIHR could alter the consent provisions of the 2002 Guidelines at its November 2005 meeting. According to the *Act*, consent for stem cell research

means fully informed and freely given consent that is given in accordance with the applicable law governing consent and that conforms to the provisions of the *Human Pluripotent Stem Cell Research Guidelines* released by the Canadian Institutes of Health Research in March, 2002, as detailed in the Regulations.<sup>51</sup>

The SCOC solicited and considered the opinions of a number of experts regarding whether or not incorporation of the 2002 Guidelines in the *AHR Act* meant that the consent provisions of the Guidelines had become static (that is, not subject to change by CIHR). The position of all those questioned was that the intention of Parliament on this point in the *AHR Act* was unclear.

The legal principle of statutory construction, which maintains that Acts are to be read as a whole, not simply section by section, is relevant to the question whether the *AHR Act* incorporates the consent provisions of the 2002 Guidelines.

Baylis and McInnes overlook this principle when they claim that these consent provisions are necessarily included in the *Act*.<sup>52</sup> Kuruvila explains that “the statute itself is dependant [sic] upon the Regulations in order to be implemented.”<sup>53</sup> That is, the *Act* is a parent act authorizing delegated legislation through regulations. Section 65(2) of the *Act* provides that: “[t]he regulations may incorporate any document by reference, regardless of its source, either as it reads on a particular date or as it is amended from time to time.”<sup>54</sup> Accordingly, the embodiment of the 2002 Guidelines in regulations would mean that they are superseded by any subsequent guidelines. Indeed, since the *Act* is to be read as a whole, courts might well find that the statutory reference to the 2002 Guidelines delegates authority to CIHR to amend those guidelines with statutory force, since the sovereign Parliament does not propose to become engaged in the de-

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tails or refinements of regulatory or guideline development within the framework of the *Act*.

The view that the forthcoming regulations are intended to incorporate not only the consent provisions of the 2002 Guidelines, but also those of subsequent guidelines developed by the CIHR is further supported by section 3 of the *AHR Act* cited above.<sup>55</sup> The last clause of this section can be read as allowing for the recognition of subsequent clarifications of the consent provisions of the 2002 Guidelines.

In view of the legal complexity of these questions, the SCOC decided that it was unable to resolve this matter on its own initiative and that a prudent immediate course would be to refrain from changing the consent provisions of the 2002 Guidelines at that time. The Committee therefore recommended to the Governing Council of CIHR that the text of the June 7, 2005 updated Guidelines revert to the requirement of an initial decision (preliminary consent) as stated in section 7.2.1 of the 2002 Guidelines, and left the matter for further consideration and resolution by Health Canada. Thus, SCOC had already recommended the path subsequently suggested by Baylis and McInnes.

### **III. The Donation of Fresh Embryos for Stem Cell Research**

A second major issue of concern first raised by Jeffrey Nisker and Angela White<sup>56</sup> and then addressed by Baylis and McInnes<sup>57</sup> centres on a 2005 SCOC-recommended clarification of a section of the 2002 Guidelines which indicates that the CIHR only funds research on embryos remaining after IVF treatment that are in excess of patients' needs.

The 2002 Guidelines state that such embryos can be donated for stem cell research provided that "[t]he embryos used were originally created for reproductive purposes and are no longer required for such purposes."<sup>58</sup> The phrase "whether fresh or frozen" was introduced into the 2005 Guidelines by the SCOC. These Guidelines state that such embryos can be donated for stem cell research provided that "[t]he embryos used, whether fresh or frozen, were originally created for reproductive purposes and are no longer required for such purposes."<sup>59</sup> The SCOC recommended this modification to CIHR's Governing Council in order to make it clear that the Guidelines allow the donation of both fresh and frozen embryos that are in excess of a couple's reproductive needs for stem cell research with the informed consent of the donors.

#### **A. Whether to Inform Patients about the Full Panoply of Alternatives for Embryo Disposition Available**

Nisker and White recognize that it is legally permissible under the *AHR Act* and the SCOC Guidelines for physicians to offer patients the choice to donate fresh embryos to stem cell research.<sup>60</sup> However, they believe that doing so may be problematic according to the Canadian Medical Association (CMA) Code of Ethics, which maintains that it is the professional responsibility of physicians to consider the well-being of patients and to take steps to prevent avoidable harm to them.<sup>61</sup> This means, they maintain, that in the context of providing IVF, it is the responsibility of physicians to maximize patients' chances of achieving pregnancy and to minimize their risk of harm by not offering them the option of donating fresh embryos in excess of their reproductive needs for research. They state:

since the advent of embryo cryopreservation in the late 1980s, physicians have generally not offered their patients the choice to donate fresh embryos to research, since this choice could decrease their patients' chances of pregnancy or increase their risk of harm because of the additional cycles of menotropin drugs and oocyte retrieval surgery that may be required if the current treatment does not result in a child.<sup>62</sup>

To allow patients to choose not to cryopreserve spare fresh embryos for future use could violate the professional responsibilities delineated in the CMA Code of Ethics, they conclude.

Nisker and White recognize that physicians also have an obligation, according to the CMA Code of Ethics, "to provide information that would enable the woman to make a free and informed decision in this regard," i.e., whether to donate fresh embryos for stem cell research.<sup>63</sup> However, because women trust their physicians not to offer them options that might increase their risk of harm, physicians should not do so. Harm may arise because "these women may not understand and appreciate that there is a decrease in their likelihood of pregnancy...from donating a few fresh embryos" and because women "may feel compelled to comply with what they believe their physician wants them to do."<sup>64</sup> Nisker and White therefore conclude that physicians should not knowingly become complicit in decreasing their patients' chances of pregnancy and increasing their risk of harm by offering them the option of donating fresh embryos.



Baylis and McInnes also question the decision by the SCOC and the CIHR to explicitly include the words, “whether fresh or frozen” in the 2005 Guidelines on grounds akin to those enunciated by Nisker and White. They state:

Generally, it is not in the medical or other-regarding interests of infertile women using assisted reproductive technologies to donate their fresh embryos for research when these could be frozen for later infertility treatment.... Neither infertility patients nor their physicians can know whether non-transferred embryos will be wanted for future reproductive use unless these embryos are being discarded for morphological, biological, or genetic reasons.<sup>65</sup>

They observe that using frozen embryos in a subsequent treatment cycle decreases the number of painful and risky procedures that women must undergo, as well as the psychological stress, social disruption, and financial burden of IVF treatment.<sup>66</sup> Since patients and physicians cannot know whether spare embryos remaining at the conclusion of an IVF cycle will be needed for reproduction in the future, they state, “it follows that if embryos are truly being created for therapeutic purposes..., usually they would be frozen for such future use.”<sup>67</sup>

These commentators appear to contend that women cannot make a free and informed choice about the donation of fresh embryos to stem cell research and would therefore eliminate the phrase in the 2005 and 2006 Guidelines that explicitly allows this donation. To pursue such a path, however, would abrogate the very rights that, as Nisker and White observe, the CMA Code of Ethics explicitly recognizes and supports – the right of patients to be informed of the options available to them and to decide freely which of these options they prefer on the basis of their beliefs and values. In a now-classic article, the late Canadian bioethicist Benjamin Freedman discusses these rights, declaring:

A person who has the capacity to give valid consent...has the right to have that fact recognized by us.... From whence arises this right? It

arises from the right which each of us possesses to be treated as a person, and in the duty which all of us have, to have respect for persons, to treat a person as such and not as an object. For this entails that our capacities for personhood ought to be recognized by all – these capacities including the capacity for rational decisions, and for action consequent upon rational decision.<sup>68</sup>

*To pursue such a path, however, would abrogate the very rights that, as Nisker and White observe, the CMA Code of Ethics explicitly recognizes and supports – the right of patients to be informed of the options available to them and to decide freely which of these options they prefer on the basis of their beliefs and values.*

Freedman goes on to maintain that patients must be informed about the medical alternatives available to them and their possible outcomes, so that they can make a responsible decision about the issues at hand.<sup>69</sup> Respect for patients as persons, as Freedman explains it, means that those who are about to undergo IVF treatment should be informed by physicians of the various options available for the disposition of embryos that might remain at the completion of their current IVF cycle and

what each might involve. To refuse to inform patients about such options is to treat them with disrespect and to deny their very personhood.

Thus, physicians are obligated by their professional and moral commitments to inform patients about the various choices available to them with regard to the disposition of unused embryos, even if they believe that it would be unwise for patients to elect one of those options. They are obliged to reveal to patients that they have the option of freezing embryos that remain for future reproductive use, as well as the option of donating spare embryos, whether fresh or frozen, for research. Physicians are entitled to offer and explain their recommendation from among the alternatives available to patients in the course of discussions about the disposition of spare embryos but not to withhold information about any that they consider less than optimal.

## **B. Why Some Patients Choose to Donate Fresh Embryos for Research**

In fact, most women and their partners do choose to have their excess embryos cryopreserved at IVF clinics.<sup>70</sup> How-



ever, some elect to have just a portion of the embryos cryopreserved and to donate the remaining fresh embryos for research.<sup>71</sup> Moreover, others decide not to freeze any remaining embryos; some within this group donate their spare fresh embryos for research, rather than discard them or donate them to another couple.<sup>72</sup>

Those who donate fresh embryos for research have varying reasons for their decision. Financial hardship can lead some Canadian couples and individuals with fresh supernumerary embryos remaining at the completion of IVF treatment to choose not to freeze them. This is because they must be able and willing to pay approximately \$645 (range \$450-\$1,000) for the cryopreservation of unused spare embryos, varying additional amounts to thaw and transfer frozen embryos, and about \$300 in annual storage fees.<sup>73</sup> Provincial health programmes that otherwise fund IVF therapies do not fund such cryopreservation. If couples or individuals cannot or do not want to pay for cryopreservation, their spare fresh embryos are not frozen by infertility clinics and they may choose to donate them for research.

Further, some couples and individuals may be aware that embryos that are considered of optimal quality are given priority in transfer to a woman.<sup>74</sup> They may be concerned about whether their spare embryos remaining after an IVF cycle are of sufficiently high quality to produce living, healthy children. This concern may lead them to decide against freezing spare embryos. They may also be aware that the process of freezing can damage embryos;<sup>75</sup> it has been estimated that 35 percent of such embryos do not survive the freeze-thaw process.<sup>76</sup> The possible negative effects of the freezing process on any child that might result from the use of IVF were shown in one study to create anxiety in more than 20 percent of both male and female patients.<sup>77</sup> Couples and individuals with such information who wish to attempt to have children in the future might decide to go through another IVF cycle at a later time in order to develop embryos that they believe have a better chance of resulting in a healthy child or children and may therefore decide to donate any remaining fresh embryos for research.

Third, some women and their partners have personal reasons for deciding not to cryopreserve spare embryos. Bernard M. Dickens and Rebecca J. Cook explain:

[f]resh embryos may be acquired for research... if patients consent in advance when they have decided that the transfer of fresh embryos following induced superovulation will be the last

they intend to receive, on grounds such as age or cost, or oppose cryopreservation of untransferred embryos, for instance on religious or philosophical grounds.<sup>78</sup>

Rather than discard their spare embryos or donate them to others, these women and their partners may choose to donate them to research.

Those who consider whether they wish to freeze spare embryos that may remain at the conclusion of IVF treatment must balance the various risks and benefits involved. To deny couples or individuals who decide that they do not wish to freeze spare embryos the option of donating fresh embryos for research would be to deny their right to choose among the various options available for the use of their embryos. This is a right that, as noted above, is at the core of the moral imperative behind the requirement to obtain informed consent.

### **C. Protections Built into the Guidelines for those Who Choose to Donate Fresh Embryos for Stem Cell Research**

As further support for their position that the Guidelines should not endorse the donation of fresh embryos for research, Baylis and McInnes cite a recommendation in a report of the Ethics Committee of the American Society for Reproductive Medicine (ASRM) which states, with respect to the donation of fresh embryos for stem cell research, that a treating physician:

might induce a patient to allow insemination of extra eggs so that they may be donated for research. Moreover, this increases the chance that decisions will be made quickly and later regretted by couples. Without evidence that fresh embryos are significantly preferable to frozen embryos for ES [embryonic stem] cell use, it is appropriate to use only spare embryos that have been frozen.<sup>79</sup>

Since a committee of the ASRM recommends against the donation of fresh embryos for research, Baylis and McInnes appear to argue, this practice should not be allowed in Canada.

One assumption behind the recommendation of the ASRM Ethics Committee is that the physicians who treat patients



undergoing IVF treatment are the persons who seek consent for donation of spare embryos for research use when such patients have completed an IVF cycle. Another assumption is that the timeline for deciding on the disposition of excess fresh embryos (e.g., freezing, donation, discard) is short and infringes on the capacity of couples and individuals to make fully informed choices. However, neither of these assumptions holds in Canada.

With respect to the first embedded issue, that treating clinicians might induce women to donate spare fresh embryos for research,<sup>80</sup> that possibility is unlikely to become a reality in Canada. Articles 7.2.7 of the 2002 Guidelines<sup>81</sup> and 8.3.7 of the 2005 Guidelines<sup>82</sup> state, “[p]hysicians responsible for fertility treatment...will not be part of a stem cell research team.” Article 8.3.2 in the 2006 Guidelines goes on to state: “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.”<sup>83</sup> Thus, according to the Guidelines, not only the treating physician, but also any professionals involved in the care of specific patients undergoing fertility treatment are precluded from carrying out stem cell research and from requesting consent from patients for the donation of spare embryos at the time when those patients are asked to confirm their initial consent to such donation. These restrictions lessen the possibility that treating physicians could exercise undue influence on patients to induce them to donate spare embryos for research that physicians wish to complete.

The statement of the ASRM Ethics Committee goes on to suggest that the pressure of time may not allow potential embryos donors to give an informed consent to the donation of fresh embryos. This second concern also does not apply to the provision of fertility treatment at centres in Canada. Those seeking fertility treatment in Canada are to be informed when they first enter IVF programmes that it may be possible to cryopreserve any embryos in excess of their reproductive needs that remain at the completion of treatment and that they will have to review their decision about whether or not to freeze such embryos at the time of the transfer procedure. Thus, they know several months in ad-

vance of the IVF procedure that if they choose not to freeze excess embryos, the available options will include discard of these embryos, donation to another couple or donation for research. Therefore, the general imputation to women and their partners of an incapacity to consent freely to the donation of fresh embryos for stem cell research because the actual decision must be made very quickly does not seem plausible for those living in Canada. Because every situation is unique in its details, however, the SCOC (and presumably Research Ethics Boards) consider these issues. If there appeared to be insufficient time for consideration of risks and benefits in a specific research protocol, or any

other interference with the consent process, the SCOC would not approve the application or would call for revisions, as required by the TCPS.

The former chair of the ASRM Ethics Committee, John A. Robertson, a prominent legal scholar who remains as a consultant to that committee, has indicated that he plans to recommend to the committee that the ASRM guidelines be revised to take into consideration those couples and individuals who do not wish to freeze spare

embryos.<sup>84</sup> This could serve to reconcile the current difference between the ASRM Ethics Committee Statement and the Canadian Guidelines with regard to the alternative of donating fresh embryos remaining after the completion of IVF treatment.

#### ***Whether Frozen Embryos are Superior to Fresh Embryos as a Source of Pluripotent Stem Cell Lines***

Baylis and McInnes maintain, in addition, that frozen embryos are superior to fresh embryos as a source of pluripotent stem cells for stem cell research. They base this belief on a study in which investigators found that frozen thawed embryos gave rise to human embryonic stem cell lines at a rate that was 3.7 times higher than fresh embryos.<sup>85</sup> The frozen embryos used in this study, however, were selected because they were deemed of sufficiently high quality for future implantation, whereas the fresh embryos were not considered suitable for transfer to a woman’s uterus or to freeze.<sup>86</sup> Because of this difference in the quality of the embryos used, this study did not demonstrate that frozen

*Therefore, the general imputation to women and their partners of an incapacity to consent freely to the donation of fresh embryos for stem cell research because the actual decision must be made very quickly does not seem plausible for those living in Canada.*



embryos are superior to fresh embryos for the derivation of human pluripotent stem cell lines for research. The definitive study needed to assess whether it is preferable to use fresh or frozen embryos to generate human pluripotent stem cell lines would involve a controlled comparison of the use of large samples of both fresh and frozen embryos of similar quality. Such a study has not been reported in the peer-reviewed scientific literature to date.

Available scientific evidence suggests that the use of fresh, rather than frozen, embryos might be expected to result in a higher rate of success in yielding human pluripotent stem cell lines. Indirect support for this conclusion can be derived from studies that compare pregnancy rates resulting from the use of fresh and frozen embryos. It has been estimated that cryopreservation of embryos results in a 30 percent reduction in the potential for pregnancy when compared with fresh embryos.<sup>87</sup> In one study, for instance, when researchers removed lysed embryos that had been damaged by the processes of freezing and thawing, the pregnancy rates of women receiving the remaining embryos increased from 23 to 54 percent.<sup>88</sup> Such studies suggest that fresh embryos maintain greater viability than frozen embryos because they do not suffer the sort of damage to which embryos are exposed during cryopreservation. This, in turn, suggests that intact fresh embryos are likely to provide a higher number of human pluripotent stem cell lines than frozen embryos, rather than the reverse.

### E. Why the Term “Fresh” Was Added to the Guidelines

Baylis and McInnes also question why the phrase “fresh or frozen embryos” was included in the 2005 Guidelines. They state:

the practice with which the Stem Cell Oversight Committee and the Governing Council sought to align the guidelines – namely the ongoing research use of fresh embryos to derive stem cells – was only publicized after the 2005 Guidelines

were released...[on] June 7, 2005.... Two days later, on June 9, 2005, the successful derivation of Canada’s first two hESC [human embryonic stem cell] lines was announced and the research use of fresh embryos was disclosed. As these hESC lines appear to have been approved by the Stem Cell Oversight Committee at its January-February 2005 meeting, questions arise about the delay in reporting this scientific accomplishment to the public. For example, could it be that the announcement of the successful

derivation of these hESC lines – based on research involving the use of fresh embryos and dating back to 2003 – was delayed until the 2005 Guidelines (explicitly allowing the research use of fresh embryos) were in the public domain? *Res ipsa loquitur*?<sup>89</sup>

Thus they allege that the SCOC changed the Guidelines in order to approve proposed research involving fresh embryos that was about to be carried out or

else to justify having already done so. This is a serious allegation that imputes dishonesty and deception to the SCOC. In fact, it is untrue. It is an undeserved affront to the integrity of the SCOC and its members, who include patient and public representatives, as well as Canadian and other internationally recognized authorities in bioethics, law, and several sciences.

At the time when stem cell lines CA1 and CA2 were created, it was unclear whether or not they came under the jurisdiction of CIHR and the 2002 Guidelines. The SCOC did not consider or approve creation of those lines. Researchers submitted an application to SCOC, considered at the July 2004 meeting, to characterize the two developed lines. Accordingly, the SCOC undertook to determine whether the lines had been created in a manner consistent with the 2002 Guidelines; this was necessary to determine whether to approve the application for characterization.

The SCOC found no automatic, *a priori* prohibition in the 2002 Guidelines or in the *TCPS* against the use of fresh embryos for stem cell research. Additional information was

*Available scientific evidence suggests that the use of fresh, rather than frozen, embryos might be expected to result in a higher rate of success in yielding human pluripotent stem cell lines.*



required, however, in order to evaluate other aspects of the application. A resubmission was considered at the January-February 2005 meeting and was found to be consistent with the 2002 Guidelines and the *TCPS*. It was therefore approved. At the January-February 2005 meeting, the SCOC also considered an application for the creation of new lines from fresh embryos. That application was approved pending revisions to the proposed donor consent process, also under the 2002 Guidelines and *TCPS*.

In short, the change in wording of the 2002 Guidelines that the SCOC recommended at the January-February 2005 meeting was intended to reflect the fact that the SCOC had found the use of both fresh and frozen embryos to be approvable under the existing 2002 Guidelines. It was not made to permit new, previously unauthorized, research. As observed above, there can be good reasons for women and their partners to decide to donate fresh embryos for stem cell research. The addition was indeed seen by the SCOC as an editorial change made to clarify the policy set into the extant Guidelines, rather than a revision of CIHR policy or standards.

#### **F. Policies of Other Countries Regarding the Use of Fresh Embryos in Stem Cell Research**

The use of donated fresh embryos remaining after the completion of IVF treatment for the derivation of stem cell lines is not unique to Canada. The initial derivation of stem cell lines from human embryos permitted for use in the United States was carried out with a cohort of embryos that included some fresh embryos.<sup>90</sup> Stem cell lines have also been derived from spare fresh embryos by investigators in Australia,<sup>91</sup> Singapore,<sup>92</sup> Sweden,<sup>93</sup> Denmark,<sup>94</sup> and the United Kingdom.<sup>95</sup> Fresh embryos are employed in stem cell research in at least fifteen other countries.<sup>96</sup> Their use in stem cell research is explicitly prohibited in five countries.<sup>97</sup> Therefore, CIHR has not embarked on an extreme and unusual path in allowing the donation of fresh embryos for stem cell research with informed consent in Canada.

### **IV. The Prohibition against Allowing the Treating Physician to Seek Informed Consent from Embryo Donors to Stem Cell Research**

As noted above, there are at least two times at which the question of the disposition of spare embryos must be ad-

ressed with couples and individuals undergoing IVF treatment according to the Guidelines. The first is when they meet with the IVF physician before gametes are collected and embryos are created by means of IVF for reproductive purposes.<sup>98</sup> At this time, they must be informed by their treating physician of the options available to them for the disposition of embryos that may remain at the completion of the IVF cycle: to freeze them, donate them to another couple, donate them for research, or discard them.<sup>99</sup> They must make a preliminary decision regarding the eventual disposition of such embryos at this time as part of the informed consent process.<sup>100</sup>

The second time at which couples and individuals must consider the disposition of spare embryos is at the point of embryo transfer, after gametes have been collected and embryos have been created.<sup>101</sup> At this time, those who had earlier elected to donate spare embryos must choose whether or not to confirm this decision.<sup>102</sup> The Guidelines stipulate that at this second point, “[m]embers of the health team who are treating and/or counselling the client should not be the persons who obtain consent from the embryo provider”.<sup>103</sup> Thus, a clear distinction is built into the Guidelines between the treating physician and those who obtain final consent from patients to embryo donation for stem cell research.

#### **A. The Role of the Treating Physician with Respect to Consent for the Donation of Spare Embryos for Research**

Timothy Caulfield, Ubaka Ogbogu and Rosario Isasi, however, question whether the treating physician should be prohibited by the Guidelines from seeking re-consent from those who would donate embryos for stem cell research.<sup>104</sup> They note that Canadian law has historically placed the onus for obtaining informed consent for matters related to the provision of medical treatment on the treating physician.<sup>105</sup> In the case of embryo donation, Caulfield *et al.* argue, “the embryos are being created in a clinical situation over which the treating physician has ultimate legal responsibility.”<sup>106</sup> Therefore, the treating physician, they conclude, should be the person responsible for obtaining informed consent from couples or individuals for the donation of spare embryos for research.

According to the Guidelines, the treating physician must obtain initial consent for the donation to research of any remaining spare embryos before the development of embryos for reproductive purposes.<sup>107</sup> However, the reiteration of consent for such donation, according to the Guidelines,



does not take place until after the embryos have been created and the IVF cycle has been completed.<sup>108</sup> Thus the final decision of patients about whether to donate spare embryos that have resulted from that cycle is not made during the course of the specific IVF treatment, but after it has been completed. Consequently, those who reaffirm an earlier decision to donate remaining embryos for research a few days, weeks, or months after IVF treatment has ended are no longer under the treatment aegis of the physician for that IVF cycle. Similarly, those who opt to donate spare embryos that have been in a frozen state for years after treatment has ended do not remain in a physician-patient relationship during all those years with the physician who carried out the IVF cycle in which these embryos were developed. The argument that the treating physician is legally responsible for obtaining consent for the donation of supernumerary embryos from couples or individuals with such embryos because he or she is in a physician-patient relationship with them therefore seems unsustainable.

Caulfield *et al.* argue further that since the treating physician is familiar with the history, needs and concerns of the individual patient, he or she is in a good position to provide that patient with information about embryo donation.<sup>109</sup> However, the requirement in the Guidelines that physicians and other members of the treatment team should not seek consent from their patients for the donation of spare embryos for stem cell research<sup>110</sup> was adopted *just because* of their close relationship with these patients. The position of power and authority in which physicians stand with respect to their patients,<sup>111</sup> particularly in the assisted reproduction setting in which the life-changing opportunity to bear children seems to patients to be wholly in the hands of these professionals,<sup>112</sup> is weighty. Bernard Lo and colleagues observe that patients undergoing IVF therapy are “so dependent upon their ART [assisted reproductive technology] physician that they might consent to anything that the doctor requests or even presents.”<sup>113</sup> Indeed, the Ethics Committee of the American Society for Reproductive Medicine, which is largely composed of specialists in reproductive medicine, maintains in its guidelines regarding the donation of spare embryos for stem cell research that “[w]henver possible, someone other than the treating infertility specialist should make requests for embryos for research purposes.”<sup>114</sup> This committee recognizes that physicians might inadvertently exercise undue pressure on patients to donate spare embryos for research. Physicians who are familiar with their patients’ history, needs and concerns are in an especially good position unduly to influence – even unintentionally – the decision of those patients about whether to donate spare embryos for stem cell research. The

Guidelines therefore maintain that the treating physician should not engage in securing final informed consent to the donation of spare embryos for stem cell research.

Those professionals at IVF treatment centres who have not provided medical treatment to patients who wish to donate spare embryos for research do not have the same sort of influence over patients and are not subject to the possible conflicts of interest that a treating physician might have. Several among them would be qualified to provide couples and individuals with information relevant to the donation of spare embryos for research at the time of re-consent. These professionals could be assigned to offer them information about stem cell research projects that are in the offing and to request their voluntary and informed consent for the donation of spare embryos for one or more of these projects.

## **B. Positions of Other Bodies Regarding the Role of the Treating Physician with Respect to Consent for Stem Cell Research**

Caulfield *et al.* state in addition that “most policies [developed within the international community] contain no explicit recommendation that the treating physician be removed from the consent process” for embryo donation to stem cell research.<sup>115</sup> Thus, they suggest either that this requirement of the Guidelines of the CIHR is unnecessary or is out of step with the policies of the rest of those countries around the world that conduct stem cell research.

However, Caulfield *et al.* can find no clear consensus among the guidelines and policies of the bodies that they survey regarding who should seek consent from couples for embryo donation; they indicate that these guidelines and policies differ greatly.<sup>116</sup> Several among these bodies agree that the treating physician should not be responsible for seeking informed consent from couples or individuals for the donation of spare embryos for stem cell research. Thus, the British Human Fertilisation and Embryology Authority authorizes an individual at the fertility centre where spare embryos remain in fresh or frozen state to seek consent for the donation of supernumerary embryos for research from couples and individuals.<sup>117</sup> It states in its *Code of Practice* that:

Where embryos are used for research, the Centre shall ensure that:

- (a) a designated individual *who is not directly involved in the Donors’ treatment* is available to discuss the



project of research and the possibility of donating material to the project with the Donors,

- (b) the individual obtaining consent is suitably trained and qualified and has sufficient knowledge of the proposed research, and understands the risks involved; this person should also act in accordance to professional guidelines....<sup>118</sup>

The requirement listed in (a) rules out the treating physician as the person authorized to seek informed consent from embryo donors.

In addition, as noted above, the Ethics Committee of the American Society for Reproductive Medicine explicitly maintains that the treating physician should not be the person who requests the donation of embryos for research.<sup>119</sup> The "Sample Research Consent Form for Embryo Donation for Stem Cell Research" of the International Society for Stem Cell Research (ISSCR) states that "[i]f you are undergoing fertility treatment, your treating physician will not know what you have decided, unless you choose to provide this information."<sup>120</sup> This indicates that the ISSCR holds that the treating physician should not be the person responsible for obtaining consent to the donation of spare embryos for stem cell research. Further, the stem cell research report of the American Association for the Advancement of Science and Institute for Civil Society states "there should be a solid 'wall' between personnel working with the woman or couple who hope to get pregnant, and personnel requesting embryos for stem cell purposes."<sup>121</sup>

Thus, several respected bodies from various parts of the world that have developed detailed policies regarding informed consent to embryo donation for stem cell research maintain that the treating physician should not be the professional assigned to seek such consent. The CIHR has stated this explicitly in the Guidelines, thereby making clear the need to ensure that potential embryo donors are not subject to possible undue influence by the treating physician that might result from the pressured atmosphere inherent in the assisted reproduction setting and the close relationship in which physician and patient necessarily stand in the reproductive context.

## Conclusion

This article addresses certain questions raised by commentators with regard to specific modifications in the Guidelines of the Canadian CIHR from 2002 to 2006. These

commentators have argued that these changes conflict with the rights and interests of women who donate embryos for stem cell research; that they wrongly allow the donation of fresh embryos for stem cell research without adequately informed and voluntary consent; and that the Guidelines unwisely bar the treating physician from seeking consent for the donation of such embryos. In response, members of the SCOC explain the history of these changes and the reasons for them, maintaining that the modified provisions of the Guidelines enforce strict conditions for obtaining voluntary and informed consent from those who donate spare embryos remaining after the completion of IVF treatment for stem cell research. They also hold that to facilitate a free and voluntary choice to donate spare embryos for stem cell research, treating physicians at IVF clinics should not be the professionals who secure informed consent to the donation of such embryos from couples and individuals. They believe that the Guidelines are well designed to protect the rights, health, and safety of those who donate spare embryos remaining after IVF procedures have been completed for stem cell research.

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