Research ethics and stem cells

Is it time to re-think current approaches to oversight?

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Few areas of scientific inquiry have received the amount of attention from politicians, the media and the ethics community that research involving human stem cells has received. A large part of this attention, particularly in the early days of the field, was focused as much on the controversial nature of the research as on its scientific promise. The primary cause of controversy remains the use and destruction of human embryos to derive stem cells or create human embryonic stem cell (hESC) lines, which is considered by some constituencies to be morally problematic. A common policy response to these issues has been to subject stem cell research to heightened or additional ethics reviews and oversights. Internationally, many jurisdictions have established specific legislation, ethical guidelines and oversight bodies to govern stem cell and related embryo research (Box 1).

In Canada, for example, research that involves human embryonic stem cell (hESC) lines or the engraftment of human induced pluripotent stem cells (hiPSCs) or their derivatives into humans or animals for purposes other than testing teratoma formation, which is conducted at institutions that

receive federal funds, must comply with guidelines that were specifically created to govern human pluripotent stem cell (hPSC) research. Protocols are subject to approval by a national research oversight body—the Canadian Institutes of Health Research (CIHR)’s Stem Cell Oversight Committee (SCOC)—which was created in 2002 for the purpose of implementing the guidelines. SCOC’s oversight functions are in addition to established research ethics reviews, which are handled by institutional research ethics boards (REBs) and animal care committees. This framework, commonly referred to as ‘dual review’, was partly intended to ensure that research protocols in this complex and controversial area conformed to specific policy requirements that include informed consent for embryo donation and hPSC provenance and prohibitions on reproductive cloning, the creation of chimeras and human germ-line modification.

Canada is not the only nation that has adopted some form of dual review for stem cell research. A similar practice exists in India, where institutions are required to establish special oversight committees—the so-called Institutional Committees for Stem

Cell Research (IC-SCR)—for basic science and clinical research in this field. A variety of approaches to heightened review and oversight have been adopted in other jurisdictions, including a requirement to obtain a specific license for certain types of embryo and stem cell research in countries including Germany, the United Kingdom and Australia. In Australia, the Embryo Research Licensing Committee at the National Health and Medical Research Council (NHMRC) issues licenses for research involving human embryos and monitors compliance with the legislation.

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This regulatory oversight specific to stem cell research was, no doubt, warranted in the early years, given the degree of social controversy and the fact that many established institutional committees might not

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Box 1: Some jurisdictions with heightened ethics review process for stem cell research**CANADA****Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)**

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada (December 2010).

http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf

CIHR Guidelines for Human Pluripotent Stem Cell Research (2010)

Governs human pluripotent stem cell research using human embryonic stem cell lines, or involving the engrafting of induced pluripotent stem cells (iPSCs) into human or animal embryos or fetuses. Federally funded researchers and institutions are bound by the guidelines.

<http://www.cihr-irsc.gc.ca/e/42071.html>

The Stem Cell Oversight Committee (SCOC).

Reviews research applications dealing with human pluripotent stem cells and other ethically sensitive human stem cell research to ensure that they are in accordance with CIHR's Guidelines for Pluripotent Stem Cell Research.

UNITED STATES**National Institutes of Health Guidelines for Research Using Human Stem Cells (2009)**

Applies to NIH-funded research using hESCs and to certain uses of iPSCs.

National Academies' Guidelines for Human Embryonic Stem Cell Research (2010)

Voluntary guidelines apply to hESC research.

Institutional (or Embryonic) Stem Cell Research Oversight Committees (ISCROs/ESCROs)

Institutions may voluntarily establish ISCROs/ESCROs to provide ethical and scientific review of hESC research. Oversight functions are additional to IRB review.

UNITED KINGDOM**Gene Therapy Advisory Committee**

Provides UK-wide scientific and ethical oversight of clinical trials involving gene and stem cell therapies. Oversight functions replace REC review.

HFEA (Code of Practice and Act)

UKSCB (Code of Practice for the Use of Human Stem Cell Lines)

The Human Fertilization and Embryology (Research Purposes) Regulations 2001/188 (2001).

<http://www.legislation.gov.uk/uksi/2001/188/introduction/made>

GERMANY**The Central Ethics Committee for Stem Cell Research (2002)**

Reviews and evaluates applications for import and use of hESCs as required by the Stem Cell Act. Issues a written opinion on each application to the licensing authority—the Robert Koch Institute. 2002 Act ensuring the protection of embryos in connection with the importation and use of human embryonic stem cells (Stammzellgesetz-StZG).

<http://www.hinxtongroup.org/docs/Germany1.html>

2008 Act ensuring the protection of embryos in connection with the importation and use of human embryonic stem cells.

INDIA**National Guidelines for Stem Cell Research (2013)**

Mandatory national guidelines governing all basic and translational stem cell research, but not stem cell therapies.

<http://icmr.nic.in/guidelines/NGSCR%202013.pdf>

Institutional Committee for Stem Cell Research (IC-SCR)

Institutions conducting stem cell research governed by the National Guidelines are required to establish an IC-SCR to provide additional scientific and ethical review of stem cell research studies.

National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT)

National research review board charged with scientific and ethical oversight of research governed by the National Guidelines.

AUSTRALIA**National Statement on Ethical Conduct in Human Research (2013)**

Research Involving Human Embryos Act (2014)

Act No. 145 of 2002 as amended, taking into account amendments up to Public Governance, Performance and Accountability (Consequential and Transitional Provisions).

<http://www.comlaw.gov.au/Details/C2014C00605>

The Embryo Research Licensing Committee of the NHMRC (the Licensing Committee)

<https://www.nhmrc.gov.au/about/nhmrc-committees/embryo-research-licensing-committee>

have had sufficient expertise to address all ethical and policy concerns regarding experiments using human embryos and hESC lines. In the USA, for example, Embryonic Stem Cell Research Oversight Committees (ESCROs) were created after a 2005 report by the US National Academies identified the need for stand-alone institutional oversight committees [1].

We now have more knowledge about the relevant ethical issues [2], and global trends in stem cell research are less likely to directly engage concerns about the moral status of the embryo (<http://celltrials.info/2014/03/02/trends-2011-2013/>). Valuable experience about appropriate oversight and the practical challenges associated with the relevant research ethics has been accrued [3]. In light of this expanded knowledge base and the evolution of the field itself, it is worth reconsidering the ethics review process. Here, we consider the practice of heightened research ethics review for stem cell research through the lens of the Canadian stem cell research environment, with a focus on the issue of whether the 'dual review model' is still an appropriate approach. While the focus is on Canada, the analysis has clear relevance to other jurisdictions that have adopted a heightened review process.

In Canada, many areas of research are subject to a specific or heightened degree of ethics oversight. For example, individuals who conduct research involving Canadian First Nations, Inuit and Métis communities must comply with specific ethical requirements. Many forms of genetic research have been subject to particular and enhanced research ethics rules, with the most notable example being gene transfer research. Research that involves animals has long required compliance with specific regulations. Similarly, research involving radioactive materials requires separate licensing from the federal government. The use of specific oversight for stem cell research is not unique, and, as such, arguments based on this concern alone are not persuasive. However, as noted, much has changed since the implementation of a dual review process in many jurisdictions, including the political and cultural conditions in which the current research ethics policies emerged. Although the justifications for unique oversight of this research area differ from

jurisdiction to jurisdiction, there is little doubt that concerns over the destruction of human embryos were, in most cases, the dominant motivator for such policies. Other common justifications in the past have included concerns over the commodification of human reproductive materials; the potential for exploitation of donors (e.g. women donating eggs for the derivation of hESC lines); fears about the possibility for human reproductive cloning; and, finally, uncertainties relating to the creation and use of human–animal hybrids and chimeras for research.

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While all of these issues are, no doubt, relevant to stem cell research policy, it should not be forgotten that the sensitized political climate seems to have played a significant role, at least in some countries, in how these issues were framed and perceived by policymakers. In Canada, for example, much of the relevant policy—including the CIHR guidelines—was crafted when the controversies associated with reproductive cloning were unfolding. At the same time, the CIHR—Canada’s federal funding agency for health research, which was the successor of the Medical Research Council—was still a relatively new entity, and a high-profile and highly relevant piece of federal legislation [the Assisted Human Reproduction Act (AHRA)] was being hotly debated in both parliament and the popular press. The research ethics policies in many other jurisdictions were crafted in a similarly sensitized environment. In the USA, for instance, the policies related to stem cell research were established or revised in response to salient controversies over embryo research and abortion.

The highly polarized nature of public debates facilitated exaggerated claims about both the potential risks and benefits associated with stem cell research [4], thus contributing to the creation of a social and political environment that made heightened ethics oversight appear essential.

The science was portrayed as producing near-future breakthroughs that would revolutionize the practice of medicine. And the potential harms—be they in relation to the risks associated with women donating reproductive material for research, or to broader and more amorphous social norms—were often portrayed as grave and potentially imminent.

This trajectory of public controversy is not unique to stem cell research but rather reflects a normal development cycle for new and promising areas of science and technology innovation. As illustrated by the well-known Gartner’s ‘hype cycle’ model, a common pattern for emerging technoscientific developments is an initial wave of attention fueled by hopes for, and fear of, the new and often largely unknown research in question. It is worth considering how this hype cycle in the area of stem cell research may have influenced the development of particular frameworks for ethics oversight. This is not to say that the existing review processes were inappropriate at the times they were initiated. But more familiarity and comfort with a given area research—which, in the context of stem cells, is reflected in a noticeable shift in public perceptions and priorities [4]—may provide an opportunity for a more dispassionate appraisal of both the relevant benefits and risks.

Given the controversial nature of the field, the implementation of a heightened ethics oversight for stem cell research probably facilitated the growth of the field. The research ethics frameworks served to develop knowledge and expertise among oversight bodies and helped to build public trust [1]. They promoted scientific integrity and contributed to an environment in which public and private funding entities could invest with a degree of confidence that social controversies were being considered and addressed [3]. In addition, their existence may have helped create norms of practice—for both researchers and research ethics boards—that ensured research in this controversial area was done carefully and thoughtfully.

However, the scientific and social changes that have taken place since the start of hPSC research have been significant to the point that the field of stem cell research is now very different than it was a decade ago. While work with hESC lines remains methodologically important

and somatic cell nuclear transfer continues to be an area of interest, far fewer studies involve embryos and the derivation of new hESC lines (<http://celltrials.info/2014/03/02/trends-2011-2013/>). In Canada, for example, the 2013 SCOC report to the CIHR Governing Council showed that very few hESC derivation protocols had been submitted since 2004 and none since 2012. In addition, there has been a significant move toward research involving hiPSCs and cell lines derived from adult tissue sources. Public support has also increased as research has shifted toward clinical applications; as stem cell research moves closer to the clinic, the issues of the moral status of the human embryo and reproductive cloning are no longer at the center of the controversy. To be sure, new issues arising from the clinical translation of research are becoming increasingly contentious, be they the ethical conduct of clinical trials, the management of cell lines or the marketing of unproven stem cell treatments [5]. But these concerns are qualitatively different from the issues—particularly those associated with the moral status of the embryo—that led to the creation of current policies that require dual ethical review.

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The evolution of the way in which most stem cell research is done has also had an impact on the other issues that motivated the development of the dual review process. These issues include concerns associated with oocyte donation for the derivation of hESC lines, which some believe involves unnecessary medical risks for women, is potentially exploitative and could lead to the commodification of reproductive materials. These are, of course, issues worthy of continued consideration. But given the scarcity of stem cell research using human oocytes, the fact that the issues associated with egg donation are not unique to stem cell research and the fact that many jurisdictions have adopted laws that regulate the oocyte donation process independent of

research ethic process—for instance, in Canada, the AHRA bans the sale of oocytes—a reassessment of the use of dual review for the purpose of addressing oocyte donation issues specifically in stem cell research may also be appropriate. Moreover, we now have empirical research which suggests that the expected exploitation concerns associated with oocyte donors may not be as problematic as originally anticipated [6].

“So what characteristics, if any, make the current generation of stem cell research particularly ethically problematic such that it requires this dual level of review?”

Revisiting research ethics policy in the face of changed realities is hardly a novel concept. It has happened in the past, even in controversial areas of biomedical research. For example, public perceptions of risks associated with gene therapy have gradually evolved [7] as a result of successful gene therapy clinical trials for immune deficiencies, inherited blindness, hemophilia, beta-thalassemia, Parkinson’s disease and cancer. Many researchers have suggested that the additional review by the NIH’s Advisory Recombinant DNA Advisory Committee (RAC) is redundant and, as a result, slows progress in the field. Based on a report by the Institute of Medicine (IOM) at the US National Academies, the National Institutes of Health (NIH) decided that clinical trials protocols for human gene transfer would no longer be subject to review by RAC. Now seems an appropriate time for a similar review of the approach to stem cell research.

This is not to say that issues concerning hESC derivation can now be ignored and ethical oversight is no longer needed. The continued relevance of careful ethics review is highlighted by recent discoveries such as the derivation of hESCs by somatic cell nuclear transfer (SCNT) in 2013 by Shoukhrat Mitalipov and colleagues at Oregon Health and Science University in Portland, or the creation of the first disease-specific hESC line by a team of scientists led by Dieter Egli at the New York Stem Cell Foundation (NYSCF) Research Institute and Mark Sauer at Columbia University Medical

Center. The maintenance of public trust, which may be fragile [4], demands continued vigilance.

The key questions to ask, therefore, are: Is standard ethics review by REBs sufficient for hESC research? Beyond the issues associated with the derivation of new stem cell lines from human embryos, which rarely occurs in Canada, what is it about this area of scientific research that may warrant an additional or increased level of ethics oversight? Much of stem cell research is now, at its core, fundamentally research on human cells and tissues from non-embryonic sources. With advancements in hiPSC and other areas of biomedical research, distinctions between differentiated, multipotent and pluripotent cell types are becoming increasingly fluid. There is a complex range of research ethics challenges and unsettled policy issues associated with these areas, including those related to bio-banking, consent, privacy, incidental findings, ownership and control [8]. But these ethical and policy issues are not unique to stem cell research. While they may require careful scrutiny by an appropriate ethics committee in accordance, they do not themselves seem to justify a unique layer of oversight specific to hPSC research.

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So what characteristics, if any, make the current generation of stem cell research particularly ethically problematic such that it requires this dual level of review? Although possible applications and risks associated with pluripotency may warrant continued consideration in the ethics review processes, we must acknowledge that a range of scientific developments have increased the complexity of all areas of tissue research. If concerns about ethics review exist, they would seem to apply to a broad range of areas involving human tissue research, thus suggesting the need for a more comprehensive oversight approach that does not exceptionalize stem cell

research. And even if it might not be appropriate to eliminate all aspects of a specialized ethics review process—for example, the review of research that involves creating stem cell lines from human embryos—it is still worth considering the possibility of narrowing the field of application. In other words, we may want to apply general ethical principles as broadly as possible and to limit distinct rules and processes to issues that truly demand them.

To summarize, a particular set of political and scientific circumstances led to research ethics frameworks throughout the world that are somewhat, though not entirely, unique to the hPSC context. Over time, we have observed a gradual moderation of the rhetoric surrounding the field and, at least to some extent, the settling both of expectations and debate. Increasingly, the focus and priorities surrounding stem cell research appear to be on clinical translation and on research that move the field in this direction. As such, it seems an appropriate time to pause and reflect on current research ethics structures to determine whether they continue to be justified and appropriate.

There continue to be a number of pressing ethical and policy issues associated with this field, but many are also common to other areas of human tissue research, and it is worth reassessing whether a kind of heightened level of ethical review specific to stem cells is indeed justified. When comprehensive research ethics guidelines exist, it seems reasonable to suggest that many of these appropriately address these issues by the overarching principles that govern biomedical research more broadly. If there are unique ethical concerns about hPSC research, it might be that these are differences of degree rather than of kind. It is important that research ethics rules are applied in a conceptually consistent manner in order to promote equity and sustainable policy. Exceptions to general principles should be robustly justified.

We are not suggesting that expediency should take precedence over protection of research participants. On the contrary, history tells us that public trust in research can be lost quickly, as illustrated by the well-publicized case of Jesse Gelsinger’s death in gene therapy clinical trials, and it is entirely appropriate that governance regimes to focus on ensuring the highest ethical

standards. Indeed, it would be useful to have more evidence on the effectiveness and impact of the existing research ethics approach. Nonetheless, the changing realities of hPSC research and the surrounding social context raise important questions about whether the current research ethics review processes are still necessary to reach those goals. In addition, the efficient use of researchers' and administrators' time and resources remains a salient consideration, particularly where public funds are used to support the work. Heightened oversight of stem cell research may therefore not always be the best way to ensure public confidence and trust.

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Conflict of interest

The authors declare that they have no conflict of interest.

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