Stem Cell Rev and Rep (2009) 5:108–115
DOI 10.1007/s12015-009-9067-z

HYPOTHESIS AND COMMENTARY

Policy Interoperability in Stem Cell Research: Demystifying Harmonization

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Published online: 31 March 2009

Abstract Scientific developments in the field of stem cell research continue to emerge at incredible speed and so too has the contentious debate surrounding their broad implications. Though economic, socio-ethical and legal concerns remain, at both national and international forums; we are witnessing a departure from an "embryo-centric" approach, to one that is focused on the globalization of research and to the ensuing need for policy interoperability. The common response to the challenges associated with the meaning, scope, and ethical significance of variance in national policies, is a call for the creation of uniform legal and ethical standards. However, this call towards policy convergence on the fundamental ethical and governance principles underpinning policies choices has led to confusion and to the mystification of the notion of harmonization. In this article we aim demystify the notion of policy harmonization in the context of stem cell research. We will do so by surveying the diverse elements to be harmonized. We will then present the problems of policy interoperability in the context of the globalization of SC research, in order to propose that the goal of harmonization in this field lies in the identification of prospective strategies to foster seamless cross-jurisdictional collaboration. Finally, policy interoperability will be analyzed through the lens of a range of policy approaches addressing the cross-jurisdictional transfer of hESC lines with the aim of demonstrating that the apparent ethical-political-legal divide in some contexts largely vanishes once we grasp the notion of harmonization and identify points of convergence.

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Keywords Stem cells · Ethics · Policy · Legislation · Harmonization · Transfer hESC lines · Cross-border research · International research · Law reform · Policy convergence · Stem cell tourism · Stem cell banks

Introduction

Scientific developments in the field continue to emerge at incredible speed and so too has the contentious debate surrounding the broad implications of stem cell (SC) research. Though economic, socio-ethical and legal concerns remain, at both national and international forums; we are witnessing a departure from an "embryo-centric" approach, to one that is focused on the globalization of research and to the ensuing need for policy interoperability.

A number of international initiatives, such as the International Society for Stem Cell Research (ISSCR) and the International Stem Forum (ISCF), are addressing harmonization processes. They provide guidance on how to navigate the "policy patchwork" which characterizes the current state of SC research. The aim is to promote international collaboration towards the timely realization of the scientific promise offered by this research. These initiatives see policy harmonization along with the unification of technical standards and safety requirements as meaningful and justifiable goals.

The common response to the challenges associated with the meaning, scope, and ethical significance of variance in national policies, is a call for the creation of uniform legal and ethical standards. However, this call towards policy convergence on the fundamental ethical and governance principles underpinning policies choices has led to confusion and to the mystification of the notion of harmonization. An illustrative example of this confusion is found in

the following statement made by the Hinxton Group "although we should not expect harmonization of international laws with respect to stem cell research, we should strive to develop international consensus on ethical and scientific standards and practices..." [1].

Harmonization is generally defined as the process in which diverse elements are combined or adapted to each other so as to form a coherent whole while retaining their individuality [2]. One attribute essential to this notion is that it presupposes and preserves the diversity of the objects to be harmonized. The Oxford English Dictionary [3] indicates that the earliest sense of harmony arises in relation to music; it is therefore not surprising that we can better understand the fundamental characteristics of harmonization when we rely on the use of a musical analogy. Music theory tell us that harmony consist on the vertical integration of notes, while melody represents their horizontal integration. "Vertical integration means the simultaneous sounding of different notes or pitches. Harmony, therefore, requires diversity and eschews uniformity" [2]. Another essential characteristic of harmony "is that its components, while retaining their individuality, form a new and more complex sound. Virtually anyone who has listened to music can attest to the richness of a melody played in multiple tones or chords as opposed to single note form [2].

We see then that harmonization is a process of recognizing and reconciling differences, and hence, conveys a meaning of accord or comparability between differing elements. Thus, in the context of SC research and inter-jurisdictional transactions, harmonization does not require similarity but rather compatibility or complementariness across policies.

Accordingly, harmonization and standardization have very distinct goals. Harmonization processes do not seek uniformity as the end result. Unification seeks standardization of policies by means of uniform model codes, guidelines or treaties which adopted and consistently applied by sovereign states. The standardization of national policies in a highly sensitive (morally and politically) field such as SC research and in the context of cultural diversity, is not only doubtful, but more importantly, highly undesirable[1].

[1] Given the conceptual differences between the notion of harmonization and standardization, in this paper we will reserve the use of the term "standard" to refer to those requirements or regulations surrounding the characterization, validation, storage and distribution of stem cell lines, or in a nutshell, to strictly technical and scientific aspects. We follow the approach taken by the International Conference on Harmonisation which defines standardization as the process towards scientific guidance in the adoption of uniform scientific and technical requirements and common guidelines. (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, www.ich.org).

Comprehensive harmonization is composed of four related features. The first deals with the diverse elements to be harmonized, the second, with the rationale for the problem to be resolved by the harmonization process. The third feature relates to the ultimate goal of harmonization, and the fourth feature to the methodology by which these goals are to be achieved.

In this article, we aim to briefly address these four features by surveying the diverse elements to be harmonized, i.e. the existence of diverse policy frameworks with their respective substantive ethical requirements and procedural safeguards. We will then present the problems of policy interoperability in the context of the globalization of SC research in order to propose that the goal of harmonization in this field lies in the identification of prospective strategies to foster seamless cross-jurisdictional collaboration. Finally, policy interoperability will be analyzed through the lens of a range of policy approaches addressing the cross-jurisdictional transfer of hESCLs with the aim of demonstrating that the apparent ethical-political-legal divide in some contexts largely vanishes once we grasp the notion of harmonization and identify points of convergence.

Policy Interoperability: The context

The approaches that countries worldwide have taken to develop policy in the area of hESC research are varied. They range from constitutional and legislative to administrative approaches and differ in degree from liberal to intermediate and restrictive [4].

Similarly, there is a gulf of approaches - within and across jurisdictions -dealing with the permissibility of conducting SC research at all its stages: from the derivation and use of hESCLs, to their storage and distribution. At one end of the policy spectrum, we find countries that prohibit embryo research in general, and thus the derivation of hESCLs from any source. A controversial compromise approach, found within this restrictive policy framework is to allow for the use of imported hESCLs while banning further derivation and uses. Other jurisdictions have opted for an intermediate position, by allowing hESC derivation and research use from excess IVF embryos, though in some circumstances additional restrictions are in place to further limit the use of IVF embryos (cryopreserved vs. fresh) or by banning hESC derivation and use from other sources (e.g. SCNT, human-animal combinations). Finally, at the other end of the spectrum, we have a more liberal approach in jurisdictions that allow hESC derivation and research use from a wider range of technologies (Fig. 1).

For a thorough interpretation of any policy framework, we should go beyond a limited focus based on the permissibility of hESC derivation, to include a careful

analysis of the corresponding ethical principles, substantive requirements as well as procedural safeguards that inform and shape the respective policy frameworks. Likewise, the socio-cultural, historical and political contexts that greatly shape the debate and policy outcomes should also be taken into account [4].

While policy convergence exists with respect to the regulation of fundamental ethical principles and research governance requirements across jurisdictions, divergence in detailed provisions add another layer of complexity to the already multifaceted policy patchwork. Specifically, policy convergence is amenable to core ethical principles such as the respect for autonomy (i.e. informed consent, avoidance of conflict of interest between the IVF medical staff and researchers conducting hESC research), respect for privacy and confidentiality (i.e. protections for donor identity given the potential traceability of hESC lines), and non-commercialization of human reproductive materials (translated in restrictions on monetary compensation for gamete and tissue donation).

Informed consent requirements relate to the general rules for research participants and for donors of tissue and reproductive materials but significant variations are present with respect to the process. For instance, provisions vary with respect to the following: who should consent (e.g. the gamete donor, third party gamete donor and/or embryo donor, or a combination thereof), who should seek consent (e.g. ART physician, hESC researcher, ART staff, donor advocate?) and the timing of the consent process (e.g. reflection period, re-consent). In addition, one can discern differences in the scope of information that should be disclosed (e.g. scope of risks, benefits, researchers' financial interests and other disclosures), secondary use of reproductive materials, and the right to withdraw consent once the hESCL has been derived.

A wide range of options is also present with respect to measures to ensure donor privacy and confidentiality. Similarly, although there is international consensus that commercializing or obtaining financial gains for the donation of human reproductive materials is not permissible, divergence exists on various issues: what constitutes reasonable compensation, the conditions under which compensation should be granted, and the type of compensation that is appropriate (e.g. cash vs. in-kind services) [5].

As concerns the governance of research there is general consensus that the establishment of a centralized, independent, and transparent public authority empowered to grant licenses and strictly control or monitor the conduct of research is essential. The stringency of regulatory responses is only one factor relevant to oversight and compliance. Adherence to ethical standards in the conduct of scientific research is of key importance. For this reason, many countries – albeit with a high degree of difference among their statutory and non-statutory provisions, foresee ethics review by a local, regional or national ethics committee or equivalent institution.

There is also agreement that good governance calls for provisions contemplating sanctions and enforcement mechanisms. Countries have adopted statutory responses which range from designating engaging in prohibited activities or violating regulatory requirements as felonies, punishable by severe prison terms, to punishing transgressions through civil fines. Moreover, this patchwork of national policy approaches is often accompanied by overlapping or coordinated sets of regional and international regulatory responses (from binding national legislation to regional regulations and professional guidelines) and oversight mechanisms. Notwithstanding all of the above, the regulation of hESC research continues to be, by far, a domestic matter.

Thus it comes as no surprise that the adoption of cross-jurisdictional provisions resolving the conflict of norms and policy approaches in research has seldom occurred. In the absence of domestic or international action on this issue, these differences can thwart the advancement of research by potentially limiting some trans-national transactions, narrowing the availability of hESCLs, and consequentially impacting the quality and nature of the research [6].

The transnational sharing of SC materials and related data is largely dependent on the ability of countries to harmonize in many crucial areas – not least those regarding normative and ethical principles, oversight, governance mechanisms, technical and security standards, quality assurance, and scientific practices. Policies should be evaluated in terms of their ability, or lack thereof, to transcend jurisdictional boundaries and hence promote or curtail international collaboration.

Much has been said about the existence of the "patchy" SC policy landscape, however, few studies have explored its implications and offer practical solutions [7, 8]. In this brief study we will survey how some jurisdictions have addressed policy interoperability in the context of cross-jurisdictional SC research. It is beyond the scope of this paper to provide a comprehensive analysis of the wide range of alternative policy responses and their implications. However, we want to provide a starting point for discussion surrounding key questions and challenges: which criteria should be applied to judge policy convergence; how to assess variations in the regulation of core ethical requirements across jurisdictions; how to determine which variations should be deemed significant as to erode the core ethical principles and moral values enshrined in a given jurisdiction; and, how to approach the sharing of hESCLs derived under technologies sanctioned as a criminal activity in some jurisdictions (i.e. cloning, SCNT).

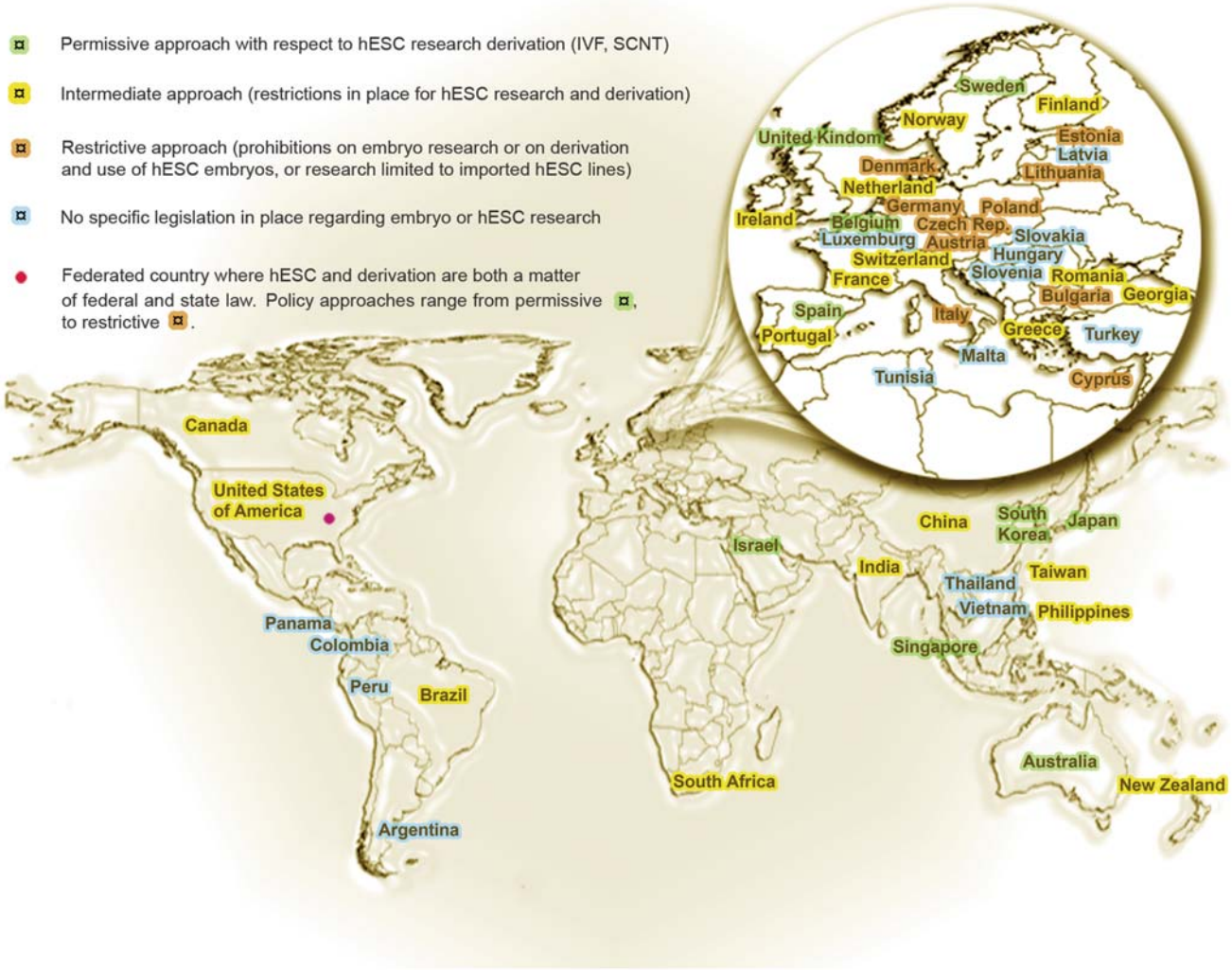

Fig. 1 The stem cell policy landscape

Policy Interoperability: The Transnational Transfer of HESCL

When dealing with the transnational transfer of hESCLs we should approach policy interoperability from several perspectives: the researchers, the licensing bodies, and, in the case of hESC banking, the depositor, the users, and the bank or registry itself. In all those circumstances and regardless the policy approach adopted, a two-step process must be satisfied. It is necessary to demonstrate compliance with regulatory requirements (i.e. ethical and legal) of the jurisdiction where the hESCL was derived along with compliance with the legal and ethical requirements of the jurisdiction where the research will be performed [9].

To attest compliance with the two-step process is challenging. Documenting and evaluating prior local ethical and scientific review and approval, as well as compliance with licensing requirements by the appropriate local entities when foreign jurisdictions are involved can be quite cumbersome. As one author has noted "the complexities of national policies are multiplied exponentially" for each additional jurisdiction involved in a given project [10].The requirement of demonstrating the provenance of the hESCL as a condition of obtaining a license is the one procedural mechanism with the greatest systemic impact. Such an oversight mechanism can effectively frame and even curtail access and thus influence the conduct of research itself.

Uncertainties surrounding the legality, as well as ethics, of cross-border material and data use and sharing pose a good example of the challenges posed by policy interoperability. Researchers and their institutions have dealt with these uncertainties by resorting to the use of some legal forms (e.g. MTA's) and ad-hoc agreements [7]. However, they often provide limited or temporary solutions and run the risks of being inconsistently applied or even subjecting their users to liability [11].

Finally, it is interesting to note that few jurisdictions have taken pro-active action by explicitly grandfathering

hESCLs derived under past and more lenient ethical requirements. The US National Academy of Sciences [12] has grandfathered all hESCLs approved by the NIH previous to the year 2005 (the so called "Presidential hESCLs"). The rationale found in NAS guidelines is founded on the recognition that norms and procedures evolve over time and "unnecessarily rigid" rules discourage researchers from working with hESCLs that were derived under protocols consistent with the ethical norms of the time. We concur with the NAS approach – accepting previously-derived hESCLs that followed the fundamental ethical principles but differed in some insubstantial detail does not imply a breach of ethics. However, the rationale underpinning such decisions should always be clearly articulated. Jurisdictions should act in a pro-active manner and adopt such grandfathering clauses in order to facilitate research and avoid unnecessary hESC derivation or duplication of research.

Policy Options

There is an emerging trend towards streamlining review processes and the verification of transnational practices and standards. These efforts range from the establishment of an ambitious international registry documenting the ethical provenance of hESCLs (ISSCR) to the adoption of specific mechanisms via national policies (e.g. UK, California - CIRM, US NAS). Here we focus on three emerging policy options present either in the literature or in certain jurisdictions. (Fig. 2)

Absolute Ethical and Legal Equivalency Criterion:

Requiring absolute ethical and legal equivalency across national policies confuses policy convergence with unification or standardization. In jurisdictions adopting this criterion, local laws and regulations provide the only acceptable model. Any departure from entrenched ethical-legal requirements is considered to contravene the ethical integrity of the research. Consequently, cross-jurisdictional collaboration would only take place if derivation or research use (including banking) takes place under identical legal and ethical frameworks. Clearly, this approach presents several disadvantages.

This criterion was included in the original draft of the Czech Republic's stem cell legislation; however it was later abandoned as it was deemed excessively stringent and unfeasible. Moreover, this approach ignores sovereignty and moral diversity, and as such is in itself morally problematic.

Assessment and review of foreign policies under this approach is ostensibly clear-cut as even slight variations or nuances in detailed policies are not tolerated. However, can one ever clearly confirm that foreign review (i.e. ethical and scientific), licensing, or oversight processes are identical? Which criteria should be used to ascertain such equivalency? How does one assess the influence of the

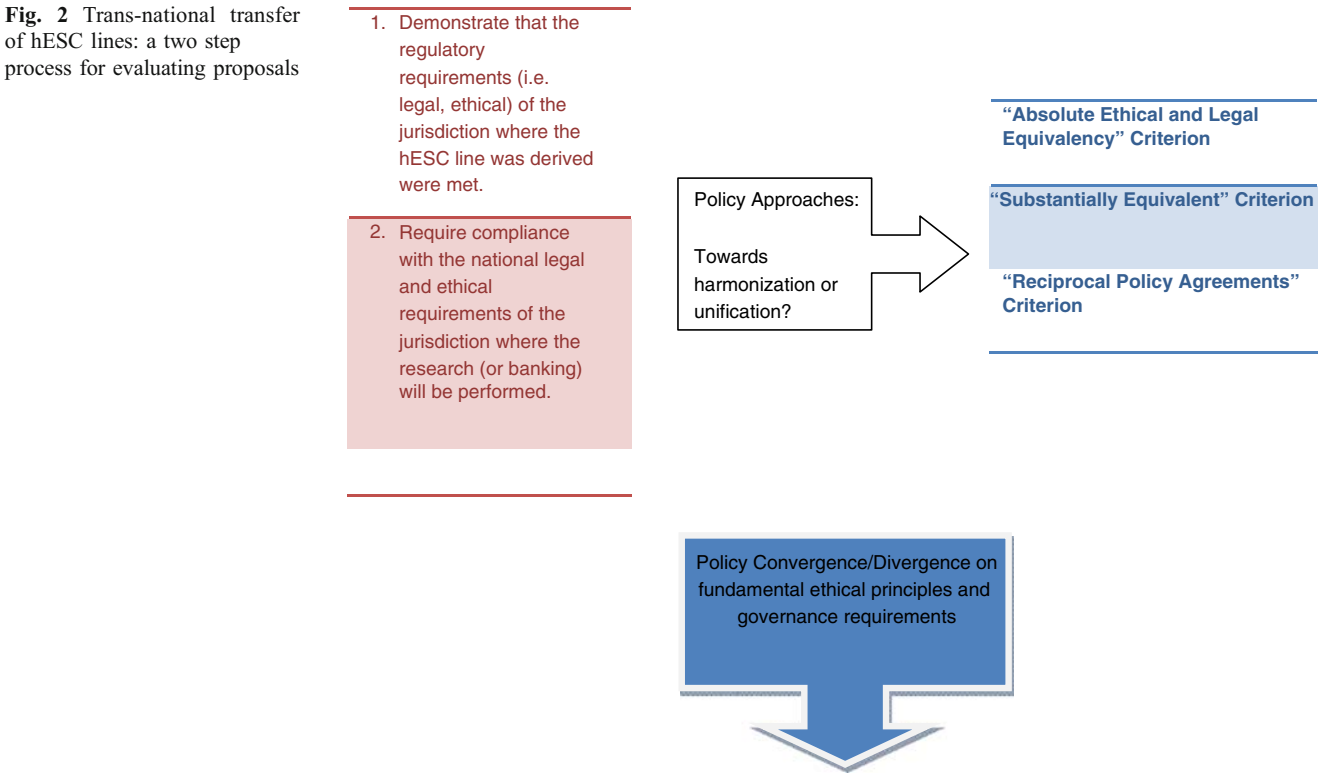

Fig. 2 Trans-national transfer of hESC lines: a two step process for evaluating proposals

particular context within which derivation or research takes place?

Additionally, this approach poses disadvantages from a scientific standpoint. For instance, under this approach the grandfathering of hESCLs derived under more lenient ethical requirements, as was the case with the US NAS, would have to be prevented in order to maintain internal consistency. However, this neglects the evolving nature of ethical principles as well as narrows the availability of hESCLs for research. Applying the principle of absolute equivalency could bar researchers from the most suitable hESCLs and impedes progress in the field.

Substantially Equivalent or the "Acceptably Derived" Criterion:

The criterion of "substantial equivalency" is the most commonly adopted across jurisdictions (e.g. UK, US: California-CIRM, NAS). Under this criterion, hESC derivation, research, and banking are permissible provided that the jurisdictions involved adopt ethical and legal requirements that are deemed to be substantially equivalent. Here the relevant policy of the jurisdiction is characterized by a high degree of similarity in core principles but not in detailed provisions. This equivalency of requirements arises from policy convergence towards core socio-ethical concerns and fundamental ethical principles.

The adoption of the abovementioned criterion is the result of a true harmonization process in which points of policy convergence are identified and nuances in their detailed provisions are accepted as part of the realities of policy making activities across sovereign states. It also has the advantage that "it makes the process of practical and moral reasoning more explicit" [13].

A major advantage of this approach is that it encourages cross-jurisdictional collaboration and represents a realistic recognition of the diversity and the evolving nature of ethical requirements. This criterion means that fundamental principles surrounding donor protections and governance requirements are consistent among jurisdictions so as to guarantee the integrity of the research.

A potential challenge is to maintain internal consistency when judging the "substantial" equivalency of policies and to prevent arbitrary application. Moreover, in certain cases assessing compatibility of requirements (e.g. when compensation amounts for material donation entails undue inducement, when informed consent by all gamete donors should be obtained for secondary uses) could be challenging. Similarly, assessing or deferring ethics review and oversight practices, along with their implications can be a difficult task. What is the tipping point in which a detailed feature should be considered a substantial ethical disagreement? Particular challenges would arise when dealing with hESCLs derived under more relaxed ethical requirements, in the absence of grandfathering clauses, appropriate justification should be provided to demonstrate their substantial equivalency. Moreover, it could be argued that by opting for the 'substantially equivalent' approach, we've merely reformulated the mechanism of distinction as '*what* makes something different' rather than '*how* are they different'. Decision-makers will face the same uncertainties under this approach.

This approach has additional advantages however: for one, it removes significant restrictions to the benefit of international collaboration and ultimately, the research without crossing new ethical boundaries. The deference to slight variations in policy approaches "shows proper respect for diversity of authority in this area" [12]. Finally, we maintain that under this criterion, it is clear that it would never be ethically defensible to allow the use of hESCLs derived by techniques prohibited in the partnering jurisdiction, even when extant ethical principles and other governance requirements are deemed substantially equivalent among them. Such a contravention would represent the denigration of another jurisdiction's ethical principles and in certain circumstances the circumvention of criminal sanctions. Furthermore one must be acutely aware of the potential slippery-slope effect of promoting forum shopping.

Reciprocal Policy Agreements:

Mutual recognition via reciprocal policy agreement is one mechanism to solve coordination problems in cross-jurisdictional research. Under this approach, the transnational sharing of hESCLs is accepted provided that they were derived by, deposited in, or approved for use by a licensing entity formally recognized as having adopted consistent ethical and legal requirements. Adopting a reciprocal or institutional policy agreement is a harmonization effort aimed at avoiding patchworks within a jurisdiction by consistently requiring compliance with certain ethical and other requirements that are deemed to be convergent.

Several jurisdictions, funding agencies, and oversight bodies (European Union) have favoured this approach. For instances, California's CIRM has adopted such agreements with similar institutions in Canada, the UK, and Japan. Likewise, the UK's Stem Cell bank has adopted reciprocal policy agreements with Canada and US institutions by deeming hESCLs derived under their regulations as "acceptably derived". Adopting institutional policy agreements has several advantages, for one it facilitates research cooperation through a delicate balancing of upholding international principles but recognizing and respecting divergence in national policy approaches [14]. In addition, it is an efficient and transparent approach that allows for access to a wide range of hESCLs and provides a solid ground for quality research.

However, there are some dangers in adopting a mutual recognition approach. It could mean a race to the strictest of approaches or a race to the bottom in upholding core ethical requirements. Most importantly, there are dangers of internal inconsistencies with respect to national policies. For instance, a society that opposes the provision of monetary payments or financial incentives for oocyte donation (therefore protecting donors from undue inducement) and prohibits commercialization of gametes and embryos should maintain similar donor protections in their reciprocal policy agreements. In the case of California CIRM which prohibits the importation of hESCLs obtained using monetary payments in excess of reimbursement of direct out-of-pocket expenses. This would mean then that a researcher (bound to CIRM regulations) would be prevented from using or importing hESCLs derived under egg-sharing agreements in the UK.

As in the case of "substantial equivalency criteria", under this approach it should be impermissible to use or distribute hESCLs derived from sources or technologies banned in the partnering jurisdiction. Furthermore, this approach is compatible with grandfathering hESCLs when retroactive application of policy is not warranted and when they were derived under protocols that are deemed to be substantially similar to those contemplated in a particular jurisdiction. However, the justification for such policy choice should be made transparent.

Finally, we cannot leave aside an additional yet important approach towards harmonization or policy convergence, which is emulation and transnational promotion. Countries might be motivated to adopt certain policy models due to legitimacy pressures emerging from the promotion of policy models adopted by reputable scientific institutions (e.g. ISSCR, NAS). Here, policy convergence is not created by joint problem solving [14] by jurisdictions involved in transnational networks but driven by the active role of international institutions promoting the spread of policies and seeking harmonization of fundamental ethical principles and governance requirements. Institutions like ISSCR, ISCF and the European Union play a highly active role in this process. They function as mediators of cross-national policy transfer, urging governments to adopt normative action. The power of this transnational promotion of policy models should not be underestimated. Jurisdictions that deviate from recommended policies could face pressure, in the form of international scrutiny, to legitimate their policy approaches [15].

Conclusion

Some authors have interpreted the fragmentation of policy approaches as a sign that "no global regulatory framework for stem cell science is emerging at this time" [16]. We beg to differ and through this article, we hope we have demonstrated that indeed there is a trend towards policy convergence surrounding fundamental ethical issues (e.g. respect for autonomy and confidentiality, respect for the human body by restricting the use of monetary payments and financial incentives for donation, ethics review and oversight etc.). This is apparent from the policy approaches of several jurisdictions in the context of cross-jurisdictional research.

Certainly, divergence in fundamental and nuanced legal and ethical requirements could pose to be an obstacle for the feasibility of many trans-jurisdictional projects. However, these obstacles could be adverted by adopting policy mechanisms that pro-actively acknowledge and address the international realities of SC research. It is indeed the globalization of the research what may have generated some degree of convergence among different jurisdictions.

Harmonization occurs when the policy community comprehends that the benefits of convergence outweigh the cost of divergence. There are substantial incentives for countries to adopt such mechanisms as they could reduce the costs of transactions, promote their scientific platforms, and strengthen their competitiveness. But most importantly, it will facilitate the timely realization of the therapeutic potential of SC research.

Harmonization is a process of recognizing and reconciling differences. National policies should be written taking into account their potential for discordance given international policy interoperability. Consequently, and without comprising their own moral values, they should be written so as to foster commonalities by advancing a process of coordination and harmonization of outputs and outcomes.

Past attempts to adopt binding policy at the international level (e.g. UN Cloning Declaration) have ended in pyrrhic victories. This failure has been the result of not only the inability of policymakers to reconcile differences over values (i.e. the moral status of the human embryo), but also to their inability to grasp a true understanding of the science (i.e. confusion between human research and therapeutic cloning vs. hESC research) [17].We remain somewhat sceptical that in a near future an international binding instrument will be adopted regulating this often controversial area of research. However, policy developments by international professional organizations (i.e. ISSCR, ISCF) and some state actors encourage us to remain positive that enforceable international norms could become actual and that our search for policy convergence or harmonization of research policies is a realistic endeavour.

While adopting international binding policies is often difficult to achieve in this sensitive area, setting ethical, professional as well as quality and safety assurances and

standards that are reasonable and coherent for all members of a pluralistic society should be an achievable goal. Regardless of the policy approach adopted, scientific responsibility and integrity must be promoted. Incentives for open exchange, registration and validation of results need to be promoted.

Acknowledgements The author would like to thank the Canadian Stem Cell Network, the International Regulome Consortium and the International Stem Cell Forum for their funding support. The author would also thanks Professors Bartha M. Knoppers and Timothy Caulfield for their comments and thoughtful suggestions on an earlier version of the present article. The opinions are those of the author alone.

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