Perspective

Regenerative Medicine

Modeling policy development: examining national governance of stem cell-based embryo models

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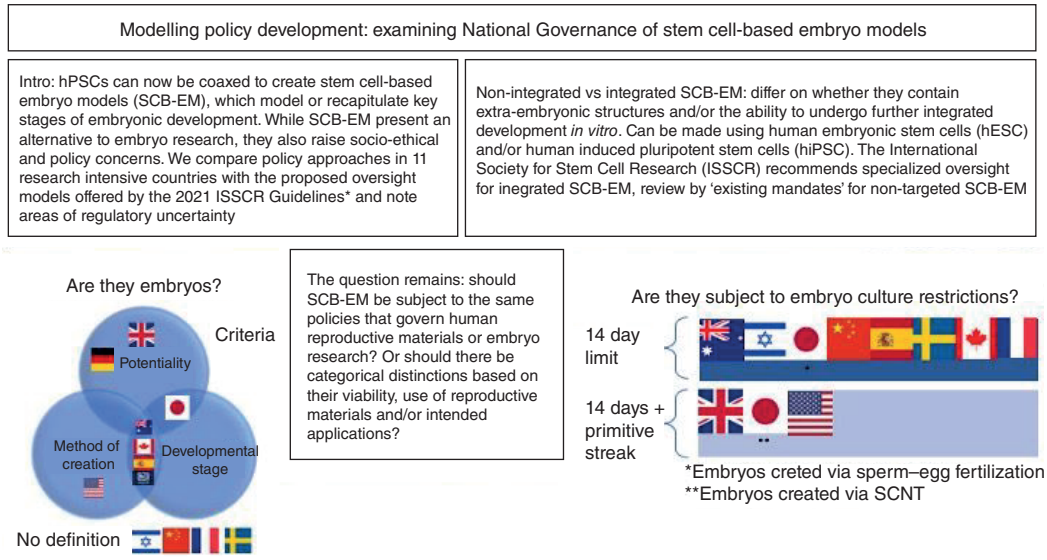
Researchers can now coax human pluripotent stem cells to imitate the structure and spontaneous self-organization of the developing human embryo. Although these stem cell-based embryo models present an advantageous alternative to embryo research, they also raise ethical and policy challenges. In 2021, the International Society for Stem Cell Research revised its Guidelines for Stem Cell Research and Clinical Translation, providing contemporaneous best practices for ethical conduct in the field. The Guidelines complement national governance frameworks; however, they also contain contentious and aspirational norms that might catalyze change in research practice and in the enactment of national policies. Using a sample of 11 research-intensive countries, the authors compare research policy frameworks against the International Society for Stem Cell Research Guidelines to showcase how developments in global and national policies might affect stem cell-based embryo model research governance and illustrate fertile areas for ethical reflection and policy development.

Plain language summary: Following scientific advances, researchers can induce stem cells to model the development of the human embryo with increasing accuracy. The International Society for Stem Cell Research Guidelines for Stem Cell Research and Clinical Translation provide contemporary standards for research on so-called stem cell-based embryo models (SCB-EMs). However, because SCB-EMs are not mentioned in national policies and do not fit neatly into existing regulatory categories, it is unclear how countries intend to regulate them. In this article, the authors compare policy frameworks in 11 research-intensive countries to analyze how the influential Guidelines both complement and catalyze change in national policies. The Guidelines provide specific instructions for assessing and monitoring different kinds of SCB-EM research proposals, serving as a useful reference to bolster open-ended national policy requirements. However, in some areas the Guidelines appear to conflict with national policies governing stem cell and embryo research, reflecting divergent priorities and ethical assessments. Without policy review to address regulatory and ethical uncertainty, researchers may default to adherence to the Guidelines, a global standard that does not necessarily reflect local historic, legal and cultural influences. Evidence from France and Israel indicates that comprehensive legislative review is both useful and can proceed without eroding compromises designed to uphold plural beliefs regarding the moral status of the human embryo. As exemplified in countries such France and Israel, mandated legislative review processes are useful tools that can be deployed in manner that upholds pluralistic beliefs regarding the human embryo's moral status. They can serve as a pathway to re-engage the public and ensure diverse viewpoints are reflected in governance of SCB-EM research, ultimately facilitating public trust in science.

Tweetable abstract: The International Society for Stem Cell Research Guidelines are the eminent global standard for ethical conduct in stem cell research. Although they complement national governance frameworks, they also contain contentious and aspirational norms that should catalyze policy review.

Future Medicine

Graphical abstract:



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Advances in *in vitro* culture conditions have enabled researchers to direct human pluripotent stem cells (hPSCs) to differentiate into sophisticated and increasingly accurate models of *in vivo* processes [1], including aspects of the developing human embryo [2]. These stem cell-based embryo models (SCB-EMs) have emerged as an important tool for studying embryonic development. For instance, 'non-integrated' SCB-EMs [3], which lack extraembryonic tissue and other features necessary for embryonic implantation and viability, provide snapshots of human gastrulation [4] and neurulation [5]. Early pregnancy loss [6] often occurs during these stages, which occur too early to be observed *in vivo*, so *in vitro* research is critical to improve assisted reproductive technology. Furthermore, in recent years, researchers have created 3D models of mouse [7] and human [8] blastocysts, representing integrated development of the entire embryo, including its extraembryonic membranes. In a recent study, mouse stem cells were aggregated to form a synthetic embryo with sustained development beyond the initiation of organogenesis [9]. A model's fidelity to embryogenesis is vital to ensure knowledge gained about the principles and mechanisms of cellular organization is biologically meaningful and clinically relevant [10]. As such, scholars envision that with sustained *in vitro* culture, human 'integrated' SCB-EMs [3] may consequently approach benchmarks considered morally relevant on the human embryonic developmental timeline [11].

Despite these advances, knowledge of embryonic development is still hampered by technical, regulatory and ethical limitations, such as the widely adopted 14-day regulatory limit on embryo cultivation (so-called 14-day rule) [12–15], thus preventing the validation of SCB-EMs in weeks 3 and 4 of development. SCB-EMs defy easy associations with common moral reference points and regulatory categories defining human reproductive materials: they are not functionally equivalent to embryos but have become increasingly similar through technical advances in stem cell culture [11]. They also raise concerns over the adequacy of current regulatory frameworks and oversight processes governing their creation and use in research. In this article, the authors will address these concerns as they relate to national regulation, highlighting opportunities to deliberate on appropriate policy and governance of SCB-EM research.

The International Society for Stem Cell Research (ISSCR) Guidelines for Stem Cell Research and Clinical Translation (hereafter Guidelines) have gained legitimacy over time by raising awareness of new ethical challenges, guiding scientific practice and aiding in the interpretation and implementation of national policy. Reflecting evolving science, the 2021 update to the Guidelines revises the recommended levels and types of oversight allocated to different forms of SCB-EM research, suggesting new ways to define and standardize SCB-EMs. However, the Guidelines also suggest relaxing the long-preserved 14-day rule, reflecting optimism about the utility of embryo

research and faith in institutional oversight. Given the ISSCR's global influence on ethical conduct, it is timely to assess how the Guidelines might influence policy development and oversight mechanisms for SCB-EM research.

Materials & methods

Previous scholarship has demonstrated how diversity in national policy governing embryo and stem cell research reflects unique social, cultural and political histories [16]. Through juxtaposition with national policies in 11 research-intensive countries (UK, Australia, Israel, Japan, China, Spain, Sweden, Germany, France, USA, Canada), the authors will examine the Guidelines' new categorization of SCB-EM research as well as the ways in which the Guidelines might fill national regulatory gaps and their potential in prompting policy review. The goals of this article are twofold: to articulate national norms that currently govern SCB-EM research by comparing with current best practices (e.g., the Guidelines) and to establish the utility of scheduled policy review so as to respond to scientific developments. A thorough account of the tools available to policymakers (e.g., governments, professional organizations, researchers) can expand imaginations for policy development, facilitating the alignment of SCB-EM governance with societal interests. It also sheds light on areas where further ethical reflection and policy development might be needed in order to foster advancement of the stem cell field.

The authors' study was conducted by employing standard methodology for international comparative policy/law research and analysis, drawing on primary (e.g., laws, statutes, professional guidelines) and secondary (e.g., academic literature) sources identified through standard tools/databases (e.g., Lexis-Nexis, Westlaw, Google Scholar, PubMed). Focus was given to both self-regulation or 'soft laws' (e.g., best practices, professional guidelines) and legislative approaches or 'hard laws' (e.g., laws, statutes, regulations) in the areas of embryo, human biomedical, reproductive and stem cell research. The authors built this methodological approach on previous comparative policy studies and employed similar classification models to categorize policy approaches [17–20]. Following standard legal methodology, the authors did not set a specific time period of inquiry, but rather focused on current national law or policy.

What is in a name?

Central to the SCB-EM discourse is whether (or not) existing research policies for human reproductive materials (e.g., gametes, embryos) and stem cells are appropriate to guide SCB-EM research. Whether embedded in hard or soft laws, concepts describing the nature of an entity (e.g., embryo, SCB-EM, gamete) are important, as they impact the governance pathway and also convey moral or social judgment about the said entity. Definitions are the source of an entity's legal status and of moral justifications for limiting the purposes for which it can be studied, created or used in research. This is why socioethical considerations have acquired substantial importance as a tool for policymaking.

Recent calls for policy review have focused on how definitions taken *ad litteram* (e.g., the text of the norm) influence the permissibility and oversight of SCB-EM research [21]. Human embryo definitions are useful starting points to help determine which regulations may apply to SCB-EMs in lieu of explicit guidance, but policy definitions vary in scope. In some countries, they refer either to the embryo's potential to become a human individual (e.g., Germany [22], Japan [23]) or to a point in time, such as when they reach a morally relevant developmental stage (Australia [24]). Definitions also establish governance pathways. For example, recently, Australian regulators determined that the country's expansive statutory embryo definition encompassed so-called iBlastoids, an integrated SCB-EM formed from reprogrammed human fibroblasts [25], and thus these models required regulation and oversight from Australia's national embryo research licensing committee [26]. Although Australia's statutory embryo definition was last revised in 2006, before the advent of SCB-EMs, its breadth indicates the policymakers' intent for research on embryos and embryo-like entities to be subject to similar ethical review processes. However, this situation is unique, as in most national policies it is not evident whether the intent was to also encompass SCB-EMs or similar entities and therefore subject them to extant regulation and oversight.

The ISSCR's approach to SCB-EMs has evolved over time, reflecting both scientific advances and ethical reflection. For instance, the 2016 version of the Guidelines introduced the term 'embryo-like structures' to guide oversight of "*the assembly, differentiation, aggregation, or re-association of cell populations in a manner that models or recapitulates key stages of embryonic development*" [27]. This version tethered increased scrutiny to these entities' capacity "*through engineering or self-organization*" to manifest "*human organismal potential*" if maintained in culture. According to the 2016 version, research on embryo-like structures with "*human organismal potential*", such as embryo research, should be subject to a "*specialized*" oversight process that would account for the unique ethical concerns that arise

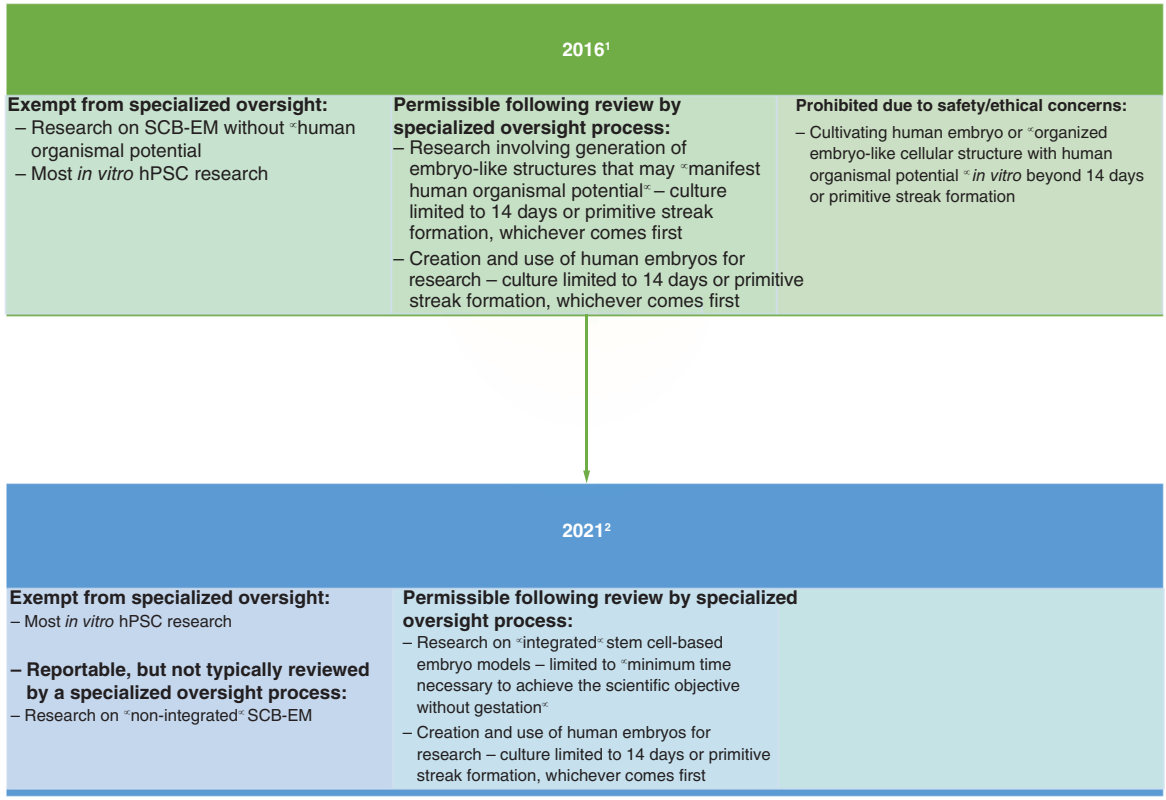

Figure 1. New International Society for Stem Cell Research categories for stem cell research oversight.
hPSC: Human pluripotent stem cell; SCB-EM: Stem cell-based embryo model.
Data taken from [3,27].

when an *in vitro* research object itself has been attributed certain moral status. However, although the organismal potential criterion has a sound theoretical basis, it cannot be measured or validated for SCB-EMs because of ethical concerns and gaps in knowledge about embryonic development, thus rendering it a useless regulatory tool. For this reason, the updated 2021 Guidelines [3] replace the nebulous 'embryo-like structures' terminology with a new term – SCB-EM, abandoning the organismal potential criterion and adopting integrated versus non-integrated SCB-EMs as criteria. Integrated SCB-EMs are defined as entities containing embryonic and extraembryonic structures necessary to represent development of the entire embryo. Non-integrated SCB-EMs are categorized by their ability to recapitulate some, but not all, aspects of the peri-implantation embryo.

New categories and applications of existing oversight models: the ISSCR paves the way

One overarching goal of the Guidelines is to provide guidance for appropriate levels of ethical review and oversight of *in vitro* research involving stem cell-based entities that could be deemed ethically or socially controversial. To this end, the Guidelines changed the categorization of permissible types of research and corresponding oversight recommendations (Figure 1). For integrated SCB-EMs, specialized oversight is prescribed by subjecting them to the same oversight process as *in vitro* embryo research, including the derivation of human embryonic stem cells (hESCs). As with embryos, the creation and study of SCB-EMs merit cautious and transparent monitoring as well as justification for performing experiments "*in a human rather than animal model system*" [3]. The Guidelines thus extend a premise reflected in policies in most research-intensive countries, "*that research on entities with questionable moral status should proceed with caution*" [18]. For non-integrated SCB-EMs, review by existing mandates for laboratory research is recommended, thus conceptually distancing SCB-EMs from the embryos they attempt to replicate, reflecting the fact that SCB-EMs can only emulate embryogenesis through sustained and intentional external influences.

Just as the updated Guidelines expand research frameworks to encompass integrated SCB-EMs, they also address potential incompatibilities with national policy. By replacing a 14-day limit on integrated SCB-EM culture with

Table 1. National restrictions on human embryo culture.

Policy criteria	Countries
Embryos cannot be cultured past 14 days of development	Australia, Israel, Japan†, China, Spain, Sweden, Canada, France
Embryos cannot be cultured past 14 days of development or appearance of the primitive streak	UK, Japan‡, USA§

†Embryos created via sperm–egg fertilization.
‡Embryos created via somatic cell nuclear transfer.
§Refers to the National Academies' *Guidelines for Human Embryonic Stem Cell Research*, which has been widely adopted across major US stem cell research institutions. There is no federal legal restriction on research embryo cultivation in the USA.

the suggestion that SCB-EMs be cultivated "*for the minimum time necessary to achieve the scientific objective*" [3], the Guidelines exempt SCB-EM oversight from bright-line prohibitions common to national embryo research policy (Table 1). The recommendation is grounded in an ethical and practical rationale: SCB-EMs are (currently) incapable of full human development (and thus ethically distinct from human embryos), and a discrete temporal limit may not be appropriate, as they may develop at different rates than human embryos and spend extended time in culture as stem cells [28]. However, opponents of the relaxation of the 14-day rule argue that discrete barriers on embryo research "*remind us to maintain a sense of reverence as we try to understand life's mysteries and to promote the flowering of human wellbeing*" [29].

Although the ISSCR represents global professional consensus, national embryo and stem cell research policy is heterogeneous. To forecast how the Guidelines might complement or conflict with these policies, it is necessary to consider how existing norms may inform SCB-EM governance. In the countries surveyed, stewardship is often exercised through statutorily established licensing and oversight requirements. Based on the premise that standard oversight procedures may not provide sufficient scrutiny for what could be considered morally contentious research, countries often require additional approval from a specialized deliberative body equipped to critically examine these projects. In the majority of countries surveyed, a central governing body is charged with specialized review of embryo research. However, in countries such as Sweden [30], China [31] and the USA [32], embryo research is reviewed entirely at the regional or institutional level. Most countries surveyed process embryo research proposals through both standard and specialized processes of research oversight (except Sweden, which does not require specialized review of embryo research [33], and Germany, which forbids human embryo research). However, despite sharing common goals, reflected in dual review, considerable heterogeneity exists in the remits attributed to review committees.

The Guidelines further offer guidance about the composition and remit of specialized committees, which is generally followed by national embryo/stem cell oversight committees (typically multidisciplinary, featuring experts in law, ethics and stem cell/embryo research as well as lay public representatives). In terms of competency, the Guidelines recommend that these bodies review, approve and conduct ongoing monitoring by rigorously evaluating the scientific, ethical and legal aspects of research involving both embryos and integrated SCB-EMs [3]. Although central embryo research licensing authorities in the UK and Australia actively monitor research, national policies, such as those in Israel [34], Spain [35], Canada [36] and Japan [37], entrust direct supervision of ongoing research to local research teams and institutions. In these countries, specialized review bodies monitor embryo research from a distance, mainly receiving reports on major protocol changes and project termination.

As the ISSCR has become a transparent, globally respected source of ethical standards and best scientific practices in the field, the impact of the Guidelines cannot be underestimated. Their uptake is exemplified by ethics statement sections in contemporary SCB-EM research articles, which, in addition to describing standard review and approval processes, either claim compliance with [8] or use verbiage from the Guidelines [4]. However, the Guidelines classify embryo and stem cell research in ways that fundamentally differ with some national policies, indicating that their approach to SCB-EMs may also be in conflict with these norms.

Sanctions are common to embryo research governance, but are they useful for SCB-EMs?

Across the globe, policies often buttress restrictions on embryo research with criminal sanctions, reflecting forceful societal views regarding the potential for commodification. The imposition of criminal sanctions for misconduct is commonplace, yet countries vary significantly in their approach to misconduct with regard to *in vitro* embryo research. In relatively lenient examples, Japan [23] and Sweden [30] levy mild (imprisonment for 1 year or less) sanctions, whereas China and Israel [38] do not criminally punish any specific *in vitro* research techniques. Other

countries impose longer prison sentences for performing prohibited techniques. For instance, France [39], Canada [40] and Germany [22] threaten harsh (imprisonment for 3 years or more) penalties for creating an embryo for research purposes. Punishments for regulatory noncompliance also vary: avoiding embryo research licensure requirements in the UK [41] and Australia [24] can be met with a prison sentence, whereas Spanish law punishes regulatory noncompliance with fines and administrative penalties [35].

Advances in SCB-EM research should prompt policymakers to consider not only whether and to what extent punishments for embryo creation and culture beyond 14 days should apply to SCB-EMs but also the criminalization of such misconduct. The threat of severe punishment may deter SCB-EM researchers from acknowledging the ethical ramifications of their own work, incentivizing them to emphasize the ways in which SCB-EMs are not equivalent to embryos. Although box-checking with reference to decades-old legal definitions may suffice for legal compliance, it may also undermine the more nuanced (and needed) ethical assessments and public debate essential to responsive regulation.

Intent or inertia? Existing mandates & discrepancies between Guidelines & national policies

Although national policies governing embryo and stem cell research vary (Table 2) [16], there is near consensus that this research should only proceed following specialized review, albeit using different oversight approaches. For example, in the UK [42], Australia [43], Israel [34] and Sweden [33], research on anonymized hESC lines may proceed without ethics review because it is deemed to pose minimal risk of harm to participants (i.e., embryo donors who consent to hESC derivation), whereas policies in the US [32] and France [44] require research teams to notify specialized review bodies of new hESC research projects. In China [31], Japan [45], Spain [35], Canada [36] and Germany [46], specialized review committees must verify the ethical provenance of cells prior to approval (Figure 2). By contrast, the Guidelines posit that *in vitro* hESC research should be exempt from specialized reporting and review requirements, imposing a less stringent standard than that present in most countries surveyed. Furthermore, the Guidelines view the creation of human embryos for research purposes as permissible with appropriate oversight, whereas nearly half of countries surveyed either discourage (Israel [34]) or prohibit (Australia [47], Spain [35], Germany [22], Canada [40]) research embryo creation. Considering that human induced pluripotent stem cell research apparently "*avoids the ethical problems specific to embryonic stem cells*" [48], most national policies place this type of research outside the purview of specialized review bodies, categorizing projects according to standard protocols for research with human participants. Because stem cells are widely regarded as research artifacts with negligible moral worth [49], their study has been encouraged to answer research questions related to embryogenesis without using human embryos, and this regulatory approach has likely stimulated growth in the field. Thus, the question emerges: how should these criteria be extrapolated to SCB-EMs?

The Guidelines advance a policy of equivalence between human embryos and integrated SCB-EMs by recommending they undergo the same process of specialized review. The ISSCR recognizes that it may not be within the competence or responsibility of laboratory research review bodies to consider the moral, scientific and societal implications of integrated SCB-EMs when evaluating the acceptability of proposed research. However, the Guidelines entrust "*existing mandates and committees for laboratory research*" [3] with review and monitoring of non-integrated SCB-EMs, implying that their research does not generate similar ethical concerns. They further suggest that non-integrated SCB-EMs should be "*reportable but not typically reviewed*" by a specialized review process, echoing a common national approach to hESC research governance. Essentially, this categorization allows specialized review bodies to monitor and guide research on non-integrated models "*from a distance*", entrusting research teams with primary oversight responsibilities.

Although the Guidelines' proposed oversight pathways mirror existing national processes, discrepancies between the Guidelines and national policies demonstrate different evaluations of the ethical concerns and likely benefits of stem cell research. For example, the suggestion that countries should consider relaxing the widespread 14-day limit on human embryo culture following 'broad public support' [3] would overturn a standard upheld in every country surveyed (except Germany, which prohibits embryo research entirely) (Table 1). However, although divergent ethical evaluations are reflected in national embryo research policies (Table 2), with the recent exception of France (discussed in more detail later), most countries have not contemplated how to categorize SCB-EMs. Because SCB-EMs are not currently viable and may be formed without using human reproductive materials, they are likely exempt from the stringent justificatory burdens and technical restrictions on embryo creation and use as imposed by national statutes. Remaining oversight requirements will pertain to the cells that comprise SCB-EMs, with scant normative guidance on how they should be used *in vitro*.

Table 2. Summary of national embryo and stem cell research policies.

Country	Embryo definition	Limits on research embryo cultivation	Oversight of embryo/stem cell research	Status of research embryo creation
UK	Potentiality	Until primitive streak formation (embryos); until 14 days or primitive streak formation (human admixed embryos)	Embryos: HFEA (specialized) + research ethics committees Stem cells: UK Stem Cell Bank if embryonic; unspecified if iPSCs	Permitted with HFEA license; legally prohibited otherwise
Australia	Potentiality, method of creation and developmental stage	Until 14 days, excluding when development is suspended	Embryos: NHMRC Embryo Research Licensing Committee (specialized) + HRECs Stem cells: unspecified but possibly HRECs; possibly no ethical review if research is 'low-risk'	Permitted with NHMRC Embryo Research Licensing Committee license; legally prohibited otherwise; must minimize number of embryos created to total necessary for research
Israel	NA	No research "*beyond the earliest stages of development*" (2 weeks)	Embryos: Supreme Helsinki Committee (specialized) Stem cells: unspecified	Not legally prohibited, but sperm–egg fertilization for research is discouraged
Japan	Potentiality and developmental stage	Human fertilized embryos until 14 days of development, excluding time spent frozen; 'specified' embryos until 14 days or primitive streak	Embryos: MEXT review if created by SCNT or animal–human chimeras; otherwise, institutional review (specialized) + MEXT notification Stem cells: institutional ethics review (specialized)	Sperm–egg fertilization for research permitted only for research-assisted reproductive medicine; SCNT permitted with approval from MEXT
China	NA	Until 14 days from the beginning of fertilization or nuclear transfer	Embryos: institutional ethics review (specialized) Stem cells: institutional ethics review (specialized) if hESCs; unspecified if iPSCs; State Council Department of Science and Technology oversees 'genetic resources'	Not prohibited
Spain	Developmental stage ("*pre-embryos*" defined in terms of method of creation)	Until 14 days following fertilization of the oocyte, excluding time spent frozen (applies to "*human pre-embryos*")	Embryos: guarantee commission (specialized); review by competent state or regional authority Stem cells: guarantee commission (specialized); National Bank of Cellular Lines	Legally prohibited with exceptions (e.g., SCNT to obtain hESCs); guarantee commission approval required for embryo/stem cell research
Sweden	NA	Up to and including the 14th day after fertilization and cell nucleus transfer	Embryos: ethics review authority; notification of National Board of Health and Welfare and medical ethics council Stem cells: ethics review authority	Not prohibited
Germany	Potentiality	Prohibited	Embryos: prohibited Stem cells: Robert Koch Institute and Central Ethics Commission (specialized) for stem cell research if embryonic; unspecified if iPSCs	Legally prohibited
Canada	Method of creation and developmental stage	Until the 14th day of development following fertilization or creation, excluding when development is suspended	Embryos: institutional research ethics boards Stem cells: Stem Cell Oversight Committee (specialized) if embryonic or transferred into humans/non-animals; research ethics boards if iPSCs	Legally prohibited
USA	Method of creation	Prohibited by federal research funders; per NAS guidelines, until 14 days or primitive streak	Embryos: prohibited by federal funders; privately funded research overseen by institutional EMRO (specialized) review per widely adopted guidelines Stem cells: NIH Registry; institutional EMRO if hESC research; unspecified if iPSCs	Prohibited by national funders; no national statutory prohibitions, but states can make their own laws
France	NA	Until 14 days	Embryos: ethical review by personal protection committee + authorization from the National Agency for the Safety of Medicines and Health Products + review by Biomedicine Agency (specialized) Stem cells: ethical evaluation by independent personal protection committee + notification of Biomedicine Agency	Legally prohibited

EMRO: Embryo research oversight; hESC: Human embryonic stem cell; HFEA: Human Fertilization and Embryology Authority; HREC: Human research ethics committee; iPSC: Induced pluripotent stem cell; MEXT: Ministry of Education, Culture, Sports, Science and Technology; NA: Not applicable; NAS: National Academy of Sciences; NHMRC: National Health and Medical Research Council; SCNT: Somatic cell nuclear transfer.

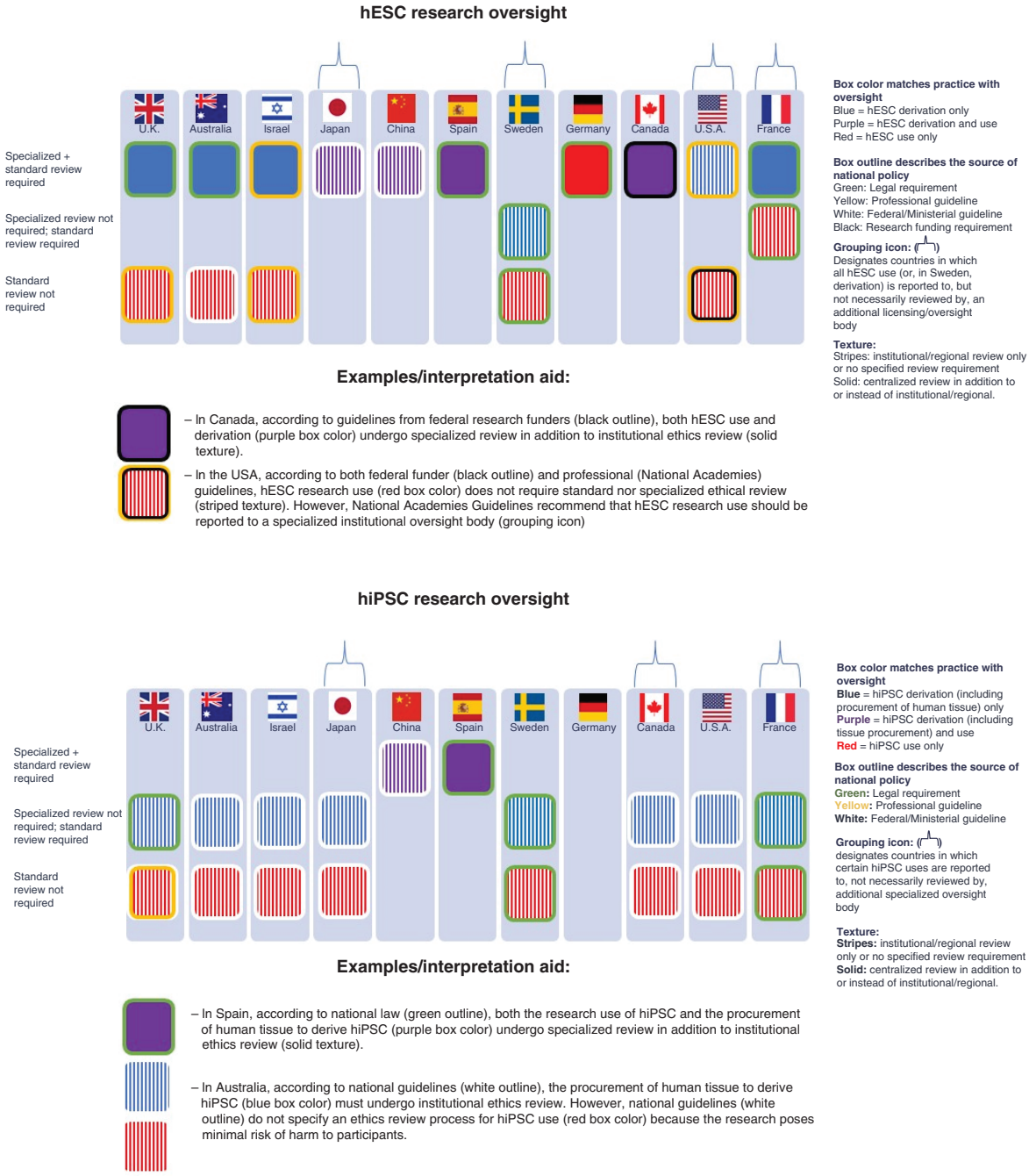

Figure 2. National governance of embryo/stem cell research.
hESC: Human embryonic stem cell; hiPSC: Human induced pluripotent stem cell.

Furthermore, in contrast to the Guidelines, national policies governing *in vitro* embryo and stem cell research have scarcely been revisited over the past decade. Periodic review ensures that policy remains relevant. Without it, it is unclear whether the status quo reflects a satisfaction with the ability of national rules to govern scientific developments (e.g., SCB-EMs) or, rather, a lack of political will to reopen contentious societal dialogues. ISSCR's efforts to continuously update best practices demonstrate reaffirmation of their commitment to balance scientific freedom with cautious regulation.

Revisiting embryo & stem cell research governance

Legislative change poses a substantial procedural burden, and legislators are accountable to constituencies with a wide range of views, including communities that might oppose embryo and stem cell research. A lack of periodic policy review may reflect a political strategy so as not to reopen contentious public debate that could adversely affect the direction of a scientific field. Countries that have engaged in policy review may provide a blueprint for countries seeking to incorporate governance of SCB-EMs into embryo research governance frameworks.

France's recent legislative review provides us with an interesting example. France has continuously revised its laws on bioethics in response to evolving ethical standards and scientific developments. It has relaxed its oversight requirements for hESC research, changing the remit of the federally appointed specialized review body, the Biomedicine Agency, for instance. Following a statutorily required "*public debate in the form of general statements*" and reports from several deliberative bodies evaluating the impact of the 2011 bioethics law [50], the 2021 law on bioethics imposed a statutory 14-day limit on embryo cultivation where there previously was none, removed regulatory barriers to *in vitro* hESC research and required researchers to declare projects that use hPSCs to model embryos to the Biomedicine Agency. Interestingly, a February 2020 version of the proposed new bill by the French Senate would have allowed *in vitro* embryos to be developed for up to 21 days for the purpose of studying gastrulation [51], but the National Assembly ultimately chose to mirror the prevailing international consensus. The review process also addressed the potential for litigation over the acceptability of contentious hPSC research which was left entirely to the discretion of the Biomedicine Agency [50]. Based on the understanding that hESCs, like human induced pluripotent stem cells, should not be legally equivalent to embryos but can be used to generate "*ethically sensitive cells*", the new law is also the first to threaten criminal sanctions for regulatory noncompliance specific to SCB-EMs. It is worth noting that although France's legal and regulatory framework continues to evolve, statutory prohibitions on human cloning and research embryo creation have remained in place.

Israel's legal framework is less comprehensive than France's – limited to a moratorium on human reproductive cloning and reproduction using genetically modified reproductive cells subject to periodic review [52]. Here the use of legislative review helps clarify legislative intent. With this review process, Israel renewed its decision to eschew legal sanctions and prescriptions, thereby reflecting its trust that researchers and institutions will remain scrupulous in evaluating evolving international standards. It remains to be seen whether this approach can be extrapolated to the governance of SCB-EMs.

Identifying likely sites of policy adaptation and the factors that facilitate or block their activity is crucial to forecasting responses to the Guidelines. Although Israel and France and Australia, which scheduled parliamentary review of a recently passed law approving mitochondrial donation [53], are the only countries surveyed that regularly schedule review of legislation related to embryo research, other national policies also contain built-in avenues for revision. In the UK [41], Australia [24], Spain [35], Germany [46], Sweden [30] and France [44], a combination of federal laws, regulations and ministerial ordinances outline the powers, remits and compositions of bodies that review embryo research (or, in Germany's case, hESC research, as all embryo research is prohibited). Government officials are empowered to issue regulations to further the effects of the overarching legislative framework, but significant modifications require broader input; for example, the 2015 UK regulations that permitted mitochondrial donation in human reproduction required approval from both Houses of Parliament [54]. Japan [23], Israel [52] and Canada [40] also use legislation to prohibit certain research techniques, but ethics oversight is described in guidelines designed by committees within or adjacent to federal ministries of health and/or education. For instance, Japan's permissive legal framework has enabled the Ministry of Education, Culture, Sports, Science and Technology (MEXT) to streamline hESC research ethics review, facilitating the use of hESCs in regenerative medicine [55], without renewing parliamentary deliberation [56]. In the US, federal *in vitro* embryo research policy is limited to an annually renewed prohibition on funding for embryo research [57], so privately funded embryo research is governed by state laws and, commonly, through institutional adoption of professional guidelines [32]. In China, prohibitions and governance structures stem almost entirely from guidelines [31] developed and "*enforced by the ministries with binding effect*" [58], without a clear blueprint for revision.

In other countries, Japan for instance, a technocratic approach to policy development reflects legislative intent. The Japanese Act on Regulation of Human Cloning Techniques [23] called for a one-time report 3 years after its passage that would review how human fertilized embryos should be handled "*as the emerging potential of human life*". The ensuing report [59] advanced their ethical assessments – that human fertilized embryos should not be created for the purpose of harvesting stem cells, that cloned embryos are "*ethically similar*" to human fertilized

embryos and that primitive streak formation marks the beginning of the human individual – that continue to guide Japanese policy. The MEXT minister organizes ethical review of research according to these basic principles. The Specified Embryo Research Committee, a subcommittee of MEXT staffed by medical professors, law and social science experts and embryologists [60], meets roughly five times annually to review guidelines within its purview, reviewing new articles and technological developments [56]. Through iterative review in tandem with an exhaustive list of conceptual definitions contained in foundational legislation, Japanese ministers actively apply a permissive approach with regard to *in vitro* embryo research to incorporate evolving science into existing guidelines. Although the MEXT minister has not yet issued specific guidelines for SCB-EMs, the litany of recently updated guidance contains ethical hierarchies and oversight models into which SCB-EMs can fit.

Even in the UK, a paradigmatic example of centralized embryo research governance and public engagement, explicit policies for SCB-EMs have yet to be developed. UK policy attaches special legal and regulatory provisions to the human embryo via statutory definition. Rather than specifying intrinsic qualities or technical origins that qualify an entity as an embryo, the UK statutory definition is intentionally left vague to encourage continuing discourse on the meaning and value of the embryo [61]. In recent years, absent legislative change, the ethical principles that apply to embryo research have been affirmed and expanded upon through updates to the Human Fertilization and Embryology Authority's Code of Practice, which is subject to approval by both Houses of Parliament [41]. However, if, as was asserted by a recent blog post on the Human Fertilization and Embryology Authority's website [62], SCB-EMs are not encompassed by the statutory definition of an embryo, then they are outside the remit of the UK's embryo research regulations and federal oversight. Under current UK policy, laboratory-based research involving hPSCs does not require approval by a research ethics committee [42]. Because of a dearth of guidance regarding the ethical evaluation of SCB-EM research, it is unclear which precedents UK stakeholders should rely on to develop uniform standards for such research.

The advent of human cloning and, later, gene editing, with the ensuing international debates, prompted *ad hoc* overhauls of policies. The disruptive potential of SCB-EMs has yet to provoke similar revisions. Scheduled legislative review in Israel and France has offered an opportunity to proactively reflect on whether laws function as intended, providing ethical clarity for researchers, regulators and the public, without removing extant restrictions. Although this tool is seemingly available to policymakers in many contexts, it has seldom been used. Will this change if integrated SCB-EMs continue to push ethical boundaries?

Concluding remarks: modeling SCB-EM policy with public engagement?

As with human embryos, popular conceptions of the moral significance and scientific utility of stem cells, distilled through local, national and international dialogue over the past decades, underlie regulations that define what is deemed ethical research. Although the nature of the human embryo has not changed over time, the capacity of researchers to manipulate stem cells to simulate embryogenesis has developed rapidly.

In tandem with new recommendations for SCB-EM oversight, the Guidelines encourage academic stakeholders and policymakers to "*lead public conversations touching on the scientific significance as well as the societal and ethical issues raised*" by relaxing the 14-day limit on *in vitro* human embryo culture, which prevents researchers from validating models of embryonic development beyond formation of the primitive streak [13]. The ISSCR challenges society to evaluate whether the knowledge and therapeutic potential of embryo modeling may generate compelling scientific rationale for permitting parallel advances in embryology. By increasing public familiarity with stem cell research governance and the ethical concerns contained therein, such dialogue may facilitate increased citizen engagement with the stem cell field, further promoting its advancement.

Thus far, there has been little movement toward inclusive, bottom-up public engagement surrounding shifts in embryo research policy [63]. In theory, mandatory legislative review can inspire or promote active public participation in policy debates. Comprehensive review provides an opportunity to address and engage a broad range of stakeholder perspectives. However, even in countries that have engaged in public polling and other dialogues around embryo and stem cell research, questions have persisted regarding the framing of ethical dilemmas [64] and the weight afforded to perspectives outside the technocratic world (e.g., beyond scientists, clinicians and ethicists) [65].

The Guidelines outline a useful conception of the appropriate norms for SCB-EM research governance. They reopen the dialogue on aligning critical scientific innovation with socioethical priorities and concerns together with public trust in science. In the past, this dialogue has elicited strong and diverse responses from societal and governmental institutions alike, particularly when dealing with practices involving early human development. As certain SCB-EMs could be considered morally contentious entities, public engagement in the development of

policies and practices governing their creation and use is essential to maintain public trust and support. As a tool for interpreting and developing policy, the Guidelines facilitate public engagement, but the Guidelines alone are not sufficient to connect researchers with the communities they serve. To nourish mutually beneficial growth, researchers and regulators familiar with the nuances of research governance should actively seek dialogue with other stakeholder groups (e.g., governance bodies, scientists and policymakers) to ensure that the categorization and oversight of SCB-EMs respect pluralistic societal values.

Future perspective

Although it may yield long-term societal benefits, the short-term political consequences of reopening potentially controversial or socially sensitive dialogues around human embryo and related research might discourage public dialogue and policy action on this topic. The Guidelines' influence on professional conduct may end up driving the development of policy and the creation of specialized governance infrastructure where none previously existed. Whether bounded by hard (e.g., legislation) or soft (e.g., professional best practices) laws, the collective action of stakeholders, in the form of adherence to robust ethical standards and responsiveness to societal concerns and priorities, will ultimately shape the direction of the stem cell field.

Executive summary

Background

- Stem cell-based embryo models (SCB-EMs) have emerged as a promising tool for studying human disease and embryonic development. The International Society for Stem Cell Research (ISSCR) revised its Guidelines for Stem Cell Research and Clinical Translation (Guidelines) to ensure that SCB-EM research proceeds within ethical limits. The Guidelines should prompt countries to revisit long-standing restrictions on embryo research, evaluating whether they should also apply to certain kinds of SCB-EM research.

Materials & methods

- Through juxtaposition with national policies in 11 research-intensive countries, the authors examined how the Guidelines may inform and shape national norms that govern SCB-EM research. This study draws on standard methodology for comparative policy research and analysis and incorporates both 'soft laws' (e.g., best practices, professional guidelines) and 'hard laws' (e.g., laws, statutes, regulations).

What is in a name?

- Recent scholarship has examined the role of legal definitions (or lack thereof) in shaping the permissibility and oversight of SCB-EM research. This is a useful starting point, and the Guidelines' updated terminology reflects an evolution driven by both scientific advances and ethical reflection.

New categories & applications of existing oversight models: the ISSCR paves the way

- The Guidelines' recommendations for SCB-EM oversight are influential in part because they help interpret how existing regulatory frameworks should apply to new science. However, they also classify embryo and stem cell research in ways that fundamentally differ from some national policies, indicating that their approach to SCB-EMs may also conflict with some national norms.

Sanctions are common to embryo research governance, but are they useful for SCB-EMs?

- Sanctions on human embryo research misconduct reflect powerful societal interests. However, their relevance may be muted following changes in the practice and governance of stem cell research.

Intent or inertia? Existing mandates & discrepancies between Guidelines & national policies

- Divergence in national policies governing stem cell research reflects policy choice driven by diverse ethical assessments. The Guidelines appear to clash with national policies. Without evident national policy review, it is unclear whether discrepancies stem from legitimate ethical disagreements.

Revisiting embryo & stem cell research governance

- In Israel and France, scheduled legislative review has led to renewed engagement with ethical principles underlying laws. However, this tool has not been widely used, and the advent of SCB-EMs has not prompted *ad hoc* revisions.

Concluding remarks: modeling SCB-EM policy with public engagement?

- The Guidelines encourage academic stakeholders and regulators to engage with communities to gauge appropriate governance of SCB-EM and embryo research. National models for engagement are needed to nourish the collaboration vital to responsible governance of contentious research.

Author contributions

M Fabbri, R Isasi and M Ginoza reviewed the literature and national policy documents for relevant examples of trends referenced in the article. M Fabbri and R Isasi structured the article. M Fabbri, R Isasi, M Ginoza, L Assen and K Jongsma wrote the manuscript.

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M Munsie of the University of Melbourne was an early collaborator who shaped the direction of the article. A Bredenoord read and offered minor edits to the manuscript.

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References

Papers of special note have been highlighted as: • of interest

1. Munsie M, Hyun I, Sugarman J. Ethical issues in human organoid and gastruloid research. *Development* 144(6), 942–945 (2017).
2. Rivron N, Pera M, Rossant J *et al.* Debate ethics of embryo models from stem cells. *Nature* 564(7735), 183–185 (2018).
3. International Society for Stem Cell Research. Guidelines for Stem Cell Research and Clinical Translation (2021). www.isscr.org/guidelines

• **Leading global professional standard for stem cell and stem cell-based embryo model (SCB-EM) research.**

4. Moris N, Anlas K, van den Brink SC *et al.* An *in vitro* model of early anteroposterior organization during human development. *Nature* 582(7812), 410–415 (2020).
5. Haremaki T, Metzger JJ, Rito T, Ozair MZ, Etoc F, Brivanlou AH. Self-organizing neuruloids model developmental aspects of Huntington's disease in the ectodermal compartment. *Nat. Biotechnol.* 37(10), 1198–1208 (2019).
6. Clark AT, Brivanlou A, Fu J *et al.* Human embryo research, stem cell-derived embryo models and *in vitro* gametogenesis: considerations leading to the revised ISSCR guidelines. *Stem Cell Reports* 16(6), 1416–1424 (2021).
7. Rivron NC, Frias-Aldeguer J, Vrij EJ *et al.* Blastocyst-like structures generated solely from stem cells. *Nature* 557(7703), 106–111 (2018).
8. Liu X, Tan JP, Schröder J *et al.* Modelling human blastocysts by reprogramming fibroblasts into iBlastoids. *Nature* 591(7851), 627–632 (2021).

• **One of the first examples of a human integrated SCB-EM; the ethics statement section catalogs researchers' paths through various oversight processes.**

9. Tarazi S, Aguilera-Castrejon A, Joubran C *et al.* Post-gastrulation synthetic embryos generated *ex utero* from mouse naive ESCs. *Cell* 185(18), 3290–3306.e25 (2022).
10. Rossant J, Tam PPL. Opportunities and challenges with stem cell-based embryo models. *Stem Cell Reports* 16(5), 1031–1038 (2021).

• **Introduction to the current science of SCB-EMs.**

11. Pereira Daoud AM, Popovic M, Dondorp WJ *et al.* Modelling human embryogenesis: embryo-like structures spark ethical and policy debate. *Hum. Reprod. Update* 26(6), 779–798 (2021).

• **Thorough overview of ethical and policy challenges posed by current and future SCB-EMs.**

12. Hyun I, Bredenoord AL, Briscoe J, Klipstein S, Tan T. Human embryo research: beyond the primitive streak. *Science* 371(6533), 998–1000 (2021).
13. Hyun I, Wilkerson A, Johnston J. Embryology policy: revisit the 14-day rule. *Nature* 533, 169–171 (2016).
14. Appleby JB, Bredenoord AL. Should the 14-day rule for embryo research become the 28-day rule? *EMBO Mol. Med.* 10(9), e9437 (2018).
15. Cavaliere G. A 14-day limit for bioethics: the debate over human embryo research. *BMC Med. Ethics* 18(38), 1–12 (2017).
16. Isasi R, Knoppers BM. Mind the gap: policy approaches to embryonic stem cell and cloning research in 50 countries. *Eur. J. Health Law* 13(1), 9–25 (2006).
17. Ginoza MEC, Isasi R. Regulating preimplantation genetic testing across the world: a comparison of international policy and ethical perspectives. *Cold Spring Harb. Perspect. Med.* 10(5), 1–13 (2020).
18. Isasi R, Ginoza M, Jongsma K, Assen L, Fabbri M. Mending the gaps: ethically sensitive cells and the evolution of European stem cell policy. *Regen. Med.* 17(8), 581–595 (2022).
19. Knoppers BM, Isasi R. Stem cell banking: between traceability and identifiability. *Genome Med.* 2(10), 2–7 (2010).
20. Annas GJ, Beisel CL, Clement K *et al.* A code of ethics for gene drive research. *CRISPR J.* 4(1), 19–24 (2021).

21. Matthews KR, Moralí D. National human embryo and embryoid research policies: a survey of 22 top research-intensive countries. *Regen. Med.* 15(7), 1905–1917 (2020).
22. Germany – Law On the Protection of Embryos (Embryo Protection Act – ESchG) (1990), Germany.
23. Japan – Act On Regulation of Human Cloning Techniques (Act No. 146 of 2000) (2000), Japan.
24. Australia – Research Involving Human Embryos Act (2002), Australia.
25. Ankeny RA, Munsie MJ, Leach J. Developing a reflexive, anticipatory, and deliberative approach to unanticipated discoveries: ethical lessons from iBlastoids. *Am. J. Bioeth.* 22(1), 36–45 (2022).

- **In-depth analysis of how Australian researchers and regulators have responded and should respond to challenges posed by integrated SCB-EMs.**

26. National Health and Medical Research Council. NHMRC statement on iBlastoids (2021). www.nhmrc.gov.au/about-us/news-centre/nhmrc-statement-iblastoids
27. International Society for Stem Cell Research. Guidelines for Stem Cell Research and Clinical Translation (2016). https://static1.squarespace.com/static/611faaa8fee682525ee16489/t/62f2d083d0b7a55e403b3afc/1660080259822/isscr-guidelines-for-stem-cell-research-and-clinical-translationd-2016.pdf
28. Lovell-Badge R, Anthony E, Barker RA *et al.* ISSCR Guidelines for Stem Cell Research and Clinical Translation: the 2021 update. *Stem Cell Reports* 16(6), 1398–1408 (2021).

- **Explains International Society for Stem Cell Research (ISSCR) rationale for the Guidelines.**

29. Peters T. Keep the 14-day rule in stem cell research. *Theol. Sci.* 19(3), 177–183 (2021).

- **This Perspective article provides a dissenting opinion regarding ISSCR/professional consensus.**

30. Sweden – Genetic Integrity Act (2006), Sweden.
31. Chinese Ministry of Science and Technology and Ministry of Health. Guiding principles of human embryonic stem cell research ethics (2003), China.
32. National Academies of Sciences, Engineering and Medicine. Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research. The National Academies Press WA USA (2010).
33. Sweden – Act on Ethical Review of Research Involving Humans (2003), Sweden.
34. Israeli National Academy of Sciences. Report of the Advisory Committee on Bioethics: the use of embryonic stem cells for medical research purposes (2003). www.medethics.org.il/wp-content/uploads/2020/02/R0751010a.html
35. Spain – Law 14/2007 of July 3 on Biomedical Research (2007), Spain.
36. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. Tri-Council Policy Statement: ethical conduct for research involving humans (2018). https://ethics.gc.ca/eng/policy-politique_tcps2-eptc2_2018.html
37. Japanese Ministry of Education, Culture, Sports, Science and Technology. Guidelines On the Handling of Specified Embryos (2021), Japan.
38. Israel – penal code (1977), Israel.
39. France – penal code (2022), France.
40. Canada – Assisted Human Reproduction Act (2004), Canada.
41. UK – Human Fertilisation and Embryology Act (1990), United Kingdom.
42. UK Stem Cell Bank Steering Committee. Code of practice for the use of human stem cell lines (2010). www.nibsc.org/asset.ashx?assetid=36019c52-bba2-497b-903f-df33e5c39dbc
43. National Health and Medical Research Council, Australian Research Council, Universities Australia. *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018).* Canberra, Australia.
44. France – public health code (2021), France.
45. Japanese Ministry of Education, Culture, Sports, Science and Technology. Guidelines On the Utilization of Human Embryonic Stem Cells (2019).
46. Germany – Act to Ensure Embryo Protection in Connection with the Import and Use of Human Embryonic Stem Cells (Stem Cell Act – StZG) (2002), Germany.
47. Australia – Prohibition of Human Cloning for Reproduction Act (2002), Australia.
48. Lo B, Parham L. Ethical issues in stem cell research. *Endocr. Rev.* 30(3), 204–213 (2009).
49. Sawai T. The moral value of induced pluripotent stem cells: a Japanese bioethics perspective on human embryo research. *J. Med. Ethics* 40, 766–769 (2014).

50. French Parliamentary Office for the Evaluation of Scientific and Technological Choices. Impact study: project of law relating to bioethics (2019). www.assemblee-nationale.fr/11/documents/index-oecst-gb.asp#Abstracts.
51. French National Assembly. Second reading of text no. 2658 transmitted to the national assembly on February 5, 2020 (2020). www.assemblee-nationale.fr/dyn/15/textes/l15b2658_projet-loi (Accessed 7 February 2022).
52. Israel – Prohibition of Genetic Intervention (Human Cloning and Genetic Alteration in Reproductive Cells) Law, 5769-1999 (1999), Israel.
53. Australia – Mitochondrial Donation Law Reform (Maeve's Law) Act (2022), Australia.
54. UK – Human Fertilisation and Embryology (Mitochondrial Donation) Regulations (2015), United Kingdom.
55. Japanese Ministry of Education, Culture, Sports, Science and Technology. Advisory no. 4: report on 'Guidelines for Distribution and Use of Human ES Cells' (2014). www.lifescience.mext.go.jp/files/pdf/n1430_10.pdf (Accessed 1 February 2022).
56. Japanese Specified Embryo Research Special Committee. List of proceedings (simplified version) (2021). www.lifescience.mext.go.jp/files/pdf/tokuhai_ichiran.html
57. US – Consolidated Appropriations Act, 2021 (2021). www.congress.gov/116/plaws/publ260/PLAW-116publ260.pdf
58. Song L, Isasi R. The regulation of human germline genome modification in the People's Republic of China. In: *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies.* Boggio A (Ed.). Cambridge University Press, Cambridge, UK, 469–499 (2019).
59. Japanese Council for Science and Technology Policy. Basic concept regarding the handling of human embryos (2004), Japan.
60. Japanese Science and Technology Council. Bioethics and Safety Subcommittee Specified Embryo Research Special Committee member list (draft) (2019). www.lifescience.mext.go.jp/files/pdf/n2132_02.pdf
61. UK Human Fertilization and Embryology Authority. 'And if the body were not the soul. . . ': the status of embryos created artificially from human and non-human components (2006). https://webarchive.nationalarchives.gov.uk/ukgwa/20130403013026/http:/www.hfea.gov.uk/docs/ELC_Committee_if_the_body_were_not_the_soul_May06.pdf (Accessed 8 February 2022).
62. Greenfield A. Embryos, genes and regulation: the impact of scientific progress on future reproductive medicine and the HFEA (2022). www.hfea.gov.uk/about-us/30th-anniversary-expert-series/embryos-genes-regulation-the-impact-of-scientific-progress-on-future-reproductive-medicine-and-the-hfea/ (Accessed 8 February 2022).
63. Adashi EY, Cohen IG. Who will oversee the ethical limits of human embryo research? *Nat. Biotechnol.* 40(4), 463–464 (2022).
64. Mohr A, Raman S. Representing the public in public engagement: the case of the 2008 UK Stem Cell Dialogue. *PLOS BIOL.* 10 (11), e1001418 (2012).
65. Ankeny RA, Dodds S. Hearing community voices: public engagement in Australian human embryo research policy 2005-7. *New Genet. Soc.* 27(3), 217–232 (2008).