Perspective

Regenerative Medicine

Mending the gaps: ethically sensitive cells and the evolution of European stem cell policy

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The past decades witnessed the slow evolution of Europe's heterogeneous stem cell (SC) policy and substantial scientific advances in the field. Parallel to these developments, professional organizations have grown in influence. With the recently revised International Society for Stem Cell Research's Guidelines as a backdrop, we address the evolution of SC policies in 46 European countries and discuss how they fare against evolving ethical standards, societal views, and scientific advances. We identify areas of convergence, divergence, and the suitability of extant governance mechanisms to meet their stewardship roles. Europe represents a rich case study as it encompasses a wide range of policy approaches present worldwide. Comparative studies provide an opportunity to promote insight into national frameworks and to foster international harmonization.

Plain language summary: European countries have adopted different types of rules or policies, including laws and professional standards, to regulate stem cell research. These differences are because each country has different history and cultures. Also, individuals and institutions (e.g., religious leaders, politicians and advocacy organizations) have different degrees of power to influence the type of policies that are adopted in each country. Over the past decades, stem cell policies have evolved slowly even with significant scientific advances. Yet, during this time, professional organizations have grown in influence, for example, the prominent International Society for Stem Cell Research, whose guidelines (or rules) are considered 'best practices' in the field. In this article, we identify and analyze stem cell policies in 46 European countries, comparing them against the International Society for Stem Cell Research's new Guidelines. In addition, we show the similarities and differences amongst these policies. Europe presents an interesting case study because the region includes a wide typology of policies like those adopted in the rest of the world, making this comparison useful for other countries as they consider the suitability of their own policies.

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In Europe, the stem cell research–clinical translation continuum is characterized by a heterogeneity of governance and policy frameworks reflecting the continent's diverse socio-cultural, economic and historical contexts. In the region, national and international sets of 'hard' (e.g., legislation, treaties) laws are supplemented by 'soft' ones (e.g., professional guidelines, funding policies, codes of conduct) offering different tools for enforceability and governance. Importantly, regardless of the approach, ethical considerations have acquired substantial importance as a normative tool for European policy making [1]. Similarly, the public and the patient advocacy community have also gained prominence as influential policy actors, while professional organizations have maintained their persuasive role.

Future Medicine

Globally, scientific advances in the stem cell (SC) field have occurred in parallel with the growth of professional organizations operating at the national and international stage. With different degrees of success, these entities have exerted influence in shaping the contours of responsible innovation, and thereby, fostering adaptive policy and governance. A notable example of this is the International Society for Stem Cell Research (ISSCR), whose Guidelines on stem cell research and clinical translation (hereafter: Guidelines) [2] provide contemporary scientific, ethical and policy standards. Indeed, globally, ISSCR guidelines have been deemed more than metaphorically 'customary law' ever since their inception in 2006, as they have continued to gain legitimacy by raising awareness of ethical challenges, guiding scientific practice, and aiding in the interpretation and implementation of policy.

Recently, ISSCR updated its Guidelines, adopting strict recommendations for the regulation of clinical research and translation of SC-based interventions and substantially reconfiguring guidance for oversight of *in vitro* SC projects. Despite criticisms based on the absence of enforcement mechanisms and internal consistency [3,4], among other reasons, the revised Guidelines have the potential to exert influence in policy developments as they are designed to reflect community standards and, in that way, they aim to complement national frameworks for research governance.

Moreover, although both hard and soft laws affect the actual practice of SC research, it is unclear how European policy frameworks fare against evolving international norms represented, for instance, in the ISSCR guidelines. In addition, it is unclear how and why policies within European countries diverge and converge. Insights into these practices could lead to understanding possible gaps, contradictions and difficulties in governance and policy. Moreover, it could offer insights into how governance systems could equip researchers to act responsibly during the innovation process. In pursuit of these insights, this article addresses the evolution of SC policies in 46 European countries. With the Guidelines as a backdrop, we discuss central ethical and policy issues regarding contentious applications, including criteria for permissibility, oversight, and enforcement mechanisms. Comparative studies provide an opportunity to promote insight into national frameworks and to foster international harmonization.

The European region represents a rich case-study as it encompasses a wide range of policy approaches present across the globe. Thus, evaluating areas of convergence, divergence and progression in this region can contribute to policy debates and development worldwide.

Legislative building blocks past & present

With no single policy comprehensively addressing SC across the entire research cycle, European SC policy frameworks are constituted by (i) a broad cluster of laws, directives, principles and norms governing assisted reproductive technologies (ART), biobanking, biomedical and genetics research which (ii) traverse the permissive to restrictive continuum (Appendix A Governance Approaches). Underpinning these models are foundational principles reflecting a society's common vision, moral values, and beliefs. Moreover, a 'common Ethics' in the SC field is apparent from the ongoing adoption of research funding frameworks [5], which include provisions for the inescapably controversial human embryonic SC (hESC) research as well as with the 1997 passing of the European Convention on Human Rights and Biomedicine [6].

Across Europe, as in other regions, the regulation of SC research has generally followed a linear path, with discussions surrounding the human embryo's biological, moral and legal status as an early central figure in the framing of socio-ethical debates and policy outcomes (e.g. Germany's Embryo Protection Act; Belgium's Law relating to research on embryo *in vitro*). This approach stems from the fact that early policy was embedded within normative frameworks governing ART (e.g. in Estonia [7] and Greece [8]). As such, primary goals have centered on preserving human dignity (e.g., preventing commodification, protecting the interests of unborn children) as well as integrity (e.g., cloning [9] and genetic engineering bans). During these early stages, policy reforms reacted to changes in societal perceptions (e.g., toward biological parenthood) and increased technological uptake which required the promotion of the right to benefit from scientific advances and to protect welfare interests (e.g., facilitating ART research or expanding access to related services) [10]. Similarly, striving to reach political compromises, European policy moved to regulate hESC research with blanket bans (e.g., Lithuania [11]), moratoria (e.g., The Netherlands [12]) or strict laws guided by the principles of proportionality and subsidiarity as pillars (e.g. UK, Czechia, France) [13,14]. From European funding policies to national laws, the passage of time has not altered this decisive criterion: the use of embryos (and gametes) is justified if it is the only means to achieve important scientific goals for societal benefits. Furthermore, early socio-ethical debates on genetic engineering, reproductive and research cloning were also influential in the framing of policy responses [15] as reflected in the adoption of the Oviedo Convention [16].

Importantly, the debates that took place during these times have now been revisited with the advent of gene editing tools and the emergence of SC-based embryo modeling as developments unforeseen by policymakers.

Stem cell-based embryo modeling & beyond

Contemporaneous developments in SC-based embryo modeling [17], organoid [18] and human–animal chimera research [19] have triggered calls for policy review [20] based on fears of potential loopholes inadvertently allowing controversial research to proceed without appropriate governance controls or societal support. For instance, advances in embryogenesis allow for hESCs and human induced pluripotent stem cells (hiPSCs) to be coaxed to organize into structures that mimic aspects of human embryonic development. These SC-based embryo models (SCB-EMs) have been used to model post-implantation stages of human development from the formation of the amniotic sac [21] to neurulation [22]. Additionally, improvements in human-animal chimera research using SC may enable investigators to study human development and organogenesis in an unprecedented manner. Furthermore, gastruloid [23] research, which models events following the formation of the primitive streak, provides another interesting case study, as their scientific potential for disease modeling has driven a shift in well-established policy.

The possibility of yielding entities that might faithfully replicate embryonic developmental processes [24] has prompted conceptual reexaminations, as SCB-EM do not fit neatly in pre-existing regulatory categories defining human embryos, gametes, or human research subjects. Because generally European national policies were initially created to govern ART, they often contain statutory decades-old definitions of what constitutes a human embryo (e.g., Bulgaria [25], Iceland [26] and Slovenia [27]) (see Figure 2 statutory definitions of the human embryo). These definitions effectively establish distinct regulatory pathways depending on the embryo's methods of creation, which is illustrated in the (often arbitrary) demarcation between embryos created by sperm-egg fertilization or by other means. An example is presented in Spain [28] where an entity is deemed an 'embryo' or 'pre-embryo' by reference to a human fertilized oocyte. Spanish law prohibits the creation of embryos for research purposes but allows pre-embryo creation via human somatic cell nuclear transfer to harvest stem cells. Other European laws categorize an embryo in terms of its potential to develop into a human individual or to reach a significant point on the developmental timeline (e.g., Belgium [29], The Netherlands [30] and Malta [31]). In the UK, following legislative review [32], the term embryo was considerably expanded, from the product of complete fertilization [33] to "*an egg that is in the process of fertilization or is undergoing any other process capable of resulting in an embryo*" [34] using human cells; or an ad-mixed entity that is the product of hybrid and chimeric processes. Importantly, here, expansive concepts and research have been accompanied by modernized, robust licensing and oversight systems [35].

Largely, European countries have committed to ban embryo creation for research. This commitment arises by the ratification of the Oviedo Convention (albeit stipulated reservations). Furthermore, the Additional Protocol prohibiting human cloning [36] or germline genetic engineering reflects European agreement that restrained compromises are necessary to protect human dignity and identity while advancing scientific progress (Appendix A lists countries that have ratified the Additional Protocol). Even countries adopting liberal approaches by permitting the creation of embryos for research purposes via different methods (e.g., UK [37], Sweden [38] and Belgium [39]) align with this restrained approach by committing to provide "*adequate protection of the embryo*" where embryo research is allowed [40]. In contrast, the ISSCR Guidelines diverge from common European policy by permitting the creation of embryos for research if projects stop at "*well-defined timepoints*" and undergo appropriate degrees of ethical review. Furthermore, to allow validation of increasingly advanced SCB-EM research, the Guidelines have issued a controversial [41] call for governments and oversight bodies to reappraise the '14-day rule' – a gold standard preventing human embryos cultured *in vitro* from developing for longer than 14 days [42]. In the EU, regardless of where a country sits in the policy permissibility continuum, this rule continues to be ubiquitous (see Figure 1 for countries that have adopted the 14-day rule).

Similarly, the Guidelines sit in stark contrast with European policy regulating research on human–animal chimeric embryos. They recommend permitting human-animal chimera research and outline criteria for ethical review, while exempting *in vitro* culture from specialized review requirements. In contrast, almost half of European countries adopt a range of prohibitions on hybrid and/or chimera creation (e.g., Cyprus [43], Portugal [44], Switzerland [45]) (Figure 1). Only the UK regulates the practice extensively, while do not explicitly prohibit human–animal chimera research but ban different types of activities (e.g., implantation). Indeed, in most policies the term 'chimera' is either not defined, or prohibitions refer to the combination of human and animal reproductive material, with unclear implications for human–animal chimera research using hPSCs [46]. Direction from the Guidelines

ISSCR category 1A:**

Under national policies, these research practices are permitted and exempt from review by a specialized oversight process (and thus can be ethically reviewed under existing mandates):

Research practice:	Countries:
Most *in vitro* hPSC research (ISSCR category 1A)*	Albania, Andorra, Armenia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus (hiPSC only), Czechia (hiPSC only), Denmark, Estonia, Finland, France (most hiPSC research only), Georgia, Germany (hiPSC only), Greece, Hungary (hiPSC only), Iceland, Ireland (hiPSC only), Italy (hiPSC only), Kazakhstan, Kosovo, Latvia, Lithuania (hiPSC only), Luxembourg, Malta, Moldova, Montenegro, Netherlands, North Macedonia, Norway, Poland (hiPSC only), Portugal, Romania, San Marino, Serbia, Slovakia, Slovenia, Sweden, Switzerland, Ukraine, United Kingdom
In vitro culture of human embryos for research until the formation of the primitive streak or 14 days from fertilization, whichever occurs first (ISSCR category 2)	Legislative approach*: Denmark, Estonia
Derivation of cell lines from human embryos (ISSCR category 2)	Legislative approach*: Denmark, Estonia
*Note: Includes countries that do not specify oversight for *in vitro* hPSC research	*By law, these countries require ethics review for embryo research but do not specify additional oversight in legislation

**NB: Not included:
– Most *in vitro* organoid research
– Transfer of human stem cells into postnatal animal hosts

ISSCR category 1B:**

Under national policies, these research practices are reportable, but not typically reviewed by a specialized oversight process

Research practice:	Countries:
Non-integrated stem cell-based embryo models (ISSCR category 1B)	Legislative approach: France (declaration made to biomedicine agency)
In vitro culure of chimeric embryos (human cells into non-human embryos)* (ISSCR category 1B)	Legislative approach: France (declaration made to biomedicine agency)
Integrated stem cell-based embryo models (hereafter: SCB-EM) (ISSCR category 2)	Legislative approach: France (declaration made to biomedicine agency)
In vitro culture of human embryos for research until the formation of the primitive streak or 14 days from fertilization, whichever occurs first (ISSCR category 2)	Legislative approach + Ministry of education ordinance: Sweden (copy of ethical review decision sent to Swedish research council, national board of health and welfare)
Derivation of cell lines from human embryos (ISSCR category 2)	Legislative approach + Ministry of education ordinance: Sweden (copy of ethical review decision sent to Swedish research council, National board of health and welfare)
Procurement of embryos, or gametes, for the creation of embryos, for *in vitro* research (ISSCR category 2)	Legislative approach + Ministry of education ordinance: Sweden (copy of ethical review decision sent to Swedish research council, National board of health and welfare)
(*NB: Certain kinds of chimeric research)	

**NB: Not included:
– *in vitro* gametogenesis without fertilization or generation of embryo

ISSCR category 2:

Under national policies, these research practices are only permitted following review by a specialized oversight process

Research practice:	Countries:
Most *in vitro* HPSC research (ISSCR category 1A)	Legislative approach: Spain
In vitro research on hESC specifically (ISSCR category 1A)	Legislative approach: Cyprus[1], Czechia, Gemany[2], Hungary[1]
In vitro culture of chimeric embryos (human cells into non-human embryos)* (ISSCR category 1B)	Legislative approach[7]: Netherlands, United Kingdom
Integrated SCB-EM (ISSCR category 2)	No country other than France specifically regulates SCB-EM, so regulation of SCB-EM would likely follow regulatory path for *in vitro* hPSC research
In vitro culture of human embryos for research until the formation of the primitive streak or 14 days from fertilization, whichever occurs first (ISSCR category 2)	Legislative approach: Belgium, Bulgaria[3], Cyprus, Czechia[4], Finland, France, Greece, Hungary, Iceland, Latvia, Montenegro, Netherlands, North Macedonia, Norway[3], Portugal, Serbia[3], Slovenia, Switzerland[4,5], United Kingdom
Derivation of cell lines from human embryos (ISSCR category 2)	Legislative approach: Belgium, Bulgaria[3], Cyprus, Czechia, Finland, France, Greece, Hungary, Iceland, Latvia, Montenegro, Netherlands, North Macedonia, Norway[3], Portugal, Serbia[3], Slovenia, Switzerland, United Kingdom
Procurement of embryos, or gametes, for the creation of embryos, for *in vitro* research (ISSCR category 2)	Legislative approach: Belgium, Iceland[6], Portugal[6], Spain[6], United kingdom
(*NB: Certain kinds of chimeric research)	Footnotes: 1. Criteria for hESC ethical evaluation not specified in law 2. Research only permitted on imported hESC lines, as hESC derivation is prohibited by law 3. Ministry of health permit required to perform ART; additional embryo research oversight not specified 4. Embryo culture limit set lower than 14 days 5. Emryo research is only permitted for the purpose of deriving hESCs 6. Permits embryo creation for research via hSCNT but prohibits sperm-egg fertilization for research purposes. 7. In both of these countries, the culture of chimeric embryos is limited to 14 days

**NB: Not included:
– Genetic alteration of embryos or gametes
– Human cells transplanted into nonhuman embryos that are gestated in a non-human uterus
– Transferring human embryos following MRT into a human uterus

ISSCR category 3:

Under national policies, these research practices are prohibited, either due to safety concerns, ethical concerns or a lack of compelling scientific rationale

Research practice:	Countries:
In vitro research on hESC (ISSCR category 1A)	Legislative approach: Lithuania Funding approach: Ireland, Italy, Poland Guidance: Turkey
In vitro culture of chimeric embryos (human cells into non-human embryos)* (ISSCR category 1B)	Legislative approach: Cyprus[1], Greece[1], Portugal[1], Estonia[2], Montenegro[2], North Macedonia[2], Slovenia[2], Switzerland[3]
In vitro culture of human embryos for research until the formation of the primitive streak or 14 days from fertilization, whichever occurs first (ISSCR category 2)	Legislative approach: Albania, Andorra, Austria, Bosnia and Herzegovina, Croatia, Germany, Italy, Kazakhstan, Kosovo, Lithuania, Malta, Slovakia Professional guideline: Poland
Derivation of cell lines from human embryos (ISSCR category 2)	Legislative approach: Albania, Andorra, Austria, Bosnia and Herzegovina, Croatia, Germany, Italy, Kazakhstan, Kosovo, Lithuania, Malta, Slovakia Professional guideline: Poland
Procurement of embryos, or gametes, for the creation of embryos, for *in vitro* research (ISSCR category 2)	Legislative approach: Albania, Andorra, Austria, Belarus, Bosnia and Herzegovina, Croatia, Cyprus, Czechia, Denmark, Finland, France, Germany, Hungary, Italy, Kazakhstan, Kosovo, Latvia, Lithuania, Malta, Montenegro, Netherlands, North Macedonia, Norway, Romania, Serbia, Slovakia, Slovenia, Switzerland, Pan-EU Regulation[4]: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Georgia, Greece, Hungary, Iceland, Latvia, Lithuania, Moldova, San Marino, Turkey, Italy[8], Luxembourg[8], Netherlands[8], Poland[8], Sweden[8], Ukraine[9] Via professional guideline: Ireland, Poland
Human cells transplanted into non-human embryos that are gestated in a non-human uterus (ISSCR category 2)	Legislative approach[5]: Belgium, Serbia
Transferring human embryo(s), irrespective of origin, to an animal uterus (ISSCR category 3B)	Legislative approach: Bosnia and Herzegovina, Czechia, Iceland, Latvia
Cloning for research (ISSCR category 2)	Legislative approach: Andorra, Cyprus[6], France, Georgia, Germany, Italy, Kazakhstan, Lithuania, Moldova, Norway[2], Serbia, Slovakia, Slovenia, Switzerland Legislative prohibition on embryo creation for research[7]: Albania, Austria, Belarus, Bosnia and Herzegovina, Denmark, Finland, Kosovo, Malta, Netherlands Pan-EU Regulation banning cloning[8]: Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czechia, Estonia, Finland, Georgia, Germany, Greece, Hungary, Latvia, Lithuania, Moldova, Montenegro, North Macedonia, Norway, Romania, Slovakia, Slovenia, Switzerland, Turkey, Denmark9, France[9], Italy[9], Luxembourg[9], Netherlands[9], Poland[9], San Marino[9], Serbia[9], Ukraine[9], Iceland[10], Portugal[10], Spain[10], Sweden[10]
Human reproductive cloning (ISSCR category 3B)	Legislative approach (upstream): Andorra, Cyprus[6], France, Georgia, Germany, Italy, Kazakhstan, Lithuania, Moldova, Norway[2], Serbia, Slovakia, Slovenia, Switzerland Legislative approach (downstream)[11]: Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Denmark, Greece, Hungary, Iceland, Malta, Montenegro, Netherlands, North Macedonia, Norway, Portugal, Romania, Sweden, Ukraine, United Kingdom Pan-EU regulation banning cloning[8]: Bulgaria, Croatia, Czechia, Greece, Hungary, Latvia, Montenegro, Romania, Turkey Luxembourg[9], Poland[9], Portugal[10], Spain[10], Professional guideline: Ireland, Poland
(*NB: Certain kinds of chimeric research)	Footnotes: 1. Also prohibits human-animal hybrid creation generally 2. Also prohibits creation of hybrid embryos 3. Also prohibits import of chimeras/hybrids 4. Convention on human rights and biomedicine,Council of Europe Treaty no. 164 (Oviedo, 1997) 5. Countries prohibit the creation of "chimera or hybrid beings"–unclear if this prohibits chimeric embryo research or is limited to prohibiting reproduction of chimeria embryos 6. Prohibits import of human reproductive tissue resulting from cloning 7. Refers to countries that do not prohibit hSCNT specifically but prohibit embryo creation for research by any means 8. Cloning protocol, Council of Europe Treaty no. 168 (Paris, 1998) 9. Signed, but did not ratify, treaty 10. Legislation permits cloning for research despite ratification of international convention 11. List of countries that do not prohibit the technique of hSCNT in legislation but specifically prohibit reproductive cloning.

**NB: Not included:
– Heritable genome editing
– Transferring mtDNA-modified (not including MRT) embryos into a uterus
– Using gametes differentiated from human stem cells for reproduction
– Gestating human SCB-EM
– Breeding human-animal chimeras where there may be human germ cells
– Transferring human-animal chimeric embryos to a human or ape uterus

Figure 1. A comparison of ISSCR oversight categories with European policy.

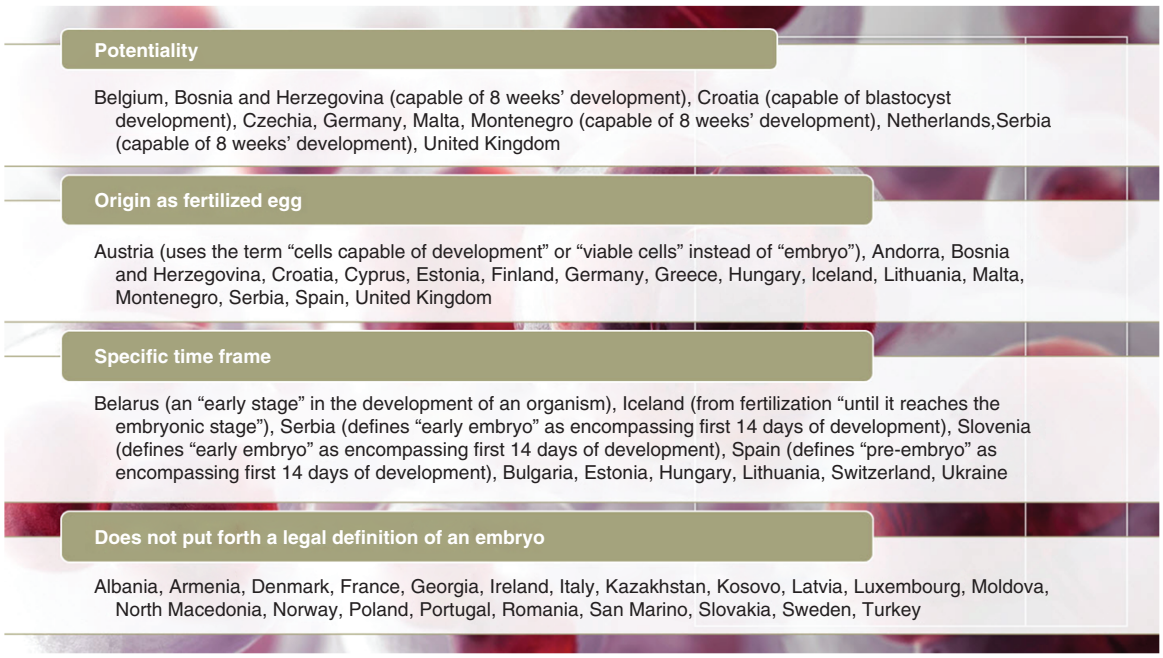

Figure 2. Statutory definitions of the human embryo.

alone might prove to be insufficient to clarify the scope of extant legal prohibitions for research areas not explicitly described in law.

The gradual liberalization of EU national policy

A discrete trend toward policy liberalization continues to slowly emerge in Europe, which in turn, may have transformational effects in the entire region. Indeed, policy transfer might occur through joint problem solving in challenging issues such as with the curtail of unproven stem cell interventions or the regulation of interventions in early human development (e.g., embryo or germline). Alternatively, the promotion of more liberal policy models could happen by the active role of countries or international actors promoting their own models to foster their interests or seeking policy harmonization (ISSCR, European Commission). Finally, it can ensue as result of pressure exerted in the form of international scrutiny directing countries to legitimate their policy approaches.

Policy liberalization is particularly revealed in the progression of French law, which lifted its restrictive approach of the '90s toward hESC and chimeric research' [47,48]. In 2021, France became the first country to specifically regulate the use of hPSC for gametes and SCB-EM creation, subject to the robust governance of the Biomedicine Agency and of local institutional ethics review bodies [49]. Unlike many of its contemporaries, France did not place a legal temporal limit on embryo cultivation until 2021. Following a previous National Consultative Ethics Committee [50] recommendation that embryo culture and research must stop after 7 days of development and, contemporaneous calls from researchers to not impose strict time limits, the revised law implements the 14-day rule. In addition, the law refines its prohibition on chimeric embryo research, forbidding the modification of human embryos by adding cells from other species but permitting the insertion of hPSC into animal embryos "*for the purpose of its transfer to the female*", "*subject to declaration to the Biomedicine Agency*" [51].

Similarly, several other countries have relaxed restrictions on hESC research over the past 15 years, while attempting to de-exceptionalize the SC field. For example, in the mid-2000s, moratoria were dropped and prohibitions on embryo research in countries such as Denmark [52], Norway [53] and Iceland [54] were rescinded in favor of regulations allowing research on supernumerary embryos. Other countries shifted to allow cloning research (e.g., in Spain [55], Iceland [56] and the U.K. [57]). The evolving power of stakeholders influenced some of these developments, albeit with different degrees of success. For instance, in Germany, the influence of the National Ethics Council and the German Research Foundation [58] was effective for the relinquishment of blank prohibitions and for relaxing cut-off dates for the import and use of hESC lines. Also, in Ireland, the role of stakeholders (e.g., Catholic Church [59]) was influential in maintaining a status quo [60], despite calls from their National Bioethics Committee and other

actors to adopt a more permissive approach [61]. As a result, Ireland remains without specific stem cell legislation, while embryo research is considered a permissible activity since a ruling from its Supreme Court [62] provided legal certainty regarding the *in vitro* embryo's legal status. Across European countries (as in the rest of the world), religious [63] and other cultural authorities continue to wield varying degrees of influence as stakeholders shaping policies related to embryo and stem cell research. Notable has been the uncompromising position of the Catholic Church, yet its influence has varied. For instance, in Italy [64,65] it continues to be a prevalent stakeholder hindering progressive stem cell policy, while in Spain, religious opposition was unable to stop policy liberalization [66,67]. In secular moral frameworks, permitting (under regulation) new and contentious uses of human pluripotent stem cells may be justified according to their potential for providing therapeutic benefit. Research on somatic stem cells has historically been favored as an alternative to research on the human embryo. However, it remains to be seen how SCB-EM and chimeras combining hiPSC with animal embryos fit within religious conceptions of the nature of human life.

Following decade-old attempts to shift an 'embryo'-centric approach to one that focuses on governance, the Guidelines [68] encourage nations and professional bodies to move toward a dynamic model of policy, where blanket bans are replaced by proportional and robust governance. It is thus timely to probe Europe's current situation.

Challenging the status quo: the role of regulation & oversight

The dual mechanisms of licensing and ethics oversight play a pivotal role in fostering scientific integrity by influencing collective behavior. These deliberative bodies seek to rely on precedent, referencing previous dilemmas to judge similar proposals by consistent standards. Across Europe, governance is achieved through a plurality of actors and mechanisms, where a collection of laws and best practices establish the normative framework in which safety and ethical standards are implemented [69–72]. Stewardship over SC research practices is often exercised through statutorily established licensing and oversight mechanisms. Ensuing competency and reporting requirements that guide oversight bodies are based on research stages such as tissue/embryo procurement, embryo research, derivation, and uses of hPSCs (see Figure 3 Governance mechanisms in selected countries).

As highlighted by ISSCR, prospective review and ongoing monitoring for compliance with ethical standards must be conducted and vetted by an independent committee. European approaches converge in this regard. They all establish local or national specialized oversight bodies of multidisciplinary composition (e.g., biology, law, ethics and in some instances community representatives) to conduct such activities. Moreover, most countries generally follow an ISSCR-style tiered approach to oversight, at least with respect to embryo and hESC related research, which are subject to specialized or centralized ethics review depending on pre-determined criteria. In Europe, mostly due to historical and political contexts, some entities charged with specialized oversight have as core focus licensing and oversight of ART interventions or embryo research activities (e.g., Belgium [73], Greece [74], Hungary [75], Montenegro [76], North Macedonia [77], Portugal [78], Slovenia [79], UK [80]), while others have a broader remit by evaluating biomedical research in general (e.g., Cyprus [81], Czechia [82], France [83], Spain [84], Switzerland [85]) at the local level (Appendix B governance bodies tasked with review of embryo research).

The ISSCR Guidelines, revised to reflect evolving consensus within the field, are meant to complement existing systems of oversight, aligning new research with pre-existing societal goals. Their overarching goal is to guide researchers to seek appropriate levels of ethical review for *in vitro* research involving entities that could be deemed ethically or socially controversial. Among the substantial changes introduced is the categorization of permissible types of research and their corresponding oversight models. For instance, they recommend that the derivation of hESC and research on "*integrated*" SCB-EM be subject to the same oversight process. Notably, its previous version called for heightened scrutiny for projects involving embryo-like structures that might manifest "*human organismal potential*" [86]. To this end, they abandon the latter nebulous and unmeasurable criterion and replace it with a proxy for researchers 'intent and models' capacity to "*undergo further integrated development when cultured for additional time in vitro*" [87]. Thus, reflecting that the inherent potential of human and human-like organisms can only be realized through sustained and deliberate external influences. But while this justification has evolved, the ISSCR has remained consistent with recommendations to subject embryo modeling using hPSC to a higher level of scrutiny than what might be required by national laws. The Guidelines extend a premise fundamental to European research governance, that research on entities with questionable moral status should proceed with caution. However, SCB-EM in Europe appear to be outside the purview of national systems of oversight designed

Country:	Embryo research oversight (hESC derivation)	Oversight of *in vitro* hESC research (post-derivation)	Human tissue oversight (hiPSC derivation, use of stored SC lines)
Belgium	Local ethics committee + Federal Commission for medical and scientific research on embryos	Ethics committee with "full approval"/accreditation from minister of public health	Ethics committee with "full approval"/accreditation from Minister of public health
Czechia	Ministry of education, youth and sports + bioethics commission + council for research and development	Ministry of education, youth and sports + bioethics commission + council for research and development	State Institute for drug control; institutional ethics committees
Finland	Hospital district regional ethics committee + center for the safety and development of medicines	Hospital district regional ethics committee + center for the safety and development of medicines	Hospital district regional ethics committee + center for the safety and development of medicines
France	Ethical evaluation by independent personal protection committee + Biomedicine Agency (ethical review, ongoing monitoring) + authorization from National agency for the safety of medicines and health products	Ethical evaluation by independent personal protection committee + Biomedicine agency (notification + information on movement of hESCs)	For derivation of hiPSC: Ethical evaluation by personal protection committee + biomedicine agency (ethical review) + authorization from National Agency for the safety of medicines and health products; notification of biomedicine agency also required for certain uses of hiPSC
Portugal	National council for medically assisted procreation	National council for medically assisted procreation	Institutional health ethics committees + Directorate-general for health oversees/enforces quality/safety standards for human tissue
Spain	Institutional research ethics committee + guarantee commission + competent state or regional authority (approves/rejects research)	Institutional research ethics committee + guarantee commission + National bank of cell lines	Institutional research ethics committee + guarantee commission + National Bank of cell lines
Sweden	Ethics review authority + notification of Swedish medical research council & National board of health and welfare	Ethics review authority + Swedish health and care inspectorate	Ethics review authority + Swedish health and care inspectorate

Figure 3. Governance mechanisms in selected countries.

to apply and enforce ethical norms that govern embryo research. It remains to be seen whether these changes will effectively impact European policy.

Governance & the role of criminal law

Governance mechanisms, such as those related to licensing and oversight, rest on legitimacy and accountability. Governance approaches should endow researchers to act responsibly through the research cycle while providing the necessary tools for all stakeholders to seriously commit to their moral responsibilities. In Europe, the publicly documented cases of violations of SC-based laws were mostly misconduct cases of fraud [88,89] and failure to obtain ethics approvals. As with the rest of the world, punitive sanctions for violating research integrity adopt different modalities depending on the policy's binding nature and the stringency of governance mechanisms, amongst other factors. The trend to uphold criminal law in biomedical research, while exceptional to the regulation of science itself, has been widely adopted in European SC-related policy. Indeed, a favored approach is the imposition of fines and harsh prison terms for crossing statutory boundaries. Pecuniary administrative or civil sanctions (e.g., malpractice, liability) are seldom adopted (Figure 4 Sanctions for embryo and SC research-related misconduct).

The widespread association of criminal sanctions with misconduct related to embryo and hESC research is quite notable across European policies. Criminal law constitutes an old and powerful tool which societies around the world use to send the strongest condemnatory message. At the same time, it achieves retribution, denunciation and/or deterrence. However, the use of criminal law in the biomedical research context should be used sparingly and limited to morally reprehensible behavior. Instead, other types of penalties, such as moral and professional sanctions embedded in soft law (e.g., codes of conduct, professional guidelines) could be equally powerful than criminal ones and should actively be pursued. Professional organizations have a central role in making effective the latter aided by governmental and societal support.

Country:	Offense: Embryo creation for research	(Supernumerary to IVF) embryo research	Research cloning
Austria			
Belgium			
Croatia			
Cyprus			
Czechia			
Denmark			
Estonia			
Finland			
France			
Germany			
Greece			
Italy	"Increased" from penalty for embryo research		"Increased" from penalty for embryo research
Lithuania			
Netherlands			
Portugal			
Slovenia			
Spain			
Sweden			
Switzerland	If done commercially / If done negligently		If done commercially / If done negligently
United Kingdom			

Country:	Offense: Hybrid/chimera* (*NB. certain applications)	Other sanctions for regulatory non-compliance	Embryo *in vitro* culture +14 days	Additional penalties
Austria			Embryo research not permitted	For unlicensed use of reproductive materials
Belgium	For creating "chimeras or hybrid beings"			
Croatia			Embryo research not permitted	
Cyprus				
Czechia		Noncompliance with hESC regulations / Noncompliance with embryo regulations	Embryo culture limit set at 7 days	Non-compliance at large scale carries stronger penalties
Denmark	For producing living hybrids or developing a human individual in an "alien uterus"			
Estonia				
Finland	For "human production by combining human gametes and animal genetic factors"			
France	Certain types of chimera research permitted	hPSC regulations / Embryo research regulations		
Germany		**hESC regulations** (embryo research not permitted)	Embryo research not permitted	
Greece				
Italy	"Increased" from penalty for embryo research	Embryo research not permitted	Embryo research not permitted	
Lithuania			Embryo (and hESC) research not permitted	
Netherlands	Certain applications permitted by law, subject to ethical review by Central Committee			
Portugal	For using ART techniques with the aim of creating chimeras/hybrids			
Slovenia				
Spain				
Sweden				
Switzerland	If done commercially / If done negligently	If done commercially / If done negligently	If done commercially; embryo culture limit set at 7 days. / If done negligently; embryo culture limit set at 7 days	
United Kingdom				

Figure 4. Sanctions for embryo and stem cell research-related misconduct. Pink: Unspecified penalty; Purple: Administrative penalty; Yellow: Fine, no prison; Green: Permitted following specified oversight; Blue: Maximum penalty = prison <= 3 years; Red: Maximum penalty = prison >= 3 years; Purple + yellow = Combination of fine + administrative penalty; Other combinations of colors: Different penalties for noncompliance with regulations for hESC research versus regulations governing embryo research.

Legislative review in action

Overall, European countries have several embedded mechanisms to evaluate the strength of their policy frameworks and prompt change if required. While uptake of the Guidelines is voluntary, the ISSCR aims to provoke countries to evaluate whether the results of decades-old compromises, which project pluralistic beliefs into research governance, regulate emerging technologies as intended. Reflecting the importance of iterative, flexible regulation that keeps pace with "*ill-defined and often moving targets*" [90], some European countries have adopted statutorily mandated periodic reviews to assess the implementation and effects of their laws (e.g., France [91], Germany [92] and The Netherlands [93]). An illustrative example of this is found in France, where parallel to ISSCR's policy revision process, the government conducted the mandated periodic review of its Bioethics Law [94]. As with the Guidelines, this process also concluded with significant modifications. For instance, prior approval from the Biomedicine Agency is no longer required for hESC research. Additionally, research to form gametes or embryo models from hPSC, along with certain types of chimera research, can proceed as planned under a presumption of approval, unless the Biomedicine Agency opposes the proposed project within a set period. As outlined in an impact report that accompanied scheduled Parliamentary review [95], the relaxation of requirements was due to the need to resolve regulation-induced delays which hamstrung French development in the field relative to countries like the UK, Spain, Belgium and the USA. The report shared consensus that hESCs were not "*potential persons*" and thus, hESC research was ethically distinct from research on the embryo. However, the National Consultative Ethics Committee remarked that both hESC and hiPSC can be used to produce "*ethically sensitive cells*" [96]. Thus, the law was modified to avoid litigation that would inevitably ensue if decisions on the acceptability of contentious hPSC research were left entirely to the discretion of the Biomedicine Agency.

France's legal foundations for the governance of biomedical research may facilitate adaptation as the bioethics law is entirely contained within the public health code, a feature which enable policy change when it can be justified as serving the broad and malleable goals of public health. But France pairs this feature with a tool available to legislators across EU: scheduled general parliamentary review of legislation every 5–7 years (the exact interval has varied over time) which must be preceded with public debate for "*any reform project on ethical problems and social issues raised by advances in knowledge in the fields of biology, medicine and health*" [97]. Another example is found in The Netherlands, where the Embryo Law also incorporates scheduled review, ordered by the Ministry of Health, Welfare and Sport and conducted by academic researchers, every 5 years [98]. In the most recent review, the Minister announced an intent to regulate the insertion of hiPSC into animal embryos under this law [99]. In previous years, a moratorium on the creation of embryos for research purposes morphed into a general ban, subject to societal debate. The Dutch Minister's review also stressed a need for "*broad discussion*" about the moral dilemmas arising from embryo-like structures cultured from iPSCs. French and Dutch experiences facilitating renewed public engagement with ethical dilemmas may prove instructive for other countries seeking to update legislation while balancing pluralistic moral concerns. Policy decisions informed by a broad range of stakeholders and enacted by officials who can be held democratically accountable may align scientific progress with diverse societal priorities.

While French and Dutch legislative review provisions seem to have catalyzed alignment with international norms, mechanisms for legislative evaluation do not guarantee change. However, they are still useful: for example, German legislative dormancy in the face of criticism may be interpreted as an affirmation of existing provisions. Review of German legislation by federally appointed experts has taken place continuously, and in recent years, consensus has built around a need for substantial revisions. The Stem Cell Act requires biannual evaluation by the Bundestag [100], and an associated ordinance calls for an annual activity report from the Central Commission for Stem Cell Research, a federally appointed committee which issues a non-binding opinion on every German proposal for research involving hESCs [101]. For years, the Commission's reports have called for further relaxation of the statutory cut-off date for the derivation of hESC lines allowed to be imported for research uses [102]. In addition, reports have called for other changes to keep with the spirit of the law. For instance, the Act requires that scientific research questions must have been clarified as far as possible with animal cells or experiments. However, as pointed out by the Commission, "*in the future, cells derived from hESCs can contribute to significantly reducing the number of animals currently used for medical or pharmaceutical purposes*". Proposals with this aim in view would not be eligible for approval under the act in its current iteration. In its most recent report, the Bundestag also endorsed review of the ban on the use of hESC outside of a "*research context*" and stated that the "discourse about the ethical-legal classification" of "*embryoids*" should be "*actively guided by science*" [103]. Finally, in 2014, the Conference of Health Ministers assigned the German Ethics Council, an independent council of experts [104] with evaluating current

developments in the field. A critical recommendation of the Council was to clarify and standardize the statutory definitions surrounding the human embryo across Germany's Stem Cell Act and Embryo Protection Act [105] to ensure entities like SCB-EM do not escape the reach of the law. To date, however, none of these concerns have been addressed in legislation.

The UK presents a different situation, where persistent court challenges did not impede the flexibilization of policy. For instance, in 2008, the Christian Legal Centre and Comment on Reproductive Ethics asked for a judicial review of the HFEA's decision to approve research using human–animal cytoplasmic hybrid embryos, contesting the HFEA's licensing powers and the rationality of their decisions, as they believed that such powers only covered fully human embryos, not human hybrid embryos [106]. In contrast, the HFEA argued that the term 'human embryo' was not defined by the Act and their interpretation relied on scientific expertise. The court ruled that the claimant's case to be unarguable, that the HFEA pursued appropriate scientific guidance, and that the Act allowed for revision and reinterpretation following scientific advancements. Following this, revisions to the Act continued to follow a permissive path.

Conclusion

By eschewing bright-line prohibitions and eliminating ethical distinctions based on hPSCs provenance, the ISSCR Guidelines might have moved the forum for policy debates back to the halls of national Parliaments. They have further attempted to direct them to existing systems of ethical review in which research is "*widely considered ethically acceptable*" [107]. The flexibility conferred by professional guidance (soft law) informed by discipline-specific expertise suggests this form of governance might be better suited to adapt to new ethical dilemmas posed by scientific developments. Yet, public deliberation is essential if a policy is to reflect societal values and priorities and thereby gain legitimacy.

Over the past decade, scientific organizations have repeatedly called for broad stakeholder engagement to reflect on and adapt governance strategies to address new ethical dilemmas that accompany scientific progress. True public deliberation on policy questions pertaining to stem cell research requires models for public engagement which have not yet materialized, perhaps due to lack of incentives [108]. Legislative review processes such as those adopted in France, the UK and Denmark, adapted to solicit stakeholder perspectives on the governance of related emerging technologies, may provide useful models to make technocratic governance process more accessible and reflective of public interests. Because of the absence of true commitment to inclusiveness in policy debates, we do not anticipate a change in the status quo.

Future perspective

In Europe, existing pathways to assess the suitability of policy and governance frameworks have not been widely used. As stagnant norms continue to govern a dynamic field, it is difficult to assess whether these frameworks are still fulfilling their stewardship roles and how they might evolve in the next decades. Responsible innovation is predicated on the capacity to adapt in response to changing environments. As science and society co-evolve, are extant policy frameworks meeting stakeholders' expectations as well as safeguarding important human interests? Promoting and delivering social value? Do they continue to satisfactorily reflect the socio-ethical principles that originally underpinned them? What is the weight of political, economic and other contextual factors in the adoption and implementation of policy? These are central questions to elucidate the social processes leading to, or required for, policy reform. The answers to these questions could also assist in evaluating whether governance structures are or will remain legitimate and sustainable in the future. These are all fundamental factors to support responsible research clinical translation, and we anticipate (or at least hope) that addressing these will occupy a central role in future policy and governance debates as well as their outcomes.

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Executive summary

Introduction

- In Europe (EU), the stem cell research-clinical translation continuum is characterized by a heterogeneity of governance and policy frameworks reflecting the continent's diverse socio-cultural, economic and historical contexts.

Legislative building blocks past & present

- Policy frameworks include a combination of national and international 'hard' (e.g., legislation, treaties) laws supplemented by 'soft' ones (e.g., professional guidelines, funding policies, codes of conduct) offering different tools for enforceability and governance.

Stem cell-based embryo modeling & beyond

- Recently, the International Society for Stem Cell Research (ISSCR) updated its Guidelines, adopting strict recommendations for the regulation of clinical research and translation of stem cell (SC)-based interventions and substantially reconfiguring guidance for oversight of *in vitro* SC projects.
- The possibility of yielding entities that might faithfully replicate embryonic developmental processes has prompted conceptual re-examinations, as stem cell embryo models do not fit neatly in pre-existing regulatory categories defining human embryos, gametes, or human research subjects. Because generally European national policies were initially created to govern Assisted Reproductive Technology (ART), they often contain statutory decades-old definitions of what constitutes a human embryo.
- The ISSCR Guidelines diverge from common European policy by permitting the creation of embryos for research if projects stop at "*well-defined timepoints*" and undergo appropriate degrees of ethical review.
- The Guidelines call for governments and oversight bodies to reappraise the '14-day rule' – a gold standard preventing human embryos cultured *in vitro* from developing for longer than 14 days. In Europe, this rule continues to be ubiquitous.

The gradual liberalization of EU national policy

- The Guidelines sit in stark contrast with European policy regulating research on human–animal chimeric embryos.
- A discrete trend toward liberalization continues to slowly emerge in Europe.

Challenging the status quo: the role of regulation & oversight

- European countries generally follow an ISSCR-style tiered approach to oversight, where SC research is subject to specialized or centralized ethics review depending on pre-determined criteria.
- Governance and the role of criminal law: criminal law for misconduct related to embryo and hESC research is quite notable across European policies.

Legislative review in action

- Some European countries have adopted statutorily mandated periodic reviews to assess the implementation and effects of their laws (e.g., France, Germany, The Netherlands), but they have not been widely used.

Future perspective

- As old norms continue to govern the dynamic stem cell field, it is difficult but vital to assess whether governance mechanisms are still fulfilling their stewardship roles and how policy might evolve in the next decades. However, we do not expect a significant change in the status quo.

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