

'Ceci n'est pas un embryon?' The ethics of human embryo model research

Nienke de Graeff, Lien De Proost & Megan Munsie



Increasingly advanced in vitro stem-cell-derived human embryo models raise novel ethical questions and shed a light on long-standing questions regarding research on human embryos.

With his iconic painting of a pipe, accompanied by the seemingly counterintuitive caption *Ceci n'est pas une pipe* ('This is not a pipe'), René Magritte challenged our perception of reality. This ostensibly simple yet enigmatic artwork confronts us with the notion that images can only represent a reality, not be that reality.

Just as Magritte's painting raises questions about the paradox of representation, technological advances in creating stem-cell-derived embryo models do too. This was aptly represented on the cover of *Cell* in September 2022, which showed a drawing of a mouse embryo model with the caption *Ceci n'est pas un embryon de souris* ('This is not a mouse embryo')¹.

Indeed, technological advances in human stem-cell-derived in vitro embryo models (from here on, 'embryo models') may at some point raise their own paradox: the more similar (specific types of) these models become to human embryos, the less apt they would be at circumventing the long-standing ethical questions associated with embryo research. In what follows, we therefore discuss both the novel and the familiar issues that these technological advances (re) introduce. As recent developments (Fig. 1) underline, science in this field is moving fast, so we think that it is essential to navigate these ethical questions proactively.

Novel questions raised by embryo models

What should embryo models be called? One question that embryo models raise relates to the terminology used. Many different names and acronyms have been used, including SHEEFS ('synthetic human entities with embryo-like structures'), embryo-like structures, synthetic embryos, artificial embryos (in contrast to 'natural' embryos), embryoids, stembryos, and SEMs ('stem cell-based embryo models').

These different names have stirred controversy. To start, there have been calls to steer clear of using certain names, such as the terms 'synthetic embryo', 'artificial embryo' or 'embryoid'^{2,3} as these would not accurately portray the nature and intended applications of the structures. Instead, the International Society for Stem Cell Research (ISSCR) recommends adopting terminology that conveys whether the structure models all aspects of early human embryo development (integrated embryo models) or only particular aspects (non-integrated embryo models)^{2,4}. Moreover, other researchers proposed a standardized nomenclature system that indicates cell culture specifications, cell type, species and developmental stage⁵, arguing that the current overlapping and unclear terms hinder effective communication,

complicate comprehension and add complexity in discussing how and when these models should be used.

Why are these discussions relevant? Words, like images, are a mere representation of reality, inviting questions about what words most accurately represent it and why. At the same time, language can be performative: how we name something can affect what status people attribute to it as well as ideas regarding what may, or may not, be done with these entities. The term 'artificial', for instance, may be used or interpreted in a value-laden way, which could negatively impact people's moral evaluation⁶. It should be acknowledged, however, that controlling language – especially once it has entered popular media and science communication – is challenging. We think it is crucial, amidst these linguistic debates, not to lose sight of the more fundamental questions underlying the discourse⁶.

How can and should embryo models be validated? Another pressing issue relates to how these models themselves, and the anticipated insight from their research use, could and should be validated. Generally, it would be preferable to compare models with conceptus tissues or ex vivo cultured embryos of the same species and developmental stage⁷. This means that while research on embryo models may ultimately minimize or eliminate the need for sperm–egg embryos in research, the latter will still be necessary to benchmark embryo models. However, while Magritte's painting and *Cell*'s cover image both have a clear comparator, it is not as clear what the suitable comparator would be for all embryo models. These models lack a clear 'day zero' from which to begin counting^{2,8} and need not adhere to the conventional, sequential stages of embryogenesis⁹. Moreover, comparators are not always accessible: human conceptus tissues from early pregnancy stages – when most people are not yet aware of their pregnancies – are rarely available. Additionally, comparisons with in vitro human embryos are currently constrained by the 14-day rule (see below).

Furthermore, not all functional tests that could help to validate models are permissible in humans⁷. For instance, investigating developmental potential by transferring a human embryo model to an animal or human uterus is currently, and justifiably, explicitly prohibited^{2,10}. Alternatively, while some validation may be attained by comparing non-human primate embryos and models with human embryo models^{11,12}, research on non-human primates also raises ethical issues, as well as challenges in translating findings to humans.

These constraints underline the importance of openly sharing research findings from experiments involving scarce human conceptus tissues from early pregnancy stages, along with comparisons to embryo models. Much like the historical Carnegie and Kyoto collections established in the 1920s and 1960s, which shared serial sections of human embryo development in the first eight weeks, contemporary researchers should endeavor to create a modern-day 'Carnegie collection', facilitating broad access to an extensive dataset. Sozen and colleagues have proposed a similar initiative, suggesting the need for

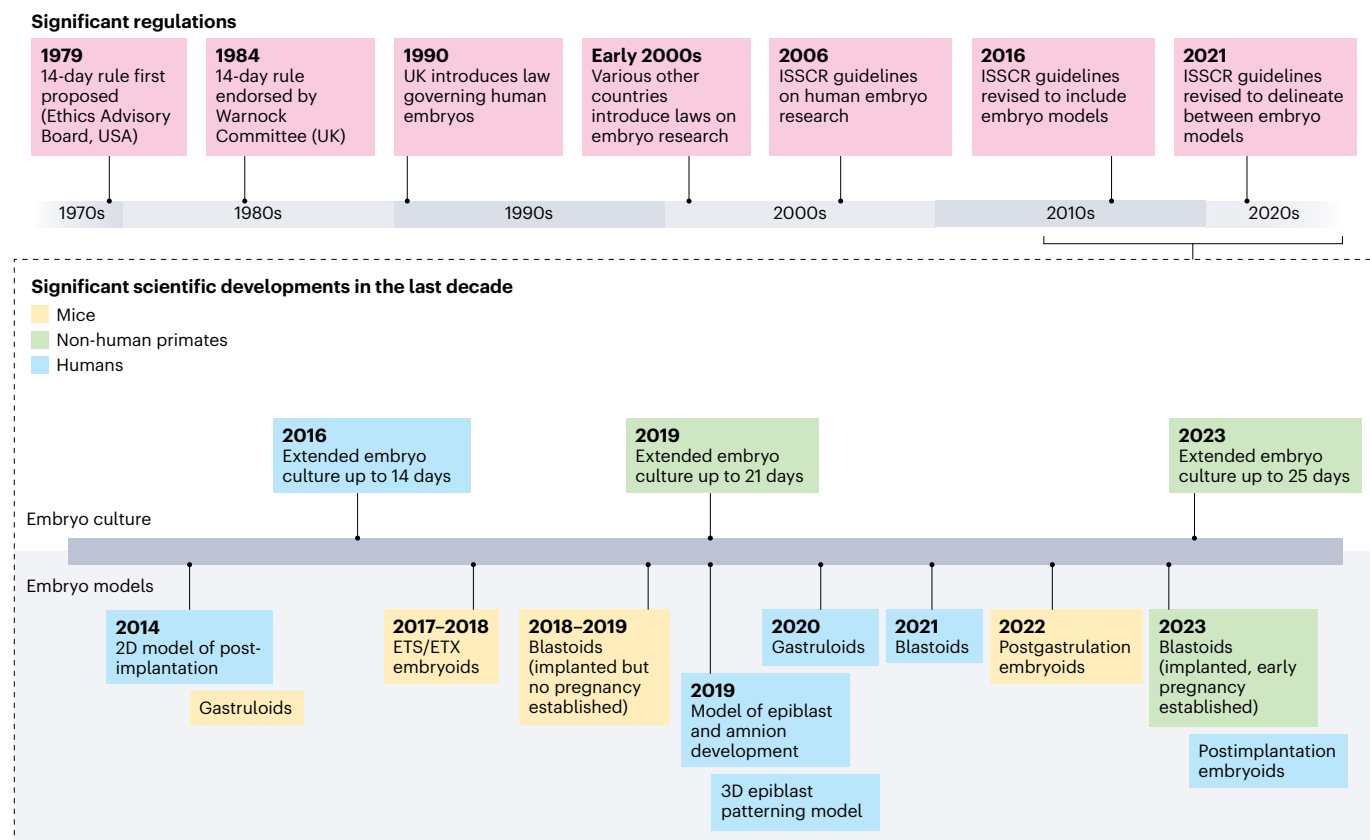


Fig. 1 | Significant regulations and scientific developments. A selection of significant regulations (above) and scientific developments related to embryo culture and embryo model research in the last decade (below). ETS, embryonic–trophoblast stem; ETX, embryonic–trophoblast–extraembryonic endoderm. Lower panel adapted from ref. 2, CC BY 4.0.

a “4D Carnegie” involving “studies of live specimens, to describe – and ultimately understand – the dynamics of human embryo development across spatial and temporal scales”¹³.

What special consideration do embryo models require? A further question is how to regulate embryo model research. Are existing guidelines for research on the differentiation of human pluripotent cells into organized structures (organoids) sufficient, and if so, to which types of models should they apply? Or do (certain) embryo models require special consideration due to the moral or biological significance of what they model or could develop into? If so, what type of oversight is appropriate, and at what stage should it apply?

Similar questions have been raised since the first report of in vitro structures mimicking the body plan of postimplantation development and with each subsequent advance (Fig. 1)^{10,11,14}. In response, the ISSCR initially proposed special guidance for structures that “might manifest organismal potential”¹⁵ and more recently argued that the degree of ethical and scientific oversight should relate to the model’s level of integration, whereby integrated models such as blastoids require full review and approval^{2,3}.

Several other critical questions also demand our attention. One pressing issue revolves around the consent of individuals who donate their cells for this type of research and whether specific consent is necessary or a broader form of consent would suffice.

Additionally, whether models are made out of induced pluripotent stem cells or embryonic stem cells may affect their legal permissibility in countries that restrict research involving human embryonic stem cells¹⁶.

Addressing these questions requires us to consider the new context that embryo models bring with them, but also necessitates a reevaluation of longstanding ethical and legal inquiries related to embryo research, some of which were initially raised decades ago.

Revisiting familiar questions regarding human embryo research

Should embryo research regulations apply, and if so, under what conditions? One question reintroduced by embryo model research pertains to the regulation of embryo research and the legal definition of an embryo. There is significant international heterogeneity in relevant policy (Fig. 2a)^{16,17}. In certain countries, such as Germany, Italy and Russia, all research involving embryos is strictly prohibited. Other nations, like Belgium, maintain permissive policies. The legal definitions of an ‘embryo’ also vary (Fig. 2b). In certain jurisdictions, such as Spain, an entity is only considered an embryo if it is formed through the fertilization of an oocyte. In countries such as Australia, the definition of a human embryo includes fertilization but also extends to creation “by other means.” Other jurisdictions include reference to the embryo’s development potential, although what is captured by this term also

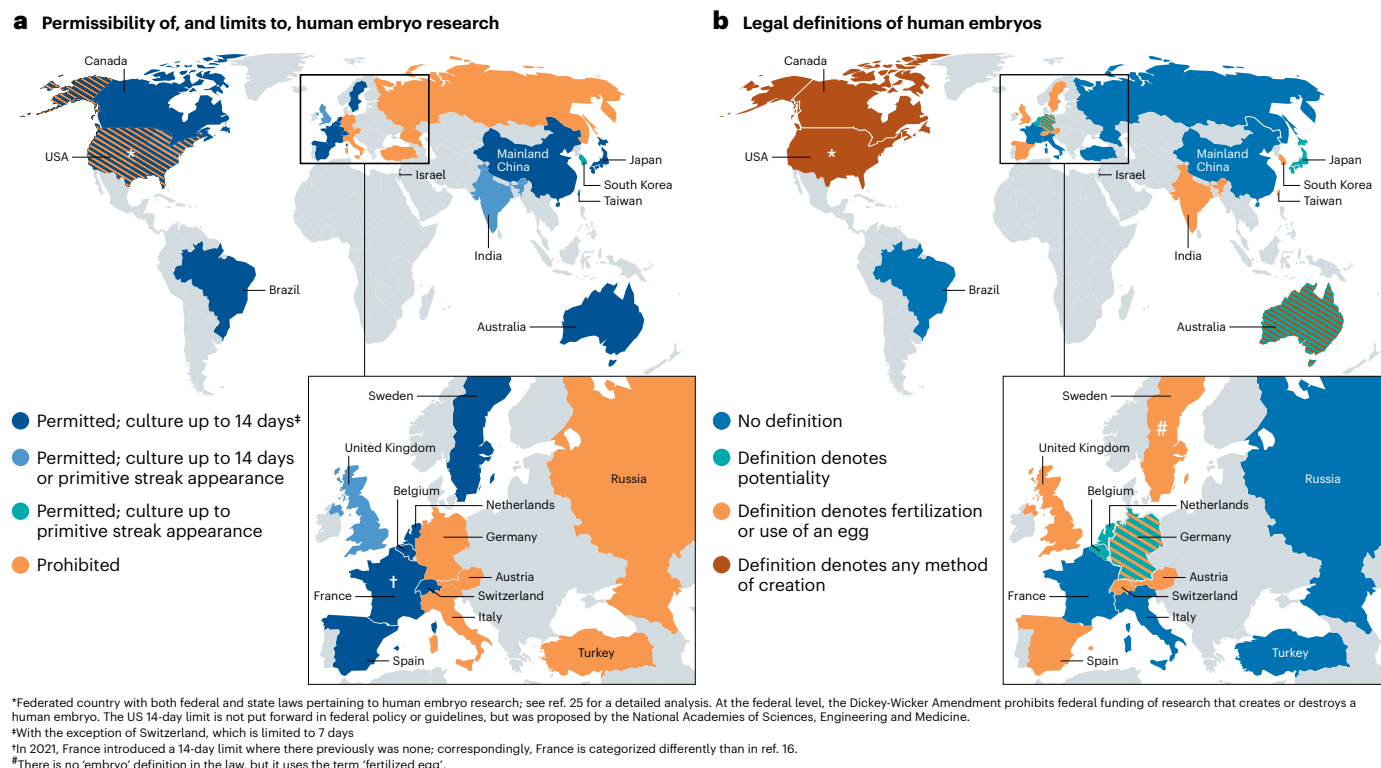


Fig. 2 | Exploring impact of existing regulations on human embryo and embryo model research in the top 22 R&D investors. a, Human embryo research policies. b, Embryo definitions. Adapted with permission from ref. 16, CC BY-NC-ND 4.0. See ref. 27 for a detailed analysis of US federal and state policies guiding embryo (model) research.

varies, adding to discussion on its ethical relevance. The Japanese law, for instance, refers to the potential to grow into an individual, whereas the Australian law refers to the potential to develop up to or beyond the stage at which the primitive streak appears. Finally, certain jurisdictions do not offer explicit definitions of embryos at all.

These varying definitions complicate determining how existing regulations and definitions may impact research involving embryo models. In countries that include fertilization in the definition of an embryo, integrated embryo models could never be considered embryos and would thus not be regulated by the same policies. In other countries such as Australia, integrated embryo models have been determined to meet the definition of a human embryo¹⁸. Contrary to what has been posited before¹⁶, this does not mean embryo model research is prohibited. Rather, it means researchers must apply for – and be granted – a license from the national regulator¹⁸. In countries where an embryo is defined on the basis of its potentiality, some have argued existing regulations might apply to (integrated) embryo models¹⁶. In contrast, others have stressed the uncertainty and complexities of determining whether embryo models have the potential to develop into human beings^{10,11}.

Ultimately, whether and how existing regulations apply to embryo models will come down to interpretation by national regulatory bodies. Where relevant, it is essential for governments to clarify whether and how existing regulations apply to (integrated) embryo models. In the Netherlands, for instance, the government has proposed to change the legal definition of an embryo to explicitly incorporate

embryo models that “can reasonably be expected” to develop the same as a sperm–egg embryo “until the point at which a primitive streak appears or could appear”^{19–21}. If this proposal is adopted, this would bring research with integrated embryo models that meet these conditions under the same regulatory framework as human embryo research. Importantly, we strongly believe the interpretation of existing regulations is best done by experts and officials within the national context who speak the local language and are able to contextualize the (definition and policies outlined in) embryo laws with other laws and regulations within the jurisdiction.

Is it morally permissible to create embryos for research? Likewise, embryo models warrant revisiting whether scientists should be allowed to create embryos for research or be restricted to the use of surplus embryos from in vitro fertilization (IVF). Currently, the creation of human (sperm–egg) embryos is prohibited in many countries. For instance, legislation in the United States prohibits the use of federal funds to create human embryos for research purposes, and the Oviedo Convention prohibits it altogether²². However, not all European countries ratified the Convention as it was regarded as too restrictive; Belgium, Sweden and the United Kingdom allow the creation of embryos for research purposes under certain conditions²².

If integrated embryo models fall under the legal definition of an embryo in particular jurisdictions, the question of whether it is permissible to create embryos for research reoccurs in this new context¹⁰. Would prohibiting the derivation of embryos for research also entail

prohibiting the creation of integrated embryo models if these met the legal definition of an embryo? And if not, what would be considered the relevant difference between embryos created by fertilization and embryos that would be created from stem cells? These new developments give us pause to reconsider the current prohibitions.

Until when should embryos be allowed to be cultured? Another critical issue pertains to the 14-day rule, which posits that embryo culture should be restricted to 14 days post-fertilization and/or until the emergence of the primitive streak (Fig. 2a). This limit was introduced in the 1980s (Fig. 1), when discussions regarding the fate of embryos remaining after IVF procedures fueled demands for more rigorous oversight²³.

While “can” does not imply “should”²³, technical advances allowing longer embryo culture (Fig. 1) and the potential insights that research beyond this limit could bring underline the relevance of reconsidering it^{8,24}. Likewise, the emergence of embryo models has also prompted calls to reevaluate the 14-day rule – as mentioned, they need not adhere to canonical embryogenesis, raise validation challenges, and are not covered by versions of the 14-day rule that only apply to products of fertilization²⁴. Furthermore, defining structures such as the primitive streak as landmarks can be subject to interpretation and may only be determined once the culture is terminated²⁵.

In their revised 2021 guidelines, the ISSCR retained the need for rigorous oversight of research involving extended in vitro culture of human embryos until the formation of the primitive streak or up to 14 days, but removed the previous explicit prohibition on extended culture and called for public discourse to reconsider this timepoint given the potential of such research to “yield beneficial knowledge that promotes human health and well-being”^{2,3}. They proposed that such research might be considered if there was broad public support, local policies and regulations were permissive, appropriate oversight approval considered the research objective necessitated such culture, and the lowest possible number of embryos were used^{2,3}.

Notably, the ISSCR does not propose an alternative limit, whether in terms of days or stages of development. While the 14-day rule is indeed incongruous in the context of embryo models, we think it is prudent to stipulate an alternative limit to create regulatory clarity, ensure proportionality and subsidiarity, and adequately protect entities that warrant such protection (including a fetus that might eventually develop from these models if they continue to advance¹⁰). Hyun and colleagues advocate for progressing in incremental, measured steps that correspond to a number of days and a Carnegie stage of development²⁶. They lay out specific conditions for each step, including subsidiarity, frequent evaluation, peer review, public dialogue, specific consent and the separation of care and research. Next to this, the creation of the contemporary ‘Carnegie collection’ could make information from such extended culture experiments accessible to all. This could decrease the need for repeated experiments and increase transparency and the sharing of research outcomes.

Conclusion

The development of stem-cell-derived human embryo models, like Magritte’s art, provokes contemplation and reflection. ‘New’ and ‘old’ ethical questions are intricately intertwined when considering such research. More pivotal than the naming of embryo models are the questions that underpin the linguistic discourse: what status should these entities be attributed, and what ethical boundaries should govern our actions with them? To navigate the validation challenges of

embryo models, prevent repeated experiments with human embryos, foster international dialogue and enable transparency in research, we think the establishment of a contemporary ‘Carnegie collection’ for embryo models from the outset is advisable. Finally, given the significant international disparities in embryo regulation, we consider it imperative for each nation to reevaluate its laws and guidelines in light of this emerging technology. Ideally, regulations should not only provide clear definitions, but also be reviewed and refined as the technology further develops, facilitating thorough discussions on the (im)possibility of novel opportunities this brings about. Discussions about these issues need to continue within the scientific community, but also beyond through ongoing dialogue with regulators and the public. Inspired by Magritte, we need to create opportunities to reflect on the merit of different embryo models, and discuss what they are or are not.

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References

- Soto, R. Cover image. *Cell* [https://www.cell.com/cell/issue/pii:S0092-8674\(21\)X0019-0](https://www.cell.com/cell/issue/pii:S0092-8674(21)X0019-0) (1 September 2022).
- Clark, A. T. et al. *Stem Cell Rep.* **16**, 1416–1424 (2021).
- ISSCR. The ISSCR statement on new research with embryo models. <https://www.isscr.org/isscr-news/isscr-statement-on-new-research-with-embryo-models> (2023).
- International Society for Stem Cell Research. *Guidelines for Stem Cell Research and Clinical Translation*. <https://www.isscr.org/guidelines> (2021).
- Matthews, K. R. W., Wagner, D. S. & Warmflash, A. *Stem Cell Rep.* **16**, 1014–1020 (2021).
- De Graeff, N., Buijsen, M. A. J. M. & Bredenoord, A. L. *On the Nature of Nature. A Study on the Use and Meaning of Naturalness in the Literature on Genetic Modification* (COGEM, 2022).
- Posfai, E., Lanner, F., Mulas, C. & Leitch, H. G. *Stem Cell Rep.* **16**, 1117–1141 (2021).
- Chan, S. *Curr. Stem Cell Rep.* **4**, 228–234 (2018).
- Aach, J., Lunshof, J., Iyer, E. & Church, G. M. *eLife* **6**, e20674 (2017).
- Rivron, N. C., Martínez Arias, A., Pera, M. F., Moris, N. & M’hamdi, H. I. *Cell* **186**, 3548–3557 (2023).
- Pera, M. F. et al. *Nat. Methods* **12**, 917–919 (2015).
- van den Brink, S. C. & van Oudenaarden, A. *Trends Cell Biol.* **31**, 747–759 (2021).
- Sozen, B., Conkar, D. & Veenfliet, J. V. *Semin. Cell Dev. Biol.* **131**, 44–57 (2022).
- Rivron, N. et al. *Nature* **564**, 183–185 (2018).
- International Society for Stem Cell Research. *Guidelines for Stem Cell Research and Clinical Translation*. <https://www.isscr.org/the-archives/#GuidelinesArchive> (2016).
- Matthews, K. R. W. & Morali, D. *Regen. Med.* **15**, 1905–1917 (2020).
- Fabbri, M., Ginoza, M., Assen, L., Jongsma, K. & Isasi, R. *Regen. Med.* **18**, 155–168 (2023).
- National Health and Medical Research Council. NHMRC statement on iBlastoids. <https://www.nhmrc.gov.au/about-us/news-centre/nhmrc-statement-iblastoids> (2023).
- Rijksoverheid. Eerste grote wijziging Embryowet sinds 2002. <https://www.rijksoverheid.nl/actueel/nieuws/2022/10/17/eerste-grote-wijziging-embryowet-sinds-2002> (2022).
- Overheid.nl. Wijziging Embryowet naar aanleiding van de derde evaluatie. <https://www.internetconsultatie.nl/wijzigingembryowet/b1> (2023).
- Overheid.nl. Concept wetsvoorstel wijziging Embryowet. <https://www.internetconsultatie.nl/wijzigingembryowet/document/11874> (2023).
- Pennings, G. et al. *Fertil. Steril.* **108**, 96–107 (2017).
- Cavaliere, G. *BMC Med. Ethics* **18**, 38 (2017).
- Hyun, I., Wilkerson, A. & Johnston, J. *Nature* **533**, 169–171 (2016).
- Hyun, I., Munsie, M., Pera, M. F., Rivron, N. C. & Rossant, J. *Stem Cell Rep.* **14**, 169–174 (2020).
- Hyun, I., Bredenoord, A. L., Briscoe, J., Klipstein, S. & Tan, T. *Science* **371**, 998–1000 (2021).
- Matthews, R. W. & Morali, D. *J. Law Biosci.* **9**, Isac014 (2022).

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Competing interests

N.d.G. and M.M. are members of the ISSCR. M.M. is also a member of the ISSCR board of directors, and was a member of the ISSCR guideline taskforces (2008, 2016, 2021). L.D.P. declares no competing interests.