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Advocating distinct regulatory paths for embryos and embryo-like structures

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ABSTRACT

Human embryo-like structures (ELSs) are novel entities emulating aspects of embryogenesis to advance understanding of early human life and enable future clinical applications. ELSs frequently fall into a regulatory gap: the laws that govern embryo research do not commonly apply, but nor are there bespoke regulatory schemes. There is international consensus that the gap must be addressed, but disagreement as to when and how this should be achieved. To date ELSs *model* embryos, mimicking aspects of embryonic development. In 2024 a UK Nuffield Council on Bioethics report recommended that these 'stem cell-based embryo models' should be regulated separately to embryos. Building on this report, this paper considers a subset of ELSs that may in future lose their model status because they replicate rather than model embryos. Distinguishing between models and replicas it considers what circumstances, in the UK and internationally, would require regulation as an embryo, the circumstances in which replicas might justifiably be regulated separately to embryos and why maintaining distinct regulatory paths for embryos and ELSs is beneficial.

KEYWORDS: embryo, embryo-like structure, regulation, research, SCBEM, stem cell, stem cell-based embryo model

† This paper supports and expands upon some of the conclusions reached by the working group in the Nuffield Council on Bioethics (NCOB) project on Stem Cell Based Embryo Models, https://www.nuffieldbioethics.org/project/stem-cell-based-embryo-models/ (accessed Jan. 1, 2025) as well as making new arguments. The author chaired the NCOB working group and co-drafted the report. She received an honorarium for four of the meetings and travel expenses for additional meetings. To the extent that this paper extends beyond or differs from the NCOB report, this paper does not represent the views of either the NCOB or the working group. The author is grateful to David Lawrence (Durham University) and Ranveig Svenning-Berg (NCOB) for comments on a previous draft and to the two anonymous peer reviewers for their helpful suggestions.

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I. INTRODUCTION

An extraordinary feature of the human body is that it is derived from a single cell. The cell undergoes divisions to build the embryonic and extraembryonic (supporting) tissues. Stem cells are undifferentiated cells that can give rise to indefinitely more cells of the same type and can differentiate into other cell types. Pluripotent stem cells can develop into the three basic body layers: ectoderm, endoderm and mesoderm, and even into primordial germ (reproductive) cells. Scientists are harnessing the capacities of pluripotent stem cells to mimic aspects of human development *in vitro*.

One such application is clusters of pluripotent stem cells that, when cultured in a laboratory, form 3D self-renewing and self-organizing structures emulating aspects of embryonic development to different degrees. As I explore below, these structures have been given various names, but a consensus has recently emerged around the term 'stem cell-based embryo model' (or 'embryo model' for short). Conducted in an increasing number of countries and labs, they were first developed in mice in 2018 and subsequently in humans from 2021 and are, as such, novel and evolving.[1] Research has already yielded valuable insights into embryogenesis, particularly in aspects that are otherwise difficult to study through conventional methods. These findings are advancing our understanding of the mechanisms underlying pregnancy loss, with the potential to inform interventions. Looking ahead, research holds promise for a range of clinical and practical applications. For instance, it could lead to improvements of IVF or serve as a tool for testing medicinal products used in pregnancy to enhance safety.[2]

Focusing on the UK but drawing lessons for international regulation I will assert that they currently model embryos, mimicking aspects of embryonic development. Imitation involves the creation of an artificial likeness—an entity that resembles the original but does not constitute an exact duplicate. As such the term 'stem cell-based embryo model' accurately describes current entities. I consider the future potential for some research to deliberately or unintentionally *replicate* embryos more closely. I argue that an entity that constitutes a close reproduction of an embryo would no longer qualify as a model of the embryo. I will consider the potential for anticipatory regulation to help maintain model status but argue that, because the point at which replication occurs is difficult to predict and define, regulation should prepare for the possibility that some research could eventually cross the boundary into replication. I challenge the assumption that replication inevitably requires that the entity is regulated as an embryo. I use the umbrella term 'embryo like structure' (ELS) to include embryo models and also embryo replicas where they can be distinguished from embryos for regulatory purposes. I will set out when that is the case and why it is valuable for states to form distinct regulatory paths for ELSs and embryos.

1 See for example Xiaodong Liu, Jia Ping Tan, Jan Schroder et al., *Modelling Human Blastocysts by Reprogramming Fibroblasts into Iblastoids*, 591 Nature 627 (2021); Leqian Yu, Yulei Wei, Jielei Duan et al., *Blastocyst-like Structures Generated from Human Pluripotent Stem Cells*, 591 Nature 620 (2021).

2 On the importance of this goal see University of Birmingham, Healthy Mum, Healthy Baby, Healthy Future: the Case for UK Leadership in the Development of Safe, Effective and Accessible Medicines for Use in Pregnancy (2022), https://www.birminghamhealthpartners.co.uk/wp-content/uploads/2022/05/Final-Healthy-Mum-Healthy-Baby-Healthy-Future-Report-AW_Accessible-PDF-REDUCED-FILE-SIZE.pdf (accessed Jan. 1, 2025).

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II. THE REGULATORY GAP

'Embryo model' is an umbrella term describing a range of model types. Some partial models mimic interactions between particular tissue or cell types of the embryo. For example, recent research has created trunk-like structures to model and better understand the co-development of the neural tube (which becomes the spinal cord) and somites (the trunk muscle and bone), which form at the same time in the embryo at around Day 28 after fertilization.[3] Other, more complete embryo models try to capture a particular embryonic stage as closely as possible. Researchers have created models of blastocysts which form in the first week after fertilization, to gain insights on human implantation in the womb.[4] This is a process where a significant number of pregnancies fail, but which is very challenging to research *in vivo*.[5] To date, these embryo models cease to develop and naturally deteriorate after a few days.[6]

It has so far proved difficult for states to scientifically or legally define embryo models. The science is developing and the categories, uses and ambits of the research are fluid. Instead, they are generally classified in relation to their purposes and how far outcomes emulate the embryo, which is also subject to varied and sometimes opaque definitions. This, as we shall see, makes for a highly complex regulatory environment.

At present in the UK and some other countries, embryo models fall into a regulatory gap: They are not generally considered to be embryos, so they fall outside any regulations that apply to embryo research, and there is no dedicated scheme of regulation to govern them.[7] Whilst most states that allow ELS research are confident that there is currently a clear line between embryo models and embryos, as the science progresses there is an increasing prospect of the line blurring. Media reports speculate that some 'human embryo models are getting more realistic'[8] raising public fears that research could cross ethical lines. The regulatory gap is therefore becoming an increasingly urgent concern,

3 Komal Makwana, Louise Tilly, Probir Chakravarty et al., *Modelling Co-Development Between Somites and Neural Tube with Human Trunk-like Structures*, bioRxiv (2024), preprint available from https://www.biorxiv.org/content/10.1101/2024.12.16.628661v1 (accessed Jan. 1, 2025).

4 See for example Harunobu Kagawa, Alok Javali, Heidar Heidari Khoei et al., *Human Blastoids Model Blastocyst Development and Implantation* 601 Nature 600 (2022).

5 N. S. Macklon, J. P. M. Geraedts, B. C. J. M. Fauser, *Conception to Ongoing Pregnancy: The 'Black Box' of Early Pregnancy Loss* 8(4) Human Reproduction Update 333 (2002).

6 Nicolas Rivron and Jianping Fu, *SnapShot: Embryo Models*, 16 Stem Cell Reports May 11, 2021.

7 The stem cells from which ELSs are derived are subject to regulation. Induced pluripotent stem cells are governed by the Human Tissue Act 2004 and Human Tissue (Scotland) Act 2006 until the point when a stem cell line is established. Embryonic stem cells are governed by the Human Fertilisation and Embryology Act 1990 (as amended). Embryonic stem cell lines must be banked at the UK Stem Cell Bank and approvals for research are overseen by the UK Stem Cell Bank Steering Committee. See Nuffield Council on Bioethics, Human Stem Cell-Based Embryo Models: A Review of Ethical and Governance Questions (27 November 2024), https://www.nuffieldbioethics.org/publication/human-stem-cell-based-embryo-models-a-review-of-ethical-and-governance-questions/ (accessed Jan. 1, 2025) at 48.

8 See Smitri Mallapaty, *Human Embryo Models are Getting More Realistic—Raising Ethical Questions* Nature, 11 September, 2024, https://www.nature.com/articles/d41586-024-02915-3 (accessed Jan. 1, 2025).

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both in the UK[9] and other countries.[10] Regulatory uncertainty threatens to inhibit research that has strong potential to benefit society. It may also constrain investment in the research infrastructure, risk unethical practices and damage public confidence. Agreeing an appropriate regulatory response, however, is complicated by uncertainties and disagreement as to the appropriate classification of both embryo models and the embryos they model.

In relation to the classification of embryos, as I explore below, there is wide international variation. This means that the point at which an ELS could fit within the definition of the embryo will vary geographically. In relation to the classification of embryo models, their novelty and potential for further development render definitions subject to change. The International Society for Stem Cell Research (ISSCR) issued guidance in 2021 distinguishing between integrated and non-integrated models and is at the time of writing debating potential revisions.[11] Integrated models contain all the supporting tissues needed for embryonic growth including both embryonic and extra-embryonic compartments. This gives them potential for onward development, should technical barriers be overcome. Non-integrated models are less 'complete', lacking the extra-embryonic compartments and with them the capability for onward development. The ISSCR currently recommends higher levels of oversight for integrated models. However, because embryo models exist on a spectrum, it is not always clear which category is most appropriate. Moreover, the categorization can change within a study because modular embryo models can be adapted to become more complete.[12]

Several attempts have been made to set out governance principles for embryo model research.[13] In the UK a Code of Practice on Stem Cell-Based Embryo Models (UK SCBEM Code of Practice) was issued by Cambridge Reproduction and the Progress Educational Trust in July 2024.[14] The Code does not adopt the distinction between integrated and non-integrated models, but does support the ISSCR recommendation that all embryo models should be subjected to ethical approval and that models are only

9 NCOB report *supra* note 7; Swedish National Council on Medical Ethics, *Letter to the Ministry of Health And Social Affairs and Ministry of Education and Research, Embryos and Embryo Models—The Need for an Updated Regulatory Framework for Research on Early Human Development* Reg. No. Komm2024/00132/S 1985:A, May 4, 2024, https://smer.se/wp-content/uploads/2024/05/smer-letter-on-human-embryo-models-and-human-embryo-reserarch.pdf (accessed Jan. 1, 2025); Health Council of the Netherlands, The 14-Day Rule in The Dutch Embryo Act, No 2023/16e, The Hague, (October 31, 2023); Yaolin Peng, Kianwei Lv, Zhenyu Xiao et al., *A Framework for the Responsible Reform of the 14-Day Rule in Human Embryo Research,* 13(8) Protein Cell 552 (2022) (on the need for reform in China).

10 See for example Insoo Hyun, Megan Munsie, Martin F. Pera et al., *Toward Guidelines for Research on Human Embryo Models Formed from Stem Cells,*14(2) Stem Cell Reports P169 (2020); Paula Nicolas, Fred Etoc, Ali H. Brivanlou, *The Ethics of Human-Embryoids Model: A Call for Consistency,* 99(4) J. Mol. Med. (Berl) 569 (2021).

11 International Society for Stem Cell Research, ISSCR Guidelines for Stem Cell Research And Clinical Translation, (2021) https://www.isscr.org/guidelines (accessed Jan. 1, 2025), at 2.2.

12 NCOB report, *supra* note 7, at 20.

13 International examples include the ISSCR Guidelines (2021) *supra* note 11; HYBRIDA, D5.1: Operational Guidelines Regarding Organoids and Organoid-Related Technologies (2024) at https://hybrida-project.eu/wp-content/uploads/2024/12/HYBRIDA_D5.2-Operational-guidelines_Final-Interactive-Version.pdf (accessed Jan. 1, 2025).

14 Cambridge Reproduction and Progress Educational Trust, Code of Practice for the Generation and Use of Human Stem Cell-Based Embryo Models (2024), https://www.repro.cam.ac.uk/scbemcode (accessed Jan. 1, 2025).

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as complex and developed in culture for as long as is justified to achieve a valid research objective, as demonstrated to the satisfaction of an oversight committee.[15]

Focusing on the longer term, in November 2024 the UK Nuffield Council on Bioethics issued a report (the NCOB report) proposing clarification of embryo models' legal status and making a set of regulatory recommendations.[16] I chaired the working group[17] and co-drafted the report. It recommended legislation to distinguish embryo models from embryos and to provide reassurance that ethical 'red lines' such as transferring an embryo model into a human or other animal, or developing models that can feel pain, are not crossed. It proposed a phased approach to formal regulation starting with the 'soft law' voluntary UK SCBEM Code, building through a process of stakeholder engagement and learning to formal regulation by existing regulatory bodies under a 'regulatory sandbox',[18] and potentially thereafter to an independent statutory advisory Committee on Stem Cell-Based Research which could oversee ELSs, alongside other emerging stem-cell based applications such as organoids and *in vitro* gametogenesis.[19] The proposals recommend that embryo models are proactively regulated separately to embryos, whilst ensuring consistent protection of morally relevant characteristics across the regulatory regimes. This would encourage responsible investment and stability, and guard against adverse outcomes. My focus in this paper is confined to the legal status of ELSs and the impact this will have on their regulation. The NCOB report details the form regulation should take and I do not repeat that here. Instead, I extend beyond the focus of the NCOB report to set out a new distinction between models and replicas, give novel justifications for separate regulation of ELSs and embryos in the UK, and identify the circumstances in which other states might justify a similar approach.

III. THREE ARGUMENTS

Considering the potential for ELS research to benefit society and its technical, classificatory and ethical complexities, I advance three principal arguments. Firstly, and relatively uncontroversially, I argue that the term 'model' is currently applicable and that embryos and embryo models can justifiably be considered distinct legal entities. As embryo model science develops, the visual and structural similarities of some embryo models to embryos is likely to increase, leading to conceptual challenges of their designation as models. My second argument rests on a distinction between models, replicas and embryos. Though the understanding of these terms can differ across scientific, legal and public discourses,[20] I seek to justify distinctions between them to improve conceptual clarity and guide their regulation. I consider how to determine the thresholds at which these distinctions can be made, and the regulatory implications that should follow. If ELSs replicate rather than model embryos, they should no longer be referred to as 'embryo *models*', but I argue that the regulatory implications that

15 See also Hybrida Operational Guidelines, *supra* note 13.

16 NCOB report, *supra* note 7.

17 NCOB, Stem Cell-Based Embryo Models: Working Group, https://www.nuffieldbioethics.org/project/stem-cell-based-embryo-models/stem-cell-based-embryo-models-working-group/ (accessed Jan. 1, 2025).

18 See NCOB report, *supra* note 7, at 12.

19 NCOB report, *id*. at 84.

20 Thanks to David Lawrence for this point.

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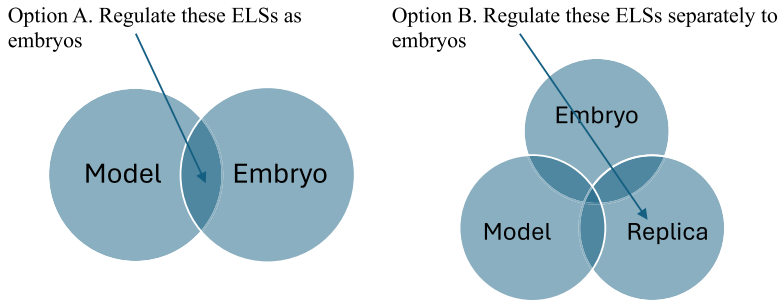

Figure 1. Two options for regulating ELSs if in future they closely emulate the embryo

flow from their reclassification are dependent on external values, including the legal definition of embryo in the particular jurisdiction. My second argument is therefore that models and replicas are normatively different, but replication does not inevitably make the replica identical to the embryo or necessarily require that it is regulated *as* an embryo, as represented in Option B in Figure 1.

Without legislative intervention to give ELSs a distinct legal status from the embryo, Option A in Figure 1 is the likely way forward in several countries. This is true in the UK where, as we shall see, the definition of an embryo is sufficiently broad to encompass certain ELSs, subject to a regulatory, judicial or secondary legislative decision. The UK Human Fertilisation and Embryology Authority (HFEA) regulates embryo research and fertility treatment, governed by the Human Fertilisation and Embryology Act 1990 (as amended). Notably, the Act does not differentiate between categories of embryos, meaning that classifying certain ELSs as embryos would necessitate the full application of the embryo licensing structure and research restrictions. Emily Jackson has provided an insightful analysis of the principles that might guide such a regulatory shift in the UK context if this option is taken.[21]

I go on to make a case for anticipatory regulation of ELSs. As such, my third argument is that regulation of embryos and ELSs as separate entities is not only feasible in certain circumstances, but optimal. Provided like entities are subjected to the consistent application of regulatory principles (which I return to below), targeted regulatory frameworks that account for specific features of production and use enable regulation to address unique ethical, practical, and societal challenges associated with each entity. As such, where two like entities present different challenges, as I will suggest they do here, it is optimal to recognize those differences in bespoke regulation.

In the next section I start by supporting the current terminology which designates the entities 'models'. By reference to both semantics and legal principles governing the definitions of embryo, I then consider the point at which that could change for some ELSs if the science continues to advance. Finally, I analyze the regulatory options, advocating a separate and anticipatory regulatory path for ELSs.

21 Emily Jackson, *Regulating Embryo Models in the UK*, 11(2) Journal of Law and the Biosciences, lsae016 (2024), https://doi.org/10.1093/jlb/lsae016.

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IV. DISTINGUISHING MODELS FROM REPLICAS

Before I examine the accuracy of its current classification as a model, it is important to note two things. First, the nomenclature is not yet settled. Scientists sometimes avoid umbrella terms altogether and refer instead to the stage of embryonic development being modelled: such as 'blastoids' modelling blastocysts and 'gastruloids' modelling gastrulas. This is effective for now as embryo models currently 'only mimic a short developmental time window of typically a few days'.[22] Alternative group categorizations include *inter alia* 'ELSs',[23] 'artificial embryos' and 'embryoids'.[24] The terminology is much debated and the NCOB report supports the term 'stem cell-based embryo model'[25] because of growing consensus around its use in influential international and national documents and guidelines.[26] Stem cell-based embryo model is a long name which, even in acronym form (SCBEM), is difficult to pronounce, but it does clearly refer to the entity's origins (stem cells), what it mimics (embryos) and its current purpose (to model). The second point to note is that designation as a model requires some fidelity to embryos. As Alfonso Martinez Arias and others have pointed out, models that aim to produce general principles of development require commitment to efficiency, reproducibility and robustness.[27]

The designation 'model' captures both intention and outcome. George E.P. Box is widely attributed to having said that: 'All models are wrong, but some are useful'.[28] His point was that statistical models always fall short of the complexities of reality but can nonetheless reveal important information. The aphorism has been applied to a wide range of scientific models used to make predictions of what will happen in research if the hypothesis is true. Scientific models are designed to study an existing or hypothetical entity for research or educational purposes. As such they often simplify details that are not pertinent to its functionality. Their aim is to understand and explore the entity they are modelling.

There is a broad, though not unanimous, consensus that the current classification of embryo models as separate entities to embryos accurately reflects current research intention and outcomes. The ISSCR describes the intention of researchers:

> Embryo models ... mimic the developmental processes that occur in early human embryos. Use of these models allows experimental modeling of the early stages of

22 See Rivron and Fu, *supra* note 6.

23 Writing Group of the Ethics Committee, Guido Pennings, Wybo Dondorp, Mina Popovic et al. *Ethical Considerations on the Moral Status of the Embryo and Embryo-Like Structures* 39(11) Human Reproduction 2387 (2024).

24 See for example the Agence De La Biomédicine, Opinion of the Conseil D'orientation: Stem Cell-Based Embryo Models (September 21, 2023) which uses the term 'embryoid' in the body of the report, but the equivalent 'SCBEM' in the title.

25 NCOB report, *supra* note 7, at 22.

26 See for example ISSCR Guidelines (2021), *supra* note 11; UK Parliament Research Briefing, Human Stem Cell-Based Embryo Models (2024), https://post.parliament.uk/research-briefings/post-pn-0716/ (accessed Jan. 1, 2025); UK SCBEM Code of Practice (2024), *supra* note 14.

27 Alfonso Martinez Arias, Nicolas Rivron, Naomi Moris et al, *Criteria for the Standardization of Stem-Cell-Based Embryo Models* 26 Nature Cell Biology 1625–1628 (2024).

28 More accurately: George E. P. Box and N. R. Draper, Empirical Model-Building and Response Surfaces, Wiley-Blackwell (1986), at 74: 'Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful.'

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> embryonic development that occur in the first few weeks of pregnancy. They can facilitate understanding of early pregnancy loss and placental failure, and help researchers gain basic knowledge of the early developmental origins of congenital defects in the heart, nervous system, and other organs.[29]

The emphasis is on 'mimicking' to 'gain basic knowledge'. A focus on the outcomes of current research also suggests that classification as a model is appropriate. As an emerging technology still in its infancy, embryo models are not yet capable of mimicking all stages of early embryonic development. Current efficiency is often low, anomalies are sometimes observed, including the appearance of cells that should not be present, and these models have not demonstrated the capacity for onward development.[30] This is not to suggest that ELS research is not both remarkable and valuable, but rather that the imperfect imitation aligns with George E.P. Box's concept of models being 'wrong'. This suggests that conceptual integrity of the term embryo model can be preserved if the entity imitates rather than replicates an embryo.[31]

This distinction does not preclude the regulation of models prior to them reaching the point of replication: Indeed, one of the recommendations of the NCOB report is that ELSs undergo anticipatory regulation.[32] One of the benefits of anticipatory regulation is that both intention and outcomes can be controlled to some extent. Regulators might seek to influence researcher intention to maintain the integrity of the model classification through a range of measures. For example, the ISSCR guidelines:

> recommend that research with integrated embryo models can only proceed with a compelling scientific rationale and after careful review and approval by a specialized scientific and ethical oversight process. Integrated embryo models should also be maintained in culture for the minimum time necessary to achieve the scientific objective.[33]

Similarly, the European Society of Human Reproduction and Embryology (ESHRE) ethics committee considers that more complex models have a higher moral status and should not be used if an entity of a lower moral status can achieve the research goals.[34] It suggests that integrated models are of most relevance to explore scalability (producing embryo models in large quantities), standardization to compare multiple genetically identical embryo models, and customizability, to model specific genetic conditions. As such, regulatory approvals might be more rigorous the more complex the embryo

29 See ISSCR, The ISSCR Statement on New Research With Embryo Models (June 26, 2023), https://www.isscr.org/isscr-news/isscr-statement-on-new-research-with-embryo-models (accessed Jan. 1, 2025).

30 See for example discussion in Bernardo Oldak, Emilie Wildschutz, Vladyslav Bondarenko *et al., Complete Human Day 14 Post-implantation Embryo Models from Naive ES cells,* 622 Nature 562 (2023).

31 Oxford English Dictionary: 'To do or try to do after the manner of to follow the example of; to copy in action.' https://www.oed.com/ (accessed Jan. 1, 2025).

32 NCOB report, *supra* note 7, at 64.

33 ISSCR (2023) *supra* note 29. And see Erica C. Jonlin, Misao Fujita, Rosario Isasi et al., *What does "Appropriate Scientific Justification" Mean for the Review of Human Pluripotent Stem Cell, Embryo, and Related Research?*, Stem Cell Reports, https://doi.org/10.1016/j.stemcr.2025.102479 (accessed Apr. 27, 2025).

34 Writing Group of the ESHRE Ethics Committee, Guido Pennings, Wybo Dondorp, Mina Popovic et al. *Ethical Considerations on the Moral Status of the Embryo and Embryo-Like Structures* 39(11) Human Reproduction 2387 (2024), at 2389.

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model, so that research which has objectives that seek to replicate rather than model the embryo will not be given the necessary approval.[35]

This is not the end of the matter, however, because it is possible to produce a replica even if the intention is to imitate. For example, if an ex-ante objective is to see how long an embryo model can be cultured to test the capacities of the culture or the reasons for cell death, then what starts as a *model* objective could one day result in an ex-post *replica* if, as Box would have it, the result is not 'wrong'. After all, a valid scientific aim in embryo model research is to produce accurate and useful models, and a subset of the research focuses on enhancing similarity with the complete embryo.

Regulation endeavoring to maintain the integrity of the model classification can also seek to control outcomes, by placing limits on what can be done. There is extensive recognition that ELSs should never be transferred to the reproductive tract of a human or non-human animal,[36] and that limits should be placed on culture time.[37] The ISSCR seeks to control outcome as well as intention, and by doing so denies that any embryo model can be considered an embryo. In its 2023 statement it said:

> While these models can replicate aspects of the early-stage development of human embryos, they cannot and will not develop to the equivalent of postnatal stage humans. Further, the ISSCR Guidelines prohibit the transfer of any embryo model to the uterus of a human or an animal.[38]

However, states may consider a precautionary approach is required to guard against the possibility of unintended replication. Additionally, at some future point, and depending on what restrictions are placed on ELSs in future, a process of ethical approval might consider some forms of replication to be justified by the promise of potential public benefit.

The terminology needs to be accurate and not mislead public audiences.[39] As such, it may prove necessary to revisit the term 'embryo model', if 'model' is no longer an accurate descriptor. It is common in emerging technologies for terminology to gain precision, as we have seen with the once broad designation of 'stem cells' to describe what are now understood to take several forms, such as pluripotent, totipotent, induced pluripotent et cetera. That said, it is also valuable to settle on terminology, particularly if, as I will recommend, the definition is to be set out in legislation. I do not engage further on the optimal nomenclature, which is considered in more detail in the NCOB report.[40]

35 See recommendations for oversight and approval in the ISSCR Guidelines (2021), *supra* note 11, at 2.2 and the UK SCBEM Code Of Practice (2024), *supra* note 14, at 5.1.

36 NCOB report, *supra* note 7, at 76; ISSCR Guidelines (2021), *id.* at 2.2; UK SCBEM Code of Practice (2024), *id.* at 5.1.

37 NCOB report, *id.* at 66; UK SCBEM Code of Practice (2024), *id.* at 5.1.

38 ISSCR (2023) *supra,* note 28.

39 See Hopkins Van Mil, Addressing the Governance Gap: A Public Dialogue on the Governance of Research Involving Stem Cell-Based Embryo Models, (2024) https://sciencewise.org.uk/wpcontent/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf, 7.3 (accessed Jan. 1, 2025).

40 On which see NCOB report, *supra* note 7, at 19–21 and 74–75.

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V. DISTINGUISHING REPLICAS FROM EMBRYOS

So far, I have argued that modelling is different to replicating, which, in a systemic manner, reproduces something closely or exactly.[41] In this section I seek to show that evidence that an ELS is replicating rather than modelling the embryo does not inevitably render it an embryo. In some situations, there will be discretion as to whether a replica should be regulated as an embryo. Where so, states could choose to regulate ELSs—both models and replicas—separately to embryos. Later, I will make the case for this approach. For now, my focus is on the nature and extent of the discretion.

A replica is not necessarily equivalent to the entity it replicates. A car may look like a Le Mans Ferrari racer, but if it is a kit car with a Mazda MX-5 engine this will be reflected in both its value and function. A synthetic diamond has the same physical and chemical properties as a natural diamond. It is equally strong and beautiful. Only by breaking it in half would it become apparent that the layers formed over millions of years in a natural diamond are not present in the manufactured one. By reason of this it is less desirable and less valuable. For ELSs too, the fact that the researcher intends to replicate rather than model embryos, or that the outcome could reasonably result in replicas, does not necessarily render it equivalent to the embryo.

Where an ELS does or might reasonably replicate an embryo, the regulatory implications are dependent on external values. These values might be legal, public, scientific, economic, or moral, and their selection depends on the specific objectives and priorities at stake. Legal considerations emphasize the need for consistency, predictability and equitable application; public values may prioritize trust, transparency, and fairness; economic values highlight efficiency, resource allocation, and the incentivization of desired behaviors; moral values bring questions of ethical responsibility, rights, and public interests into the decision-making process; and scientific values focus on precision, evidence-based distinctions, and technological capacities. In any given context, the interplay of these values shapes both the definition of categories and the principles for their application. All are relevant to ELSs, but given the pace of scientific development, the moral issues surrounding research on the embryo, and its complex and varied legal definitions, three values—moral, scientific and legal—deserve elaboration.

Moral theory might give us an answer to the question of when a replica is morally equivalent to the entity it replicates, but that answer will differ according to the moral perspective of the decision-maker. A libertarian might argue that an ELS can be distinguished from an embryo based on its different origins and the intentions of scientists. A utilitarian might claim that until its potential to generate scientific benefit for society is outweighed by the risks to humankind associated with its development, it should be considered a separate entity to the heavily regulated embryo. On the other hand, those who consider that human life has inherent value might consider that embryo status is achieved much earlier. This could flow from the religious belief in the sanctity of human life and man created in God's image or from the idea that the preservation of life is a foundational principle of natural law. The Universal Declaration of Human Rights recognizes 'the dignity and worth of the human person'.[42] Whilst there may

41 Oxford English Dictionary: 'To make a replica of (an object, picture, design etc); to duplicate, copy exactly.' https://www.oed.com/ (accessed Jan. 1, 2025).

42 UN General Assembly, Resolution 217a (iii), Universal Declaration of Human Rights, A/RES/217(III) (December 10, 1948), preamble.

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come a point where the intention of researchers and similarity to embryos would lead to wide agreement that the entity should be considered an embryo, this point would come too late from some moral perspectives. This factor is relevant to the dividing line between replicas and embryos, just as it is between embryos and persons. The state of Alabama, USA, for example, recently recognized the right to life of frozen 'children' in their 'cryogenic nursery' when a clinic allowed frozen embryos to perish.[43]

Nicolas Rivron and others have proposed tipping points by which we might scientifically recognize equivalence between ELSs and embryos as assessed by a 'Turing test'.[44] They recognize that the Turing test, named after Alan Turing's thought experiment that would identify the point where a machine could show human-like intelligence, could not be performed directly, because (as we have seen) international guidance bans the implantation of an embryo in a human or animal reproductive tract. They suggest two indirect tests: one looks for scientific evidence that the ELS mimics the embryo faithfully without aberration, the other looks for the potential of non-human ELSs to form live and fertile animals. The model is helpful but recognizing when the tipping point occurs—or even when it is imminent—remains challenging. At present, there is no effective system for tracking and monitoring such developments. While the UK SCBEM Code of Practice proposes the creation of a UK register to enhance transparency,[45] other countries have not yet made similar proposals and, in any event, progress in the field may not occur incrementally. Furthermore, advancements observed in non-human animal research—such as a pregnancy initiated and sustained in a non-human primate—may not reliably signal human applications or imminent breakthroughs.[46] Additionally, to be fully effective it would require agreement as to the legal definition of embryo, which forms another relevant external value and to which we now turn.

The legal definition of the entity being mimicked—the embryo—is varied and variable. In the words of Margaret Brazier, 'Each national jurisdiction has sought to fashion a scheme of regulation acceptable to its own culture and community'.[47] This will impact on whether an ELS must, for the sake of legal consistency and coherence, be regulated as an embryo, or whether there is potential to regulate it separately.

A broad definition of embryo in one country may encompass ELSs that in another country would fall outside their narrower definition. At its broadest, any human organism derived from stem cells that has commenced a process of development would constitute an embryo. In the European Union there is recognition from the Court of Justice of the European Union (CJEU) that this definition would be considered too wide, at least in the context of intellectual property law.[48] Narrower definitions may implicitly make clear that no ELSs currently fall within the definition and give indications of the features or capacities that would signal a change. Or, as in Australia

43 LePage v. Center for Reproductive Medicine SC02022–0151 (S Ct Alabama, 2024).

44 Nicolas C. Rivron, Alfonso Martinez Arias, Martin F Pera, et al., *An Ethical Framework for Human Embryology with Embryo Models,* 187(17) Cell 3548 (2023).

45 UK SCBEM Code of Practice (2024), *supra* note 14, at 4 and Appendix 3.

46 A point made by Søren Holm during the HYBRIDA Project final conference, held on May 15, 2024, https://hybrida-project.eu/ (accessed Jan. 1, 2025).

47 Margaret Brazier, *Regulating the Reproduction Business* 7 Med. Law. Rev. 166 (1999), 193.

48 Brüstle v. Greenpeace, Case C-34/10 [2011] ECR I-9821.

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(discussed below), a specific legal definition of the embryo that refers to features that are common to embryos and ELSs could bring those ELSs within the definition of embryo that a broader definition might not. Furthermore, the law is not static: as ELS research and other related technologies become more advanced, some states may seek to change their definitions of embryo to encompass or exclude some or all ELSs. To explore this complex situation, it is useful to briefly examine a selection of international definitions before contrasting the UK's position.

First though, as it may come as a surprise to some that there is not a universal definition of the embryo, it is pertinent to briefly address why. One reason is the scientific complexity of agreeing points in a developmental continuum that denote the start and end of embryo status. Additionally, it is possible that some of the definitional variations are accidental: that minor differences in drafting or revisions to the definition in light of new technological advances such as somatic cell nuclear replacement have an unintended impact when further unanticipated technological advances occur. Perhaps the most impactful factor, however, is the differing perspectives on the moral status of the embryo and fetus, which has resulted in variations across regions and cultures on the ethical acceptability of embryo research which is sometimes reflected in the definition of the embryo. As Margaret Brazier has said:

> Embryos as laboratory artefacts . . . remains an unacceptable resolution of the debate or basis for control of research. Embryos as human beings with independent moral claims on society and the law is (alas) equally unrepresentative of either public judgement or public sentiment.[49]

Some countries ban research that will result in embryo destruction, some allow research on embryos that are surplus to IVF requirements, whilst others such as the UK also allow the creation of embryos for research purposes.[50] The Warnock report in 1984 took a pragmatic and pluralist philosophical approach to its proposals that led to the regulation of assisted reproduction and embryo research in the UK. It recommended application of a '14-day rule' which was subsequently incorporated into UK legislation and widely accepted as a practical limit internationally.[51] Broadly construed, this rule limits research on human embryos to a maximum period of 14 days from fertilization or until the appearance of the primitive streak. The pragmatic approach taken in the Warnock report required distinctions that were not necessarily based on scientific consensus from a biological perspective but that would provide clarity and allay public fears.[52] For states that allow embryo research and ELS research alike, the law must

49 Margaret Brazier, *supra* note 47, at 188.

50 The European Convention on Human Rights and Biomedicine 1997 (the 'Oviedo Convention') Article 18 prohibits the creation of human embryos for research purposes.

51 Department of Health and Social Security, Report of the Committee of Inquiry Into Human Fertilisation and Embryology (1984), https://www.hfea.gov.uk/media/2608/warnock-report-of-the-committee-of-inquiry-intohuman-fertilisation-and-embryology-1984.pdf (accessed Jan. 1, 2025); Sarah Franklin and Emily Jackson, The 14 Day Rule and Human Embryo Research Routledge, Oxford (2024), at xi; Human Fertilisation and Embryology Act 1990, s.3(3)(a).

52 Warnock Report, *id.* at 65. Setting out a proposal for the 14-day rule the report states 'biologically there is no single identifiable stage in the development of the embryo beyond which the in vitro embryo should not be kept alive . . . this was an area in which some precise decision must be taken in order to allay public anxiety.'

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provide a framework even in the absence of moral and scientific consensus. In her introduction to the report, Dame Mary Warnock said:

> [I]t would be idle to pretend that there is not a wide diversity in moral feelings, whether these arise from religious, philosophical or humanist beliefs. What is common . . . is that people generally want some principles or other to govern the development and use of new techniques. There must be some barriers that are not to be crossed, some limits fixed, beyond which people must not be allowed to go.[53]

Turning now to a brief precis of international examples, in the United States, there is no overarching federal legal definition of 'embryo' and so the definition varies by state. The 1996 Dickey-Wicker Amendment[54] prohibited federal funding for research that involves the destruction of embryos, defining embryos for the purposes of the section as 'any organism . . . that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.' It did not prevent experimentation itself, which can be conducted using private funds. The Dickey-Wicker amendment was renewed in 2009.[55]

In Australia a detailed definition of the embryo was set out in law in 2002 as a response to scientific advances in cell nuclear replacement:

> *"human embryo"* means a discrete entity that has arisen from either:
> (a) the first mitotic division when fertilisation of a human oocyte by a human sperm is complete; or
> (b) any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears;
> and has not yet reached 8 weeks of development since the first mitotic division.[56]

The Australian Embryo Research Licensing Committee of the National Health and Medical Research Council has advised that for purposes of the Research Involving Human Embryos Act 2002 and Prohibition of Human Cloning for Reproduction Act 2002 some integrated ELSs will fall within this definition.[57] When that is the case, a license is required and the embryo must not be developed that has morphological features equivalent to the 14-day embryo or beyond.

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53 Warnock Report, *id*. at paragraph 5.

54 House Resolution (H.R.) 2880. H.R. 2880 Bill, SEC. 509 '(a) None of the funds made available in this Act may be used for—(1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289 g(b)). (b) For purposes of this section, the term 'human embryo or embryos' includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.'

55 See section 509 of H.R. 1105, the 'Omnibus Appropriations Act 2009'.

56 Research Involving Human Embryos Act 2002 (Australia), s.7.

57 See NHMRC, *Determining Whether an Embryo Model is Regulated by the ERLC*, https://www.nhmrc.gov.au/research-policy/embryo-research-licensing/commonwealth-and-state-legislation/determining-whether-embryo-model-regulated-erlc (accessed Jan. 1, 2025).

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In the European Union, the flagship research and innovation program, Horizon Europe, will only fund research using human embryonic stem cells where it is considered necessary to achieve the scientific objectives.[58] The program explicitly excludes funding 'research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement'.[59] The distinction between ELSs and embryos is therefore pertinent to EU funding, though there are other sources of available funding across Member States that are not subject to these restrictions and, indeed, some Member States might prohibit research that Horizon Europe would in principle fund.[60]

The CJEU has been highly influential on the definition of embryo in a series of decisions not on the regulation of scientific research, but the patentability of technology using human embryonic stem cells. Article 6(2)(c) of the Biotech Directive[61] says that 'uses of human embryos for industrial and commercial purposes' is unpatentable.[62] In *Brüstle v Greenpeace*[63] and *International Stem Cell Corporation*,[64] the court found that the meaning and scope of 'embryo' is to be determined by national courts, turning on whether the cells 'have the inherent capacity of developing into a human being' as judged according to the best scientific evidence.[65] This definition relies on the notion of 'potentiality' which is itself 'a spectrum of views with different moral implications', not all of which would accept that active potential to develop into a human being is morally problematic.[66] As such, the matter is not fixed and is dependent on subjective criteria. In terms of its application this approach has given states significant discretion. It is permissive of research on human embryos[67] and allows considerable scope for the patenting of embryo models by setting a high threshold for denial of patentability on the basis that they are models and not embryos.[68] But it also demonstrates the precarity of the 'model' classification and the potentially impactful nature of consensus that it no longer applies. In particular, for countries that apply the CJEU embryo definition

58 European Parliament Council and European Commission, Statements on Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 Establishing Horizon Europe—the Framework Programme for Research and Innovation, Laying Down its Rules for Participation and Dissemination, and Repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013 (1), 2021/C 185/01 at 5.

59 European Parliament, *id.* 1.

60 Horizon Europe will not fund research that is forbidden in a Member State, European Parliament, *id.* 2.

61 Directive 98/44/EC of the European Parliament and of the Council on the Legal Protection of Biotechnological Inventions.

62 Article 6 also lists as contrary to order public, and thus excluded from patentability, processes for cloning human beings and processes for modifying the germ line genetic identity of human beings.

63 Case C-34/10, [2011] ECR I-9821, 18 October 2011.

64 International Stem Cell Corporation Case C-364/13 (2014) (GC), 18 December 2014. This case broadened the range of acceptable inventions using stem cells from sources that are not excluded from patentability.

65 International Stem Cell Corporation Case C-364/13 (2014), [16].

66 A. M. Pereira Daoud, W. J. Dondorp, A. Bredenoord, G. M. W. R. De Wert, *Potentiality Switches and Epistemic Uncertainty: The Argument from Potential in Times of Human Embryo-Like Structures*, 27 Med. Health Care Philos. 37 (2024).

67 See Puppinck and Ors v. European Commission Case C-418/18 (2019) ECLI:EU:C:2019:1113.

68 See Aisling McMahon, *Patents & Stem Cell-Based Embryo Models in Europe: The Need for Nuanced Bioethics Scrutiny?* Durham Cells Blog, November 15, 2024, https://www.durham.ac.uk/research/institutes-and-centres/ethics-law-life-sciences/about-us/news/cells-blog/patents--stem-cell-based-embryo-models-in-europe-the-need-for-nuanced-bioethics-scrutiny/ (accessed Jan. 1, 2025).

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adopted to determine patentability outside that context, a finding that some ELSs have the 'inherent capacity to develop into a human being' would impact both on their classification as a model and their legal status.

The CJEU definition has been influential in the development of legal definitions of embryo in Europe. The Netherlands Embryo Act 2002, for example, defines embryos as 'a cell or group of cells with the capacity to develop into a human being' and so the question of whether an ELS is in law an embryo, turns on whether it is considered to have this capacity. The Health Council of the Netherlands advised in 2023 that research embryos should be subject to a revised time limit for culture of 28 days, after which they must be destroyed, and that the same time limit should apply to certain ELSs,[69] which it labels 'non-conventional embryos'. These recommendations have yet to be acted upon.

The ESHRE Ethics Committee writing group issued ethical guidance in 2024 on the moral status of the embryo and ELSs. It starts from the following premise in relation to the status of the embryo:

> Given that even very early embryos are already accorded some moral status, this cannot be grounded in properties that we commonly consider to be morally relevant (for example when determining the moral status of different animal species), such as the ability to feel pain, consciousness, or agency. Rather, the status at this very early stage is connected to the potential to grow into a human being with the relevant characteristics.[70]

It then recommends that the time limit for culturing embryos should be 28 days and that a similar time limit, though one based on morphological features rather than temporal considerations (the number of days post fertilization), should be placed on integrated ELSs. Unlike the Dutch recommendations, the guidance does not state that these integrated ELSs *are* embryos, but seeks to ensure that the same time limit on culture that applies to embryos developed *in vitro* for research purposes is applied to their development.

The UK approach, though compatible with the potentiality approach used to define 'embryos' in much of Europe, diverges from it in ways that could be significant to the regulation of ELSs. The term 'embryo' is defined in section 1(1) of the Human Fertilisation and Embryology Act 1990 as 'a live human embryo'. The courts have taken a purposive approach to this broad definition, reflecting the ordinary meaning of the term.[71] Should some ELSs fit within the ordinary meaning of the term 'embryo' in future, they could be regulated as embryos. This would subject ELSs to the licensing regime that applies to embryos and to licensing conditions such as the 14-day rule and the requirement that research is necessary or desirable for one of the purposes listed in Schedule 2 of the 1990 Act.[72] The HFEA has proposed an extension of the 14-day

69 Health Council of the Netherlands, the 14-Day Rule in the Dutch Embryo Act, No 2023/16e, The Hague, October 31, 2023, https://www.healthcouncil.nl/documents/advisory-reports/2023/10/31/the-14-day-rule-in-the-dutch-embryo-act (accessed Jan. 1, 2025).

70 Writing Group of the ESHRE Ethics Committee, *supra* note 34, at 2387.

71 See R (on the application of Quintavalle) v. Secretary of State for Health [2003] UKHL 13.

72 Human Fertilisation and Embryology Act 1990, Schedule 2 para 2(3A)(1).

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rule to 28 days,[73] in common with the ESHRE group and the ISSCR, both referred to above. If this were to apply, then a decision that some ELSs fit within the ordinary use of the term 'embryo' would require the HFEA to develop guidance on the morphological features that occur at Carnegie stages 12–13 in the embryo, when limb buds emerge.

Incorporation of some ELSs into the definition of embryo in the UK could be achieved through three possible routes. Firstly, as has occurred in Australia, detailed above, the HFEA could decide that some ELSs are sufficiently embryo-like for them to come within their regulatory remit, in which case they would need to regulate them as embryos unless legislative reform extended new powers to them to do otherwise. Alternatively, a court decision could confirm that certain ELSs fit within the ordinary meaning of the term 'embryo' and should be regulated as such. Finally, even if they did not fit within the ordinary use of the term, but for some other reason it was thought to be expedient to regulate them as embryos, the Secretary of State has powers to change the definition of embryo by making secondary regulations.[74] The possibility that some ELSs will eventually lose their claim to model status because they seek to or actually come close to replicating the embryo, combined with controversy as to when this point might arrive and which ELSs it would capture, emphasize the risk inherent in this approach which is both inefficient and potentially very disruptive to research.

To recap, I have argued that the definition of the embryo is internationally varied, and, in some states, its precise boundaries are opaque and variable. Whilst not claiming to capture all definitions of the embryo, I have contrasted two examples, both of which could be used in time to accommodate some ELSs within the definition of 'embryo'. One, which I will refer to as the *International Stem Cell Corporation* (ISCO) approach, relies on ELSs having the inherent capacity to develop into a human being. The other, UK model, relies on being able to identify a point at which the ordinary use of the term suggests that those ELSs are embryos. There is overlap between the two, especially as the ISCO definition is relevant to UK intellectual property law. Both are inherently subjective. But there are also differences which I have argued give greater scope to the UK to distinguish ELSs and embryos for regulatory purposes. Whilst scientific evidence and consensus is important to both, moral arguments as to potentiality and scientific arguments as to the meaning of inherent capacity are particularly relevant to the ISCO approach. Public perceptions, which will be guided by moral and scientific arguments, are more relevant to the UK approach.

There are several potential ways forward to simplify and clarify the current classificatory confusion. One would be for states to redefine the embryo. Some call for changes that will bring more ELSs within the definition,[75] whilst others seek to make clearer which modern scientific applications are excluded from it. Nicolas Rivron and others, for example, suggest that the definition should be 'a group of human cells supported

73 HFEA, *Authority Papers – 20 November 2024*, https://www.hfea.gov.uk/about-us/our-people/authority-meetings/ (accessed Jan. 1, 2025); Hannah Devlin, *Limit on Human Embryo Research Should be Extended to 28 Days, says UK Regulator,* The Guardian, December 6, 2024.

74 Human Fertilisation and Embryology Act 1990, s.1(6): 'If it appears to the Secretary of State necessary or desirable to do so in light of developments in science or medicine, regulations may provide that in this Act (except in section 4A) "embryo", "eggs", "sperm" or "gametes" includes things specified in the regulations which would not otherwise fall within the definition.' These alternatives are discussed in more detail in Emily Jackson, *supra* note 21, at 5–6; and the NCOB Report, *supra* note 7, at 55.

75 Philip Ball, *What Is an Embryo? Scientists Say Definition Needs to Change*, Nature, 18 August (2023).

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by elements fulfilling extra-embryonic and uterine functions that, combined, have the potential to form a fetus'.[76] This, they argue, would help define a tipping point at which ELSs should be given the protections afforded to embryos.

Recognizing that the current legal definitions of embryos may not remain static, the two broad approaches to its definition outlined in this section have potential to influence the regulatory classification of ELSs. According to the ISCO approach, which relies on inherent capacity to develop into a human being, the designation of 'model' might become redundant once that capacity is satisfactorily demonstrated. At this point many states are likely to consider an embryo replica not merely to require the same protection as an embryo, but to *be* an embryo.

That said, this is not inevitably the case. There is an apparent contradiction in the way the ISCO approach operates in today's scientific climate. The 'inherent capacity' to develop into a human being appears to logically exclude the necessity for active potential, yet paradoxically still depends on it. This requires further explanation. On the one hand the *ISCO* case sought to differentiate parthenotes from embryos, but today it is possible to reprogram human cells such as blood or skin cells into induced pluripotent stem cells that can, under the right conditions, form fetal and extraembryonic cell types. Taken to its limits, all differentiated adult cells have inherent capacity for onward development which implies that we are at least looking for 'active' potential for onward development for an entity to be considered an embryo under this definition. In other words, it implies that for an entity to be considered an embryo, inherent capacity for onward development should be demonstrable without reliance on scientific intervention. On the other hand, the *ISCO* approach accepts that entities that have no active potential to develop are embryos. This includes embryos that are subject to limits on culture time, such as those used in research. Moreover, many countries recognize and protect as embryos entities that due to naturally occurring genetic aberrations cannot develop into a fetus or to term. This paradoxically implies that the inherent capacity does not require active potential.

One option to resolve the apparent inconsistency, would be to vary across different entities the evidence required to show that the capacity to develop is inherent. It might be argued, in light of scientific developments and the normative values ascribed to the entities by societies, that the capacities required of an IVF embryo or a research embryo created by fertilization that render them recognizable as an embryo are different to those required of a stem cell derived organism. In other words, a higher threshold of 'inherent capacity' might be applied to some entities based on their ontological characteristics. This could be facilitated in law by recognizing that the capacity to develop into a human being is sufficient but not necessary for an entity to be considered an embryo. This would give scope to exclude ELSs from the definition of embryo if they cannot by virtue of law or genetic manipulation develop into a fetus, on the basis that they lack capacity for onward development. At the same time, it could accommodate within the definition of embryo, say, a research embryo created by fertilization, even though it is legally prohibited from onward development beyond a requisite number of days.

76 Nicolas C. Rivron, Alfonso Martinez Arias, Martin F. Pera et al., *An Ethical Framework for Human Embryology with Embryo Models,* 186(17) Cell 3548 (2023).

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By virtue of this method, a restrictive interpretation of 'inherent capacity to develop' is made possible. Whilst this would require legal clarification it is not a far reach from the current interpretation of inherent capacity to develop, which, as Hannah Schickl and others point out, ineffectively delimits human embryos worthy of protection from other sub-categories that have comparable de facto capacity to develop.[77] Consider, for example, the position in Switzerland, where, as Inesa Fausch describes, the law differentiates between *in vivo* and *in vitro* embryos.[78] An *in vivo* embryo is understood as 'the offspring, from the fusion of the cell nuclei (karyogamy) to the completion of organ development'.[79] An embryo *in vitro* is 'a surplus embryo, which means "an embryo produced in the course of an *in vitro* fertilization (IVF) procedure that cannot be used to establish a pregnancy and therefore has no prospect of survival"'.[80] The legal status of both is unclear in Swiss law, but the fact that *in vitro* embryos cannot be used to establish a pregnancy could potentially justify different legal statuses being applied to the two embryo types. As such, on my proposal the *in vivo* embryo *must* be given the legal status of embryo, if it is to comply with the *ISCO* and *Brüstle* approach; the *in vitro* embryo *may* be given such legal status by the state, and ELSs that do not fall within the definition of an *in vitro* embryo could be regulated separately as non-embryos.

In France, the Bioethics Act 2021 requires that research on ELSs is overseen by the Agence de la Biomédicine. A framework opinion by the French Conseil d'Orientation states that ELSs are not embryos in part because of their origin: they arise from stem cells and not natural conception—and in part because of their function—the intended purpose of their development is for research rather than reproduction.[81] The focus here is not how they *could* function, but how they are used and *allowed* to function. The French example shows that regulatory restrictions on developmental potential could be relevant to its fit within definitions of embryo that focus on its capacity to develop.

The *ISCO* case is influential in the UK too, but the UK legal definition of embryo is broader than the definition set out in *ISCO* and is conducive to differentiating between ELSs and embryos as separate entities in different ways. Unlike the Swiss example cited above, UK embryos can be created *in vitro* for research purposes subject to strict licensing conditions.[82] Without legislative change, this precludes a classificatory distinction between surplus IVF embryos and embryos created for research purposes. It does not, however, prevent the UK from defining the ELS as a separate entity to the embryo and regulating it consistently, but separately. Emphasis on everyday use to define the ambits of the term 'embryo' facilitates a focus on how an entity is controlled, used and understood by the public. This feature of the law can help shift the debate from a focus on equivalent features, to consideration of any differences and the advantages of bespoke regulation to manage them.

77 See Hannah Schickl, Matthias Braun, Peter Dabrock, *Ways Out of the Patenting Prohibition? Human Parthenogenetic and Induced Pluripotent Stem Cells,* 31(5) Bioethics 409 (2017), at 411.

78 Inesa Fausch, *The Law for Mini-Organ Prototypes in a Dish. Mapping the Legal Status Options for Organoids in Swiss Law,* 11(2) Journal of Law and The Biosciences lsae025 (2024) at 4–7.

79 Fausch *id.* at 4–5 citing Art. 2 lit. a Federal Act on Research Involving Embryonic Stem Cells.

80 Fausch *id.* at 5 citing Art. 2 lit. a Federal Act on Research Involving Embryonic Stem Cells.

81 Agence De La Biomédicine, Opinion of the Conseil D'orientation: Stem Cell-Based Embryo Models, Sept. 21, 2023.

82 Human Fertilisation and Embryology Act 1990, Sched 2 para (3)(1)(a) (as amended).

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The NCOB report suggests that in the UK the ELS and embryo could be differentiated for regulatory purposes, bolstered by guidance and legislative provisions that prevent reproductive use and maintain its basic research designation.[83] It is unlikely that regulation could eliminate the potential for embryo model research to transition from imitation to replication. This is due, in part, to the fact that striving for improved imitation is a legitimate research objective, as it enhances the model's ability to produce reliable and precise predictions. Furthermore, as we have seen, the entity that ELSs seek to emulate is neither consistently nor clearly defined. Taken together with the moral and scientific pluralist positions described in the previous section, the point at which ELSs move from model to replica status is unpredictable.

Two regulatory options have been described. On the first option, models that are similar enough to the embryo are regulated as an embryo. The timing of the regulation and the ELSs to which it would apply would be contentious. States would be guided by a range of factors including scientific evidence of equivalence and the legal definition of embryo. On the second (preferred) option, the loss of the classification of 'model' does not inevitably result in it being considered an embryo, but instead recognizes that models and replicas could be regulated separately from embryos. I have not set out the proposed substantive content of that regulation or how far it should mirror the regulation that applies to embryos. These matters are considered in detail in the NCOB report. In the next section I make the normative case for anticipatory regulation of ELSs as separate entities to embryos.

VI. OPTIMAL REGULATION OF THE ELS

Whilst replicas can sometimes be distinguished from the entity they replicate and the law can seek to maintain that distinction, there are clearly also many incidences where it is more efficient and consistent to regulate replicas or even broadly similar health technologies together.[84] Aristotle famously articulated the principle of equality in ethics: 'Equality in morals means this: things that are alike should be treated alike, while things that are unalike should be treated unalike in proportion to their unalikeness.'[85] This enduring idea continues to inform contemporary notions of fairness, justice, and equality. The principle demands equal treatment unless meaningful differences justify a deviation. The critical task is to identify relevant differences within a particular context and ensure that any differential treatment is justified and applied consistently.

The UK SCBEM Code of Practice sets out relevant principles and calls for a register and oversight committee to be set up. The Code recognizes that embryo models may at some future point cease to be models if they achieve certain functions at which point they should be given the status of embryos:

> ... were it ever considered, as a matter of best scientific judgment, that a SCBEM very likely has the potential to develop fully within a human host, it would no longer be appropriate

83 NCOB report, *supra* note 7, at 38.

84 One such example is software applications (apps) which are sometimes regulated as medical devices: see Medicines and Healthcare Products Regulatory Agency (UK), Medical Devices: Software Applications (8 August 2014) at https://www.gov.uk/government/publications/medical-devices-software-applications-apps (accessed Jan. 1, 2025).

85 Aristotle, Ethica Nicomachea V.3.II3Ia-II3ib (W. Ross translation, 1925).

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> to refer to it as a 'model'; rather, it should then be viewed as an 'embryo', and would be governed as such.[86]

The Code rightly observes that once an embryo model can no longer be classified as a model, the most practical option *under existing UK law* is to categorize the replica as an embryo. This is for several reasons: firstly an entity that replicates rather than models clearly requires regulatory oversight, secondly the only feasible approach without law reform would be to include it within the definition of embryo and thirdly, the HFEA would be compelled to regulate them in the same manner as embryos, as it currently lacks the statutory power to differentiate between embryo categories beyond the provisions outlined in the 1990 Act.

At first sight there are several advantages to regulating replicas as embryos within the existing legal framework. First, this approach eliminates the immediate need for specific, potentially complex new legislation, allowing regulation to adapt efficiently within established systems. Additionally, it could enhance consistency by treating like cases alike, particularly when the replicas are created through similar methods and serve comparable purposes. This alignment would help maintain coherence and fairness in the regulatory landscape.

Ostensibly regulating replicas as embryos would ensure that entities mimicking early developmental stages are subject to these consistent and rigorous controls, aligning their treatment with existing ethical, legal, and practical frameworks. This approach would arguably facilitate public trust by maintaining a consistent and principled oversight structure.

However, for states that sanction regulated embryo research, there are also at least three drawbacks to this approach. One relates to the difficulties around the timing and extent of the incorporation of ELSs within the definition of embryos, another concerns the poor fit of embryo regulation to ELSs and a third relates to the dangers of an untailored regulatory approach that is inflexible to specific needs, circumstances and risks posed by ELSs.

Taking each in turn, I have shown that difficult choices would be required to regulate ELSs as embryos proportionately and effectively because there will be disagreement as to both the point at which replication occurs, and which ESLs to include. This could lead to ineffective regulation that either over-regulates low-risk cases, stifling research that is in the public interest, or under-regulates high-risk cases which could result in unethical research that damages public trust.

Earlier in the paper I listed several factors that would shape the external values that make the assessment of equivalence between replicas and embryos so difficult. This includes scientific, moral, economic and political, public and legal values. Let us briefly return to each. We have seen that scientific values whilst reliant on technological realities and evidence-based distinctions are inevitably influenced by the regulatory environment, moral considerations and perceived scientific merits. This will result in disagreement as to the degree of variation between embryos and the range of evolving ELSs. Moral disagreement as to the status of the embryo also impacts on the status and definition of ELSs. Economic and political values may be brought to bear if states

86 UK SCBEM Code of Practice (2024), *supra* note 14, at 3.

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see the potential for investment and advancement or, conversely, view this science as a potato too hot to pick up. Public values are key to this issue, particularly in the UK where the purposive approach to the definition of 'embryo' taken by the courts will include consideration of its ordinary meaning, the potential benefits it offers, and the trust placed in scientists and relevant regulators. In the UK trust in science is currently high, and a significant proportion of the public consider that engineering biology will impact positively on science in the next 10 years.[87] However, the global Edelman Trust Barometer indicates that rapid innovation, whilst promising societal advantages and economic prosperity, risks exacerbating public trust issues leading to political polarization. Regulation can serve as a stabilizing tool, as it has done in the UK with embryo research: 'Respondents need to know that the inventions have been evaluated by scientists and ethicists, are effectively regulated, and feel in control over the impact on their lives.'[88] Finally, legal values are relevant to the point at which models, replicas and embryos overlap. We have seen that, absent a legal definition of ELSs, defining them is dependent on being able to define the embryos they model or replicate. Alas, there is wide variation in the definitions of embryo and opacity as to those definitions at national levels. Whilst diverse legal values currently contribute to the problem of knowing when, which and how to reactively regulate ELSs, *anticipatory* regulation, as is proposed in the UK context in the NCOB report, can be part of the solution. The law can reduce opacity, reassure the public and help ensure that researchers are supported to meet scientific potential without crossing ethical red lines. There are well developed principles of regulation to guide its operation, and mechanisms to enable phased and proportionate regulation that are covered extensively in the NCOB report and not repeated here.[89]

The second drawback to reactively regulating similar ELSs as embryos is the poor fit of embryo-specific regulation. This issue is considered in detail in the NCOB report.[90] Amongst the considerations, which I do not repeat here in detail, is the following:

> Consider, for example, the 14-day rule, which applies clearly to the embryo created by fertilisation, but is ill-suited to an entity that has no 'day zero' due to its stem cell-based origins and develops in a non-linear fashion. A culture might start at the equivalent of Day 21 or 28 for example, or contain elements equivalent to Day 7 and elements equivalent to Day 14. The model might not follow the normal stages of embryonic development or form a primitive streak. Whilst it would not be impossible to adapt the 14-day rule, the need to

87 Department for Science, Innovation and Technology (UK), Engineering Biology Public Trust Survey Findings (November 29, 2024), https://www.gov.uk/government/publications/engineering-biology-public-trust-survey-findings/engineering-biology-public-trust-survey-findings#executive-summary (accessed Jan. 1, 2025).

88 Edelman Trust Institute, 2024 Edelman Trust Barometer: Global Report (2024), https://www.edelman.com/sites/g/files/aatuss191/files/2024-02/2024%20Edelman%20Trust%20Barometer%20Global%20Report_FINAL.pdf (accessed Jan. 1, 2025).

89 NCOB report, *supra* note 7, at Part III referring to the Legislative and Regulatory Reform Act 2006, s.2(3)(a) 'regulatory activities should be carried out in a way which is transparent, accountable, proportionate and consistent'; and National Audit Office (2021) Principles of effective regulation, https://www.nao.org.uk/wp-content/uploads/2021/05/ Principles-of-effective-regulation-SOff-interactive-accessible.pdf (accessed Jan. 1, 2025).

90 NCOB report, *supra* note 7, at 60–62.

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> do so to incorporate SCBEMs is, we consider, an indicator of the lack of equivalence from a governance perspective.[91]

The third ground for bespoke regulation of ELSs is that by distinguishing them from embryos, even if they are similar in ethically-relevant ways, oversight could be more precisely tailored to address their unique characteristics and societal concerns, including, as detailed above, measures to limit or control the potential for the science to move from modelling to replication. A distinction between ELSs and embryos also ensures that regulations remain flexible and proportionate to the specific risks and benefits associated with each. As such, whilst there is likely to be considerable overlap in the regulatory requirements applied to embryos and replica entities, separate regulation would make safeguards more targeted to their different characteristics and intended use. For example, regulations for ELSs could focus on controlling their design to prevent them from acquiring developmental potential, while embryo regulations might prioritize ethical sourcing. In the UK the current regulation of embryos applies a single approach to all embryos. In new regulation specifically designed for ELSs a risk-based model is possible that responds to the features and capacities of different ELS categories. Replica entities that emulate the embryo closely would share similar restrictions to those placed on embryo research whilst also being responsive to any distinctive risks and benefits they pose.

I have argued that similar entities do not always require identical treatment, while acknowledging the importance of maintaining consistency in treating alike things. In Figure 2, I suggest three pertinent questions that states seeking to fill the regulatory gap around particular ELSs should ask. The first question is whether the entity can be classified as a model. Even if the answer is 'yes', the ISSCR is clear that all embryo models should be subjected to governance,[92] which may be 'soft' in the sense that it is voluntary, albeit with clear incentives to comply, or 'hard' in the form of regulation that mandates compliance. Traditionally, hard regulation is rigid and less suited to emerging technologies, but increasingly states are relying on flexible forms of anticipatory regulation such as regulatory sandboxes.[93] The NCOB report recommends a phased approach starting from a soft law basis and building via a regulatory sandbox to hard law regulation. Anticipatory regulation can address the challenges arising from the unpredictability of when research may shift in purpose or results from modeling to replication. The NCOB report sets out the principles that should apply to ensure that regulation is flexible and targeted to specific categories of ELS so that the technology can develop with the science and in line with public expectations.

The answer to question one might, in time, be 'no' because certain ELS research, approved by an oversight mechanism based on its potential value to society, does not or might not fall within the definition of 'model'. I have suggested that states can look to the purpose and results of research to help differentiate between models and replicas. Where the ELS falls into the replica category, I have argued that this does not *automatically* render it an embryo. Accordingly, the second pertinent question is

91 NCOB report, *id.* at 61.

92 ISSCR Guidelines (2021), *supra* note 11, at 2.2.

93 See for example Peter Foster, *UK Launches Regulator in Push to Speed Up Approvals for New Technology* Financial Times (8 October, 2024).

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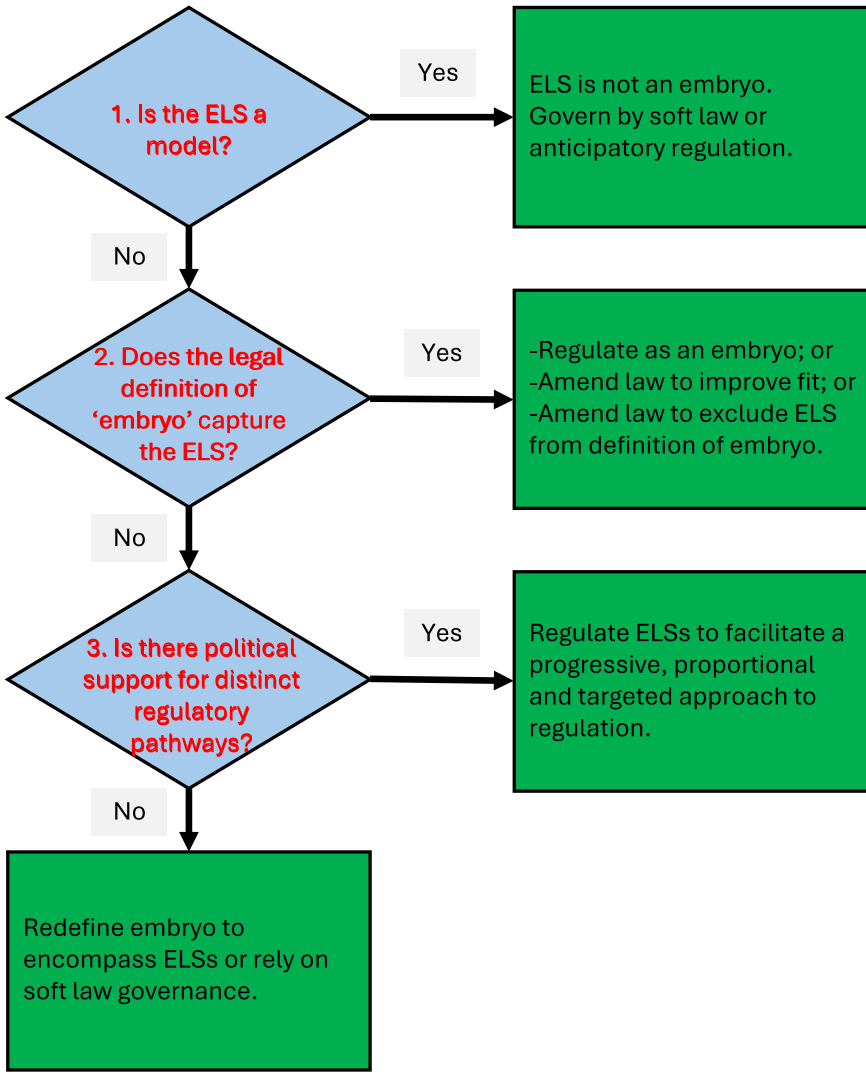

Figure 2. Regulatory options for ELSs

whether the legal definition of 'embryo' captures the ELS. If it does then it must be regulated as an embryo and the law adapted if necessary to improve fit. If this is an unintended consequence of a legal definition of 'embryo' set out before ELSs were scientifically possible, or the state considers the regulation to be disproportionate to the risks the ELSs create, then it might be feasible to clarify the law to exclude ELSs from the definition of embryo, in which case alternative regulation of ELSs should be set out.

If the legal definition of embryo does not capture the ELS, then the third question considers the appetite for separate regulatory pathways for embryos and ELSs. This has a political dimension and emphasis on the potential for the research to improve reproductive outcomes, drive economic growth and risk public distrust in science and

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regulation will vary internationally. Regulation of ELSs would require the state to put resources into precisely defining its ambits though public and stakeholder dialogue. If there is insufficient support for the separate regulatory paths I have advocated, the state could alternatively legislate to include certain ELSs in the definition of embryo. Or it could rely on soft law measures such as voluntary codes and guidelines and, as the science progresses, reactively return to question two which seeks to determine whether the ELS falls within the definition of the embryo.

VII. CONCLUSION

We are faced with an important and time-sensitive regulatory dilemma. Embryo model research has significant potential to serve the public interest both in relation to the knowledge scientists are gleaning about early human development which is currently poorly understood because it is so difficult to study, and for its potential clinical applications. But at present in the UK and several other states, they fall into a regulatory gap. One question is whether to address the gap at all. Afterall, there is a global and national move toward deregulation. However, the core aims of deregulation—such as ensuring proportionality, stimulating economic growth, and fostering emerging sectors—support the case for action in this case. Bespoke regulation would reduce the risk of over regulating ELSs by defaulting to embryo research regulation in the absence of more appropriate regulatory alternatives.

Agreeing how to address the regulatory gap is challenging due to the lack of consensus on the current legal status of embryo models, the uncertainty surrounding their future legal status and the internationally varied legal status of the embryos they model. This paper has outlined scenarios where a distinction between embryos, models, and replicas can help determine the optimal regulatory approach to each.

The current focus of research fits the definition of 'model'. The focus is on mimicking aspects of embryonic development rather than replicating it entirely, and the objective is researched-focused: to speed up knowledge acquisition on early human life, with the embryo as a reference point.[94] Anticipatory regulation could help to maintain that designation by controlling the purpose and outcomes of research. But, as the NCOB report proposes, regulation should also prepare for a future where, by design or accident, the embryo could be copied so accurately that the entity's status as a model comes into doubt.

Two regulatory approaches have been contrasted. One is to regulate replicas as embryos. This position is sometimes assumed to be an inevitable consequence of ELSs losing their status as models. I have challenged this assumption, providing relevant examples where distinct regulation of originals and replicas is justified. I have argued that in this context, separate regulatory pathways for ELSs and embryos would be optimal for three principal reasons: It would circumvent contentious debate and potentially ill-timed action around the point at which ELSs should be accommodated within embryo regulation, creating unpredictability around investment in ELS research, and risking inadequate oversight up to the point that embryo models are considered equivalent to embryos; embryo regulation would generally be a poor fit; and

94 Cheng Zhao, Alvaro Plaza Reyes, John Paul Schell *et al., A Comprehensive Human Embryo Reference Tool using Single-Cell RNA-Sequencing Data*, Nature Methods, November 14 (2024).

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separate regulation would facilitate proportionate and targeted regulation and better compliance.

I have argued that an alternative and preferable option is to provide an anticipatory scheme of regulation. The proposed regulatory scheme set out in the NCOB report, which I do not repeat in detail in this article, would exert controls on researcher intent and outcomes to help maintain the model status of most ELSs. It would also enforce regulatory oversight, anticipating the potential for some research that is approved on the basis of public benefit, to purposefully or unintentionally cross the boundary to replication. It should be phased and proportionate, swapping reliance on the point at which the ELS achieves equivalence with the embryo at which point it is perceived *as an embryo,* for a proactive focus on what makes it unique, guided by the regulatory principle of consistency where it shares morally relevant features with the embryo.

By focusing on the specific contexts of use and the implications of technological advancements, regulators can ensure that oversight remains both effective and proportionate and innovation can proceed responsibly, while also safeguarding public trust and ethical standards. The NCOB report's emphasis on anticipatory regulation acknowledges the dynamic nature of scientific developments and their potential to blur the boundaries between models, replicas and embryos. It seeks to ensure that the UK's regulatory framework can evolve alongside technological progress, rather than being constrained by static definitions. This flexibility would promote the effective balance between the need to foster innovation and the imperative to uphold ethical standards and maintain public confidence in science and regulatory systems.

None of this means that the law should not strive to identify similar features of different entities and respond to them consistently. Rather it asserts that there is potential to maintain commitment to regulatory consistency without employing equivalence as a regulatory mechanism to justify a change in classification from model to embryo. A faithful reproduction of a work of art is not the original work of art. A synthetic diamond is not a natural diamond. Whether these differences should be reflected in the regulation of each entity depends in part, as we have seen, on the legal definition, if one exists, of the entity being replicated. It also depends on the purpose of regulation. For instance, production of synthetic lab based diamonds releases more greenhouse gases than mined diamonds, which could justify differential treatment in its regulation; a chemically identical medicinal product that is a replica of a branded version might differ in formulation, quality control, and manufacturing standards that require different regulatory scrutiny; and counterfeit goods replicate luxury items but their replica status requires different regulation to the extent that they are illegal in many countries. So too, regulating a stem cell-based embryo *replica* as an embryo would likely be insufficient to tackle the regulatory issues it would pose around culture, production, genetic manipulation, consent and cloning.

In addition to making the case for classificatory distinctions between models, replicas and embryos in the UK, where the definition of embryo is flexible and focused on ordinary use of the term, I have—more tentatively and controversially—also referred to international definitions of embryo that focus on inherent capacities for development. I have argued that the focus on these inherent capacities has become increasingly problematic as stem cell research capabilities have improved. I have proposed that a way forward would be to accept that capacity to develop into a human being is

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sufficient but not necessary for an entity to be considered an embryo. This would decrease the relevance of the definition and give more discretion to individual states to accord different statuses to embryo-like structures depending on their application and state-imposed limits on development.

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