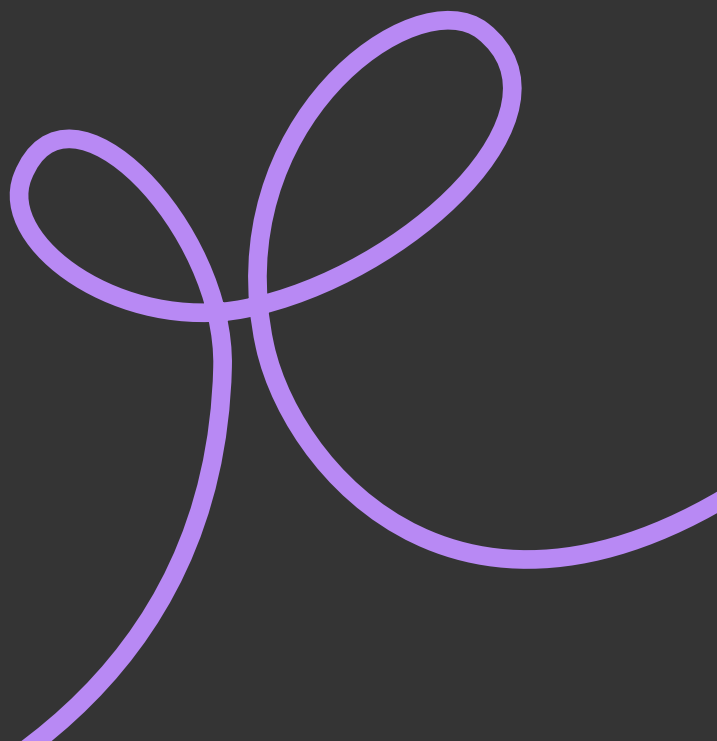
Nuffield Council on Bioethics

Human stem cell-based embryo models:

A review of ethical and governance questions



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Foreword

First, a word on terminology: the SCBEM term hardly trips off the tongue (as we touch on in the section '**Terminology**' below), but it results from careful attempts over the past decade to accurately capture both the uses and usefulness of this emerging technology, and what it is *not* – i.e., a human embryo.

From the outset of this work, we were aware both of the significant pace of developments in this field and the lack of clarity about the ethical and legal position of research involving SCBEMs. At the international level, there have been significant efforts to address this over the past decade. The most notable of these is by the International Society for Stem Cell Research (ISSCR), which has taken the lead in developing and (as we write this) updating highly influential guidelines which have both built on, and been subject to, robust discussion within the scientific community (see '**International guidance**' below). In 2024, we have also seen the development of a UK Code of Practice for SCBEM research ('the UK SCBEM Code') in acknowledgement of the need for processes to support decision making in research.[1] These initiatives both acknowledge the need for further engagement and ethical debate, which is often repeated in wider discourse around this research. When a number of high-profile papers were published in 2023, the research attracted media attention and, with it, an awareness of the potential for public concern, with the UK newspaper *The Guardian* calling for a panel akin to the 1984 Warnock Committee "to convene and find an ethical consensus".[2] We hope our work will contribute towards finding such a consensus.

It was a priority for us to come to robust conclusions and recommendations in a timely fashion. As such, our review is restricted to issues raised by *human* SCBEMs. We note the interconnectedness with related fields which raise comparable practical, ethical and governance issues, including embryo, stem cell and organoid research (including the potential to derive **gametes** *in vitro*).[3] We have not considered ethical issues that could arise from any future clinical applied research involving SCBEMs.

1 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode.

2 The Guardian (18 June 2023) *The Guardian view on stem cells and embryos: creating life's likeness in a lab*, available at: https://www.theguardian.com/commentisfree/2023/jun/18/the-guardian-view-on-stem-cells-and-embryos-creating-lifes-likeness-in-a-lab.

3 For the definition of these terms, refer to the Appendix **Glossary**.

Our primary focus has been on the UK research environment and governance context, though we have also sought to learn from colleagues and researchers working elsewhere. Given the international nature of the research, it cannot meaningfully be considered in isolation. We hope our conclusions will be of value to the international scientific community and policy makers in other jurisdictions.

SCBEMs are a rapidly-evolving emerging technology. We expect that some of the methods in use today will be outpaced by other approaches. Categorisations of SCBEMs that are currently relied on may soon become less relevant. We are encouraged by the proactive efforts within and around the scientific community to instigate discussion of ethical issues at such an early stage of technological development. This is an opportunity to ensure that careful consideration of ethical issues is embedded in the research and make recommendations for how it might be governed now and in the future.

We have been fortunate to hear from individuals and organisations directly involved in the development and oversight of SCBEMs, as well as in the wider discourse around the ethical and governance issues they raise. We have also been influenced by a handful of initiatives involving members of the public in discussion about SCBEMs and how their use might be governed. However, we recognise that ongoing and wider public engagement and dialogue, with representation from diverse groups, is needed to ensure that the governance of SCBEMs is informed by an understanding of public views, values and interests. As stem cell-based embryo modelling is a young technology, there is an opportunity for early engagement and dialogue to lead to co-creation of broader scientific aims and objectives. This should occur as the science develops rather than as a top-down communication project.[4] We also heard in our roundtable workshops that greater transparency and open dialogue with the public could help to counter misinformation and prevent or reduce mistrust and polarisation in societal debates about the research. We were frequently reminded by experts of the potentially damaging consequences of a loss of trust in science or scientists. We have indicated particular questions or areas that would benefit from wider public discussion throughout the report. This is not to say that wider public engagement or dialogue *replaces* ethical inquiry, but rather that it should be a key component of an ethical and robust approach to governance.

We are enormously grateful for the generosity and openness with which people have engaged with us during this review.[5] On a personal note, I want to thank members of the working group for their hard work, robust discussion and commitment to producing feasible recommendations. This is particularly given the highly complex and uncertain nature of this topic, and the range of experiences and perspectives on the issues we have covered. Our report owes much to the feedback generously

4 An excellent example of this was the Francis Crick embryo model display at the Royal Society Summer Science Exhibition, 2-7 July 2024. See The Francis Crick Institute (2024) *Embryo models: how stem cells reveal the mysteries of development*, available at: https://www.crick.ac.uk/research/labs/naomi-moris/embryo-models-how-stem-cells-reveal-the-mysteries-of-development

5 An overview of evidence gathering activities can be found in the Appendix **Methods of evidence gathering**.

provided by all who participated in our roundtables and meetings, and who read and commented on drafts. Finally, I would like to thank the Council members and Executive of the Nuffield Council on Bioethics (NCOB), and particularly the brilliant Ranveig Svenning Berg and Allison Milbrath who researched and managed the project and who have worked so ardently with me to draft the report.

Emma Cave
Chair of the working group

Summary

This report is concerned with ethical and governance questions arising from research involving human stem cell-based embryo models (SCBEMs). As a research tool, SCBEMs have the potential to bring public benefit through new insights around early human development. However, there is debate about their status – for example in relation to human embryos – and how they should be used.

The report provides an overview of the science, ethics and regulatory landscape in this new and fast-moving field. It sets out a clear road map for governance both now and in the future, whilst acknowledging areas of uncertainty. It details the considerations of the working group and the principles and rationale for how conclusions have been reached, with the aim of offering a useful resource to policymakers, scientists and research funders, and forming the basis of further discussion and decision making in this fast-moving area.

SCBEM is an umbrella term for a range of structures created from stem cells which resemble or replicate aspects of embryonic development. These stem cells are derived either from embryos (embryonic stem cells – ESCs) or through the reprogramming of cells from other human tissue such as skin or blood cells (induced pluripotent stem cells – iPSCs). While a number of different terms are used to describe these structures, we have adopted the term 'SCBEM' recognising the value of consistency with other formal guidelines and frameworks.

SCBEMs vary in their complexity and composition, the methods by which they are derived, and their uses in research. Given the pace of development, it is currently difficult to clearly define or categorise different types of SCBEM, both on a technical basis and according to what ethical or regulatory issues they may raise.

Research in this field is at an early stage and there is uncertainty about potential applications, but a range of possibilities are being explored. Different types of SCBEMs provide opportunities to model *in vitro* aspects of early human development and processes. These include implantation and post-implantation development and the study, at scale, of how external factors such as drug or toxin exposure during pregnancy might impact on embryonic development. In the future, this research could translate into findings or applications that improve human health and wellbeing. However, further research is needed, for example to assess and improve the validity and quality of models. While SCBEMs appear to have the potential to *complement* embryo research, they cannot at this time be considered a like-for-like alternative or replacement.

Ethical considerations: what matters?

There is considerable uncertainty about the potential of SCBEM research and what features or characteristics of models might be considered ethically significant. We recognise the need for ongoing ethical discussion as the field develops, including through wider public and stakeholder engagement. However, some general points of consensus did emerge in our review.

- There is a legitimate public stake in this research, and a clear interest in its transparency to support wider debate around its benefits, risks and costs, as well as the appropriate accountability of those involved.
- Any attempt to develop SCBEMs for reproductive use, or to transfer SCBEMs to the reproductive tract of a living person or animal to test this potential, would involve considerable risks and be widely considered to be unethical. We acknowledge that, in the future, there may come a point where SCBEMs are created which are functionally equivalent to embryos, to the extent that they may be considered for reproductive use. Such a prospect (which we believe to be distant) will require broad societal debate, with any decisions informed by that future society's interests and priorities.
- Research that is perceived to be pushing ethical boundaries could negatively impact on the overall acceptability of this field of research. We heard that any potential for SCBEMs to be developed that have the capacity to feel pain represented a 'red line' for most people. While it is less clear how other 'tipping points' might be identified, we heard a general assumption that the more *human-like* SCBEMs become, the more likely they are to cause concern.

Governance mechanisms and main recommendations

There is no specific legal or regulatory framework that governs SCBEM research in the UK, though guidance has been developed. In 2024, a UK Code of Practice was produced that sets out standards for SCBEM research. This recommends the establishment of an oversight committee and a register to review and record SCBEM research. In the first instance, **the Working Group supports the Code of Practice, and considers it to be a proportionate response that would improve transparency and accountability and serve to develop expertise in the review of SCBEMs**.

We explore options for ensuring that the oversight committee has the legitimacy and force that it will need to be effective, including through secure funding and the involvement of regulators and oversight bodies.

We identify some risks that might not be fully addressed by this governance model in the longer term. One such risk is that, as SCBEMs become more sophisticated, developments or events that raise public or parliamentary concern may trigger a reactive response that is disproportionate and disruptive to the research. For example, a decision could be made to incorporate SCBEMs within the regulatory regime that governs embryos. We heard from a range of experts, including members of our working group, that regulating SCBEMs as embryos would be inappropriate, burdensome and could insufficiently target those SCBEMs that pose ethical concerns.

Our preference is that *for regulatory purposes*, SCBEMs and embryos are considered distinct, and that this should be reflected in the Human Fertilisation and Embryology Act 1990 (as amended) that governs embryo research in the UK.

We also consider that a statutory prohibition on the transfer of human SCBEMs to the in vivo reproductive tract of a human or non-human animal is a necessary measure to provide reassurance as to the purpose and governance of future SCBEM research.

We recognise that there is merit in setting an upper limit on how far SCBEMs might be allowed to develop in culture (i.e. in a laboratory, for research purposes), but at the present time there is considerable uncertainty about how such a limit might be drawn up. Pending the scientific developments, learning, and public dialogue that would support a more reliable assessment and limit, **we propose that the Code of Practice should incorporate an interim threshold, informed by the emerging consensus we identified around the 'red lines' for SCBEM research**.

The aim of this threshold is to ensure that SCBEMs are not developed:

- that have the capacity for pain or awareness;
- with the intention of exploring the feasibility of gestation outside of the human body; or
- that model late-stage embryos which have been genetically altered to avoid pain and or awareness.

We consider it the role of the SCBEM oversight committee, proposed in the Code of Practice, to set case-by-case limits to ensure that models are cultured to the minimum stage required. The proposed interim threshold should be tested and developed on an ongoing basis, with a view to establishing clear, enforceable and proportionate upper limits in the future.

In the medium- to longer-term, we recommend a bespoke and proactive approach to the governance of SCBEMs. This approach should facilitate learning and reflection in

order to safely and incrementally build towards proportionate, targeted, and future-proofed regulation. We recognise that no single regulator is a perfect fit and set out our preference for a collaborative model. However, there is also a pragmatic case for ensuring that the necessary powers are in place for the public and Parliament to have confidence in regulators' capacity to respond to future developments.

We propose that legal provisions are put in place to enable the later introduction of a 'regulatory sandbox' for SCBEMs, as an agile form of regulation that will give researchers access to regulatory expertise and a degree of oversight, without the burdens of full regulation. We note that this option is currently being explored by the Human Fertilisation and Embryology Authority (HFEA) and might become possible through changes to the Human Fertilisation and Embryology Act 1990 (as amended), referred to throughout as the HFE Act 1990. This option would add to the legitimacy and accountability of the Oversight Committee whilst ensuring that regulators involved in its running have sufficient powers to monitor and react in a proportionate manner.

The sandbox would be used to test which SCBEMs should be regulated and on what basis. One of the possible exit strategies from the sandbox that we set out is the Oversight Committee to be put on an independent footing, with extended powers of oversight, and a remit that could incorporate other stem cell-based research. The UK SCBEM Code might similarly evolve from its initial voluntary status to give future iterations the backing of regulators and, potentially, the law.

Introduction

This report is the product of a rapid review undertaken by an expert working group, appointed in March 2024. The review has involved several workshops, small group meetings and individual interviews with scientists, ethicists and experts in law and governance, as well as those who are or might in the future be involved in funding and overseeing this research, both in the UK and internationally.

This report falls into three main parts. The first summarises the evidence we heard with respect to the state of the science and the wider context affecting research and development in this area. The second part sets out the ethical considerations that arise from this research and its potential future applications. Finally, we outline key challenges and questions for the governance of SCBEMs and make a number of recommendations to address them.

We set out our meaning for certain terms and descriptions of the stages of early human development in the **Appendix Glossary**. Those included will appear first in bold, for ease of reference.

1. Stem cell-based embryo models (SCBEMs)

Sources of human stem cells

The systems we are focused on in this report are produced with human **pluripotent stem cells** as their starting material. These are cells with the potential to differentiate into all the specialised cells and tissues of the fully developed human body. Pluripotent cells can also be engineered to give rise to the **extra-embryonic** tissues which support embryonic development, such as the yolk sac and the embryonic contributions to the placenta. There are two main types of human pluripotent stem cells: **embryonic stem cells** (ESCs) and **induced pluripotent stem cells** (iPSCs).

ESCs can be derived by culturing cells from the **inner cell mass** of the **pre-implantation** embryo. ESCs were first derived from human blastocysts in this way by Thomson *et al.* in 1998.[6] Under the right conditions, these cells can be propagated and maintained in their pluripotent state as embryonic stem cell lines, without significant changes to their genetic makeup or characteristics.[7] Stem cells can also be derived from other regions of the developing embryo, for example, from the extra-embryonic tissues. Extra-embryonic stem cells are not pluripotent but are mixed with ESCs to generate SCBEMs.[8]

In the UK, embryonic stem cells are primarily derived from donated embryos which are surplus to the treatment requirements of patients undergoing assisted conception by using methods such as *in vitro* fertilisation (IVF), for example, from couples or individuals who have completed their family.[9] Human ESC lines derived in the UK must, as a condition of the Human Fertilisation and Embryology Authority (HFEA) research licence required to access embryos for research, be deposited in the UK Stem Cell Bank (UKSCB). Researchers in the UK may also access ESC lines from abroad where other rules or regulations apply. However, researchers should

6 Thompson JA, Itskovitz-Eldor J, Shapiro SS, *et al.* (1998) Embryonic stem cell lines derived from human blastocysts *Science* **282(5391)**: 1145-7.

7 UK Research and Innovation (2010) *Code of practice for the use of human stem cell lines*, available at:https://www.ukri.org/wp-content/uploads/2021/08/MRC-0208212-Code-of-Practice-2010-use-of-human-stem-cell-lines.pdf

8 See, for example, Sozen B, Amadei G, Cox A, *et al.* (2018) Self-assembly of embryonic and two extra-embryonic stem cell types into gastrulating embryo-like structures **Nature Cell Biology 20**: 979–89.

9 They may also, under the HFE Act 1990 (as amended), be derived from embryos created for research purposes or created by somatic cell nuclear transfer, but we heard that this would currently be an unlikely source of human ESCs.

apply to the UKSCB's Steering Committee, which provides ethical guidance and assistance on best practice for any use of human ESC lines, whether or not the ESC lines are held in the UKSCB.[10]

In 2006, a method was discovered by Yamanaka et al. which allowed **somatic** cells, such as skin cells, to be reprogrammed to a pluripotent embryonic stem cell-like state, called induced pluripotent stem cells (iPSCs).[11] This technology is relatively accessible and easy to use for specialist laboratories.[12] Human iPSCs are typically derived from donated tissue, such as skin or blood (see **Box 1**). In the UK, there is no requirement to deposit human iPSC lines with the UKSCB and their use falls outside the remit of the UKSCB Steering Committee (see '**Legislative application and gaps**' below). Researchers can access tissue from donor tissue banks, or use resource banks such as the Human-Induced Pluripotent Stem Cell Initiative (HipSci) project, which facilitates access to cell lines derived using standardised methods.[13]

Both ESCs and iPSCs are used to generate SCBEMs. ESCs and iPSCs are morphologically and functionally similar, and both can be induced to differentiate into any of the cell types within the **embryo proper**.[14] If, in the future, SCBEMs are considered for personalised therapeutic uses, for example to derive cells or tissues for transplantation, it might be beneficial that iPSC-based models are genetically identical to the cell donor.[15]

10 UK Research and Innovation (2010) *Code of practice for the use of human stem cell lines*, available at:https://www.ukri.org/wp-content/uploads/2021/08/MRC-0208212-Code-of-Practice-2010-use-of-human-stem-cell-lines.pdf

11 Takahashi K, and Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors *Cell* **126:4**: 663-76; Takahashi K, Tanabe K et al. (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors *Cell* **131:5**: 861-72.

12 Kits can be purchased online, see for example, Thermo Fisher (2024) *Stem cell reprogramming tools*, available at: https://www.thermofisher.com/uk/en/home/life-science/stem-cell-research/stem-cell-engineering-reprogramming.html

13 See HipSci (2024) *Human induced pluripotent stem cell initiative*, available at: https://www.hipsci.org/#/

14 Narsinh KH, Plews J and Wu JC. (2011) Comparison of human induced pluripotent and embryonic stem cells: fraternal or identical twins? *Molecular Therapy* **19(4)**: 635-8.

15 El País (14 June 2024) Jacob Hanna, biologist: 'If a human fetus model is controversial, I will make it without a heart or brain', available at: https://english.elpais.com/science-tech/2024-06-14/jacob-hanna-biologist-if-a-human-fetus-model-is-controversial-i-will-make-it-without-a-heart-or-brain.html

Box 1: Donation of tissue and embryos

In the UK, common law and additional provisions and safeguards added through legislation require consent for treatment, research participation, and for procedures involved in donating bodily material as a living donor. Consent to such procedures will only be valid and informed if the person giving consent:

- has the legal capacity to make the particular decision;
- has been provided with information about the nature and purpose of the procedure; and
- is acting voluntarily, without pressure or undue influence being exerted.

When consent is sought for the storage and use of a person's bodily material for research purposes, the scope of that consent can vary. The person providing the material may be asked for:

- 'specific' consent: for a particular research project or projects which can be clearly described at the time the donation is made (future use for other purposes without new consent is not usually permitted); and/or
- 'generic' or 'broad' consent: permitting use in future (approved) research projects. By definition, details of such potential projects cannot be provided at the time the consent is sought.[16] For example, in consenting to the donation of surplus embryos for research in the UK, donors are required to accept that they will have no control of future uses of any embryonic stem cell lines derived from them.[17]

The consent requirements for the creation and use of embryos and gametes are set out in the Human Fertilisation and Embryology Act 1990 (as amended), and are more stringent than for other human tissue.[18] The Act requires consent to the use of embryos donated for research for specific, named projects. The HFEA has acknowledged that this can be a barrier to research, as "the current system means any embryos donated have to be suited to the needs of the specific project(s) that their clinic has links to, not all embryos will be suitable, or some clinics may not have links to any projects for embryo donation." In 2023, the HFEA recommended that the HFE Act 1990 should be amended to allow patients to donate to a research bank to store embryos (and to revoke that consent if they wish once embryos are banked).[19]

Continued >>

16 Nuffield Council on Bioethics (2011) *Human bodies: donation for medicine and research*, available at: https://www.nuffieldbioethics.org/publications/human-bodies-donation-for-medicine-and-research

17 For an example of an embryo donor consent form, see The Francis Crick Institute (2016) *Patient information sheet: furthering our understanding of early human development for the generation of stem cells*, available at: https://www.crick.ac.uk/sites/default/files/2018-07/Consent%20and%20information%20form%201.pdf

18 Human Fertilisation and Embryology Authority (2023) *Modernising fertility law*, section 3, available at: https://www.hfea.gov.uk/about-us/modernising-the-regulation-of-fertility-treatment-and-research-involving-human-embryos/modernising-fertility-law/#section-3

19 Ibid.

There is debate about what is required for consent to be genuinely informed in the context of fast-paced research that could give rise to potentially unforeseen uses of cells and tissues. HYBRIDA, an EU-funded research project focused on regulatory approaches to organoid research and technology, identified SCBEMs as a use which might raise ethical issues for donors and might require a different consent regime (see '**Consent**' below). [20]

Methods and requirements

SCBEMs exploit the inherent capability of pluripotent stem cells to '**self-organise**' or '**self-assemble**' and embark on a developmental programme, in the right conditions. In some cases, this has happened spontaneously during the manipulation of human cells for other research purposes.[21] Devising the optimal conditions and interventions to direct this organisation towards particular stages or aspects of embryonic development may involve a combination of:

- the developmental state and quality of the pluripotent stem cells;
- the composition of **culture media**, the effect of different components (growth factors) and the timing of adding these components to the culture;
- the physiological and biophysical properties of the extracellular matrix and niche (the structure or chemical environment that supports development and growth); and
- other processes, such as co-culture with other cell types or **organoids**.[22]

Whilst we did not see evidence of successful models of the **zygote**, early cleavage or morula stages of embryo development (which normally occur within the first 4 days after fertilisation), a range of systems have been produced which model later pre-implantation stage embryonic development. This includes **blastoids**, which replicate some of the cell layers and spatial organisation, as well as some key processes and functional characteristics of a pre-implantation **blastocyst**.[23] However, they may also contain 'off-target' or abnormal cells for reasons that are not yet fully understood, and they have not successfully or completely replicated important

20 Chneiweiss H, Andreescu I, Dubart-Kupperschmitt A, *et al.* (2024) *HYBRIDA Pocket-sized informed consent for research on organoids and related fields*, available at: https://hybrida-project.eu/wp-content/uploads/2024/05/HYBRIDA-pocket-sized-informed-consent-Avril-2024_VF.pdf

21 Liu X, Tan JP, Schröder J, *et al.* (2021) Modelling human blastocysts by reprogramming fibroblasts into iBlastoids *Nature* **591(7851)**: 627-32.

22 Evidence gathering meeting on the science of stem cell-based embryo models, see Appendix **Methods of evidence gathering**.

23 Liu X, Polo JM (2024) Human blastoid as an in vitro model of human blastocysts *Current Opinion in Genetics & Development* **84**: 102135; Yu L, Wei Y, Duan J, *et al.* (2021) Blastocyst-like structures generated from human pluripotent stem cells *Nature* **591(7851)**: 620-6.

structures so far, such as the **primitive endoderm** (precursor to the yolk sac).[24]

Human embryo implantation is a complex process which involves cellular interactions ('cross-talk') between the embryo and extra-embryonic tissue within the maternal environment (including the uterine **endometrium**). Current research which aims to simulate this process ***in vitro*** is focused on improving culture protocols and co-culturing blastoids together with cultured endometrial cells.[25] Developments in organoid technology and microengineering have enabled the combination of endometrial organoids and blastoids to model attachment and invasion into the endometrial tissue.[26]

To our knowledge, no attempts have been made to transfer blastoids to the reproductive tract of a person, whether for the purpose of studying implantation or to test the potential for embryo models to develop beyond this point *in vivo* (doing so would currently be in contravention of the ISSCR guidelines, though it is not explicitly prohibited under UK law – see '**Reinforcing red lines**' below). In non-human animal research, transfers have been carried out to test the *in vivo* developmental potential of cynomolgus monkey and bovine blastoids. In both cases, indications of early pregnancy (such as hormonal responses) were detected in the female host, but the blastoids either disintegrated within 20 days of transfer or showed no signs of onward development.[27]

With respect to the **post-implantation** stages, most models replicate elements of the embryo but not the entire **conceptus**, though at least one model has been reported to show some features of a complete embryo at 13–14 days of development (**Carnegie stage** 6a).[28] Whilst we have heard that there are limitations to these studies, particularly with respect to **reproducibility**, they appear to indicate that more complete models of post-implantation embryos may soon be achievable.

The early post-implantation stage of development has also been replicated in SCBEMs that have been deliberately engineered to avoid modelling the complete

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24 Luijkx D, Shankar V, van Blitterswijk C, Giselbrecht S and Vrij E. (2022) From mice to men: generation of human blastocyst-like structures in vitro *Frontiers in Cell and Developmental Biology* **10**: 838356; Liu X, Tan JP, Schröder J, *et al.* (2021) Modelling human blastocysts by reprogramming fibroblasts into iBlastoids *Nature* **591(7851)**: 627-32.

25 Evidence-gathering meeting with Peter Rugg-Gunn, see also: Kagawa H, Javali A *et al.* (2022) Human blastoids model blastocyst development and implantation *Nature* **601**: 600–5. We note that similar experiments have been undertaken involving human embryos, see, for example: Carver J, Martin K *et al.* (2003) An *in vitro* model for stromal invasion during implantation of the human blastocyst *Human Reproduction* **18(2)**: 283–90; and Teklenburg G, Weimar CHE , *et al.* (2012) Cell lineage specific distribution of H3K27 trimethylation accumulation in an *In Vitro* model for human implantation *PLoS ONE* **7(3)**: e32701.

26 Microengineering refers to the development and use of devices smaller than a millimeter; Kagawa H, Javali, A. *et al.* (2022) Human blastoids model blastocyst development and implantation *Nature* **601**: 600–5, Shibata S, Endo S, *et al.* (2024) Modeling embryo-endometrial interface recapitulating human embryo implantation *Science Advances* **10:8**: eadi4819; Ak A, *et al.* (2024) Implantation-on-chip: precise quantification for functional implantation failure studies *Human Reproduction* **39(Supplement 1)**: O-097; Rawlings TM, Makwana K, *et al.* (2021) Organoids to model the endometrium: implantation and beyond *Reproduction and Fertility* **2(3)**: R85–101.

27 Li J, Zhu Q, Cal J, *et al.* (2023) Cynomolgus monkey embryo model captures gastrulation and early pregnancy *Cell Stem Cell* **30(4)**: 362-77.e7; and Pinzon-Arteaga CA, Wang Y, Wei Y, *et al.* (2023) Bovine blastocyst-like structures derived from stem cell cultures *Cell Stem Cell* **30(5)**: 611-16e7.

28 Oldak B, Wildschutz E, Bondarenko V, *et al.* (2023) Complete human day 14 post-implantation embryo models from naive ES cells *Nature* **622(7983)**: 562-73.

human embryo (lacking primitive endoderm and the **trophoblast**, and therefore unable to form a yolk sac or placenta). This model mimicked successive key early human post-implantation developmental landmarks in the formation of the embryo, **amnion**, and **amniotic cavity**, as well as primordial germ cells (the precursor to gametes), and the cell movements associated with gastrulation.[29]

Gastrulation begins around day 14 and is the process by which the three **germ layers** form and a 'body plan' emerges. Gastruloids have been generated that closely resemble some parts of an embryo at around 18-21 days old, but lack other parts, such as the region where the brain develops. Research aiming to create a more complete model of gastrulation has yielded peri-gastruloids which recapitulate developmental processes from the immediate post-implantation stage through to early organogenesis and contain some (but not all) extra-embryonic tissues.[30]

Challenges for the categorisation and definition of SCBEMs

'**Stem cell-based embryo models**' is an umbrella term for a variety of structures with different features and uses in research. In current ISSCR guidance, SCBEMs are described as experimental systems which "make possible the assembly, differentiation, aggregation, or re-association of cell populations in a manner that models or recapitulates key stages of embryonic development".[31]

SCBEMs vary greatly in their level of complexity and the extent to which they mimic (i.e. look or function like) complete embryos, as opposed to particular parts or aspects of embryonic development.

We heard that there is a significant grey area between SCBEMs and other types of stem cell-based **organoids**, some of which model embryonic or fetal-stage organs or tissues.[32] Indeed, some SCBEMs might be cultured for the purpose of developing models of cells, tissues or whole organs at later stages of development. Furthermore, while much is still unknown, for example about the mechanisms by which stem cells organise and respond to different conditions, it is not always possible to predict the outcome of experiments. For example, in 2021, a research group reported the unexpected formation of a blastoid in culture which they had created for a different purpose.[33] There is currently no comprehensive register or database for such

29 Zheng Y, Shao Y and Fu, J. (2021) A microfluidics-based stem cell model of early post-implantation human development *Nature Protocols* **16(1)**: 309–26.

30 Liu L, Oura S, Markham Z, *et al.* (2023) Modeling post-implantation stages of human development into early organogenesis with stem-cell-derived peri-gastruloids *Cell* **186(18)**: 3776-92.e16.

31 International Society for Stem Cell Research (2021) *ISSCR guidelines for stem cell research and clinical translation*, available at: https://www.isscr.org/guidelines

32 See for example the range of methods described as having achieved a "partial reconstitution" of the human or mouse embryo in Nicolas P, Etoc F, and Brivanlou AH (2021) The ethics of human-embryoids model: a call for consistency *Journal of Molecular Medicine* **99**: 569–79.

33 Liu X, Tan JP, Schröder J, *et al.* (2021) Modelling human blastocysts by reprogramming fibroblasts into iBlastoids *Nature* **591(7851)**: 627-32.

research which would provide an overview of what is being developed in laboratories in the UK or internationally.[34]

Given this uncertainty and lack of oversight, it is difficult at this point to draw clear technical boundaries between or around SCBEMs. However, efforts have been made to organise SCBEMs into broad categories informed by ethically significant characteristics. The ISSCR guidelines are under review and may soon be updated, but the current version relies on the following distinction between integrated and non-integrated models:[35]

> **"Non-integrated stem cell-based embryo models: These stem cell-based embryo models will experimentally recapitulate some, but not all aspects of the peri-implantation embryo, for example differentiation of the embryonic sac or embryonic disc in the absence of extra-embryonic cells. These stem cell-based embryo models do not have any reasonable expectations of specifying additional cell types that would result in formation of an integrated embryo model. Gastruloids are an example of a non-integrated stem cell-based embryo model.**
>
> **Integrated stem cell-based embryo models: These stem cell-based embryo models contain the relevant embryonic and extra-embryonic structures and could potentially achieve the complexity where they might realistically manifest the ability to undergo further integrated development if cultured for additional time in vitro. [...] A guiding principle of review should be that the integrated stem cell-based embryo models should be used to address a scientific question deemed highly meritorious by a rigorous review process. Blastoids are an example of an integrated stem cell model."** [36]

We heard a number of challenges to this distinction on a technical basis:

- Some models cannot straightforwardly be classified as one or the other, but exist on a spectrum with varying presence and proportions of extra-embryonic cell populations.[37]
- The distinction might not be stable even within a single study, as embryo models are modular and could be adapted from a simpler to a more complex model.
- The reliance on extra-embryonic structures as an indicator of developmental potential (potential for onward development) does not account for possible

34 The UK SCBEM Code proposes that a UK register should be established. See Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode

35 See International Society for Stem Cell Research press release (17 June 2024) *The ISSCR forms embryo models working group*, available at: https://www.isscr.org/isscr-news/the-isscr-forms-embryo-models-working-group

36 International Society for Stem Cell Research (2021) *Guidelines for stem cell research and clinical translation*, available at: https://www.isscr.org/guidelines/glossary

37 Moris N (2023) Stem cells used to model a two-week-old human embryo *Nature* **622(7983)**: 469-70.

improvements in culture which could enable a complex model to be sustained in vitro without depending on these tissues (for example, to support gas and nutrient exchange).[38]

We return to the governance implications of these challenges in '**International guidance**' below.

Terminology

A range of terms has been used to describe SCBEMs. A Dutch study on public perceptions found that participants wanted the term to reflect these structures' (dis) similarity to human embryos.[39] 'Synthetic embryo' is a term often used by media outlets,[40] but was felt to be inaccurate on the basis that SCBEMs were perceived to be neither synthetic nor embryos.[41] 'Artificial embryos' could be taken to suggest an entity that functions like an embryo which, as set out above, currently SCBEMs do not.

'Embryoids' is the term preferred by the French Agence de la biomédecine, as set out in a 2023 report on SCBEMs by their Conseil d'orientation, and there was some support for it in our working group.[42] The suffix 'oid' means having the likeness of, without being the same, and is already used in the case of '**blastoid**' and '**gastruloid**'. One other advantage to this term is that it is aligned with other stem cell uses, such as the development of organ*oids*, some of which may raise overlapping ethical issues. An example of this might be if a neural organoid were to become capable of developing morally relevant features, such as consciousness or sensing pain.[43] Another advantage is its simplicity, which makes it easily subsumed into ordinary language.

However, a problem with using 'embryoid' in this context is that it may generate confusion with the scientific term '**embryoid body**', which describes simpler, semi-organised structures formed by the spontaneous differentiation of stem cells.[44] Additionally, a public dialogue by Cambridge Reproduction and the Progress Educational Trust refers to the potential for the term 'embryoid' to cause confusion as it could imply that an embryoid functions in all the same ways as an embryo and

38 For example, we heard that post-implantation mouse embryos can develop in culture for 72 hours without a placenta, see Aguilera-Castrejon A, Oldak B, Shani T, *et al.* (2021) Ex utero mouse embryogenesis from pre-gastrulation to late organogenesis *Nature* **593**: 119–24.

39 Pereira Daoud AM, Dondorp WJ, Bredenoord AL and de Wert GMWR (2022) Dutch perspectives on the conceptual and moral qualification of human embryo-like structures: a qualitative study *Humanities & Social Sciences Communications* **9(1)**: 151.

40 See, for example, Nature News (16 June 2023) *Most advanced synthetic human embryo models yet spark controversy*, available at:https://www.nature.com/articles/d41586-023-01992-0

41 See, for example, International Society for Stem Cell Research press release (26 June 2023) *The ISSCR statement on new research with embryo models*, available at: https://www.isscr.org/isscr-news/isscr-statement-on-new-research-with-embryo-models

42 Agence de la Biomédecine (2023) *Opinion of the Conseil d'orientation: stem cell-based embryo models*, available at: https://www.agence-biomedecine.fr/IMG/pdf/22-06_avis_du_co_embryoi_des_eng-2.pdf (Note: this is a translation).

43 At the time of writing, a separate Nuffield Council on Bioethics project is underway entitled 'Research using neural organoids' – see https://www.nuffieldbioethics.org/publications/neural-organoids-in-research

44 See, for example, Rungarunlert S, Techakumphu M, Pirity MK and Dinnyes A (2009) Embryoid body formation from embryonic and induced pluripotent stem cells: Benefits of bioreactors. *World Journal of Stem Cells* **1(1)**: 11-21.

inaccurately convey broad equivalence.[45] 'Stembryo' or 'stembryoid' might avoid suggestions of equivalence with the embryo, but at the cost of clarity. Participants in the public dialogue were clear that what is key is that the term, as far as possible, does not mislead.

The term 'stem cell-based embryo model', which is used by the ISSCR and the UK SCBEM Code, has gained traction. The term makes clear its origins (stem cells), the intention (to create a model rather than an embryo) and what is being modelled (the embryo or aspects of it). Acknowledging the importance of consistency across formal frameworks and guidelines, the members of our working group preferred 'SCBEM', which we have therefore adopted in this report.

Contribution and potential uses

SCBEMs are an emerging technology at an early stage of development, and it is not possible to predict with accuracy what applications will be realised and when they might be expected. This section notes both current promising research avenues and more speculative future applications.

SCBEMs provide opportunities for studying aspects of early human development that are difficult to access *in vivo* for practical and legal reasons, and to do this at scale, which is not possible using human embryos. This has the potential to increase understanding of the mechanisms of early human development. It has been suggested that, in time, this might give rise to new insights into causes of miscarriage and infertility, pregnancy complications, and developmental anomalies with detrimental effects on human health that arise in this period.[46] Blastoids appear to be particularly useful for studying important aspects of early implantation. Researchers have proposed that insights from such studies might be used both to improve IVF success rates and to produce new forms of contraception.[47] They might also contribute to studies to improve culture media and embryo selection criteria for IVF.[48] Combined with endometrial organoids, SCBEMs could be used to model the impact of the maternal environment on the early stages of embryonic development.[49]

45 Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

46 Rossant J, and Tam PLP (2021) Opportunities and challenges with stem cell-based embryo models *Stem Cell Reports* **16(5)**: 1031-8, Boiani *et al*. on the causes of infertility which arise in gametes, the process of fertilisation and the first cleavage stages: Boiani M, MHR-ISSCR guidelines working group (2024) The future of embryoids from a reproductive science perspective *Molecular Human Reproduction* **30(2)**: gaae009.

47 Austrian Academy of Sciences press release (2 December 2021) *Breakthrough research on human blastoids and impact on IVF and contraception*, available at: https://www.oeaw.ac.at/imba/research-highlights/news/breakthrough-research-on-human-blastoids-and-impact-on-ivf-and-contraception; and Kagawa H, Javali A, Heidari Khoei H, *et al*. (2021) Human blastoids model blastocyst development and implantation *Nature* **601(7894)**: 600-5.

48 Liu X, Polo JM (2024) Human blastoid as an in vitro model of human blastocysts *Current Opinion in Genetics & Development* **84**: 102135

49 Boiani M, MHR-ISSCR guidelines working group (2024) The future of embryoids from a reproductive science perspective *Molecular Human Reproduction* **30(2)**: gaae009.

Post-implantation models, such as gastruloids, have the potential to shed light on a period between day 14 and day 28, which is sometimes described as the 'black box' of human development because it is very difficult to study. In the UK, this is because the '14-day rule' restricts the culturing of human embryos for research purposes to 14 days, and only very few embryos at this stage of gestation have become available for study following miscarriage or termination.[50] Key references in use, such as the Carnegie Stages Collection, are valuable but limited to observable morphological features.[51]

A particular benefit for research is that SCBEMs can be generated in large numbers. They can also be genetically or otherwise physically modified, and the effects of such modifications can be studied alongside unmodified, genetically-identical counterparts (controls).[52] This possibility allows for larger-scale systematic study, and has, for example, been exploited in research which aims to understand the mechanisms of rare events, such as twinning.[53] We also heard that this makes embryo models particularly suitable for studying the impact of environmental factors or exposure to toxins or drugs. For example, one study found that gastruloids responded similarly to human embryos when exposed to a number of pharmaceutical compounds, such as ibuprofen, penicillin and thalidomide.[54] It is hoped that this could increase efficiency in further testing by, for example, helping drug developers to predict with more certainty where clinical trials might be valuable.[55] It is also hoped that SCBEMs could advance toxicology testing to address the paucity of research on the safety of medicines during pregnancy.[56]

Some researchers are exploring the potential for SCBEMs to be used in regenerative therapies; for example, to produce cells or tissues for transplantation.[57] We also

50 Tyser RCV, Mahammadov E, *et al.* (2021) Single cell transcriptomic characterization of a gastrulating human embryo *Nature* **600(7888)**:285–9; See Nuffield Council on Bioethics (2017) *Human embryo culture: discussions concerning the statutory time limit for maintaining human embryos in culture in the light of some recent scientific developments*, available at: https://www.nuffieldbioethics.org/publications/time-limits-on-maintaining-human-embryos-in-research, for a discussion of the 'black box' of embryonic development as justification for extending the 14-day limit.

51 O'Rahilly R and Müller F (2010) Developmental stages in human embryos: revised and new measurements *Cells Tissues Organs* **192(2)**: 73-84. See also HDBR Atlas (2024) *Carnegie staging criteria*, available at: https://hdbratlas.org/staging-criteria/carnegie-staging.html

52 Liu X, Polo JM (2024) Human blastoid as an in vitro model of human blastocysts *Current Opinion in Genetics & Development* **84**: 102135.

53 Luijkx DG, Ak A, Guo G, *et al.* (2024) Monochorionic twinning in bioengineered human embryo models *Advanced Materials* **36(25)**: 2313306.

54 Mantziou V, Baillie-Benson P, Jaklin M, *et al.* (2021) In vitro teratogenicity testing using a 3D, embryo-like gastruloid system *Reproductive Toxicology* **105**: 72-90.

55 The Francis Crick Institute press release (24 August 2021) *How embryo-like stem cell models could be used in drug safety tests*, available at: https://www.crick.ac.uk/news/2021-08-24_how-embryo-like-stem-cell-models-could-be-used-in-drug-safety-tests; Marikawa Y (2022) Toward better assessments of developmental toxicity using stem cell-based in vitro embryogenesis models. *Birth Defects Research* **114(16)**: 972-82.

56 University of Birmingham and Birmingham Health Partners (2022) *Healthy mum, healthy baby, healthy future: the case for UK leadership in the development of safe medicines for use in pregnancy*, available at: https://www.birminghamhealthpartners.co.uk/healthy-mum-healthy-baby-healthy-future/

57 See, for example, MIT Technology Review (4 August 2022) *This startup wants to copy you into an embryo for organ harvesting* blog, available at: https://www.technologyreview.com/2022/08/04/1056633/startup-wants-copy-you-embryo-organ-harvesting/; El País (14 June 2024) *Jacob Hanna, biologist: 'If a human fetus model is controversial, I will make it without a heart or brain'*, available at: https://english.elpais.com/science-tech/2024-06-14/jacob-hanna-biologist-if-a-human-fetus-model-is-controversial-i-will-make-it-without-a-heart-or-brain.html#

heard that fertility centres are interested in the potential use of SCBEMs to improve fertility treatment, for example for training purposes or to improve techniques to freeze and thaw embryos.[58] More speculatively, it could become possible in theory to develop SCBEMs alongside other technologies for future reproductive use.[59] This raises a different set of ethical considerations because of, for example, the potential to affect a future person.[60] We consider whether transfer to a human host should be countenanced in the governance framework later (see '**Reinforcing red lines**' below).

We noted frequent suggestions in the literature that SCBEMs offer an *alternative* to human embryo research, or that they have the potential to reduce reliance on human embryo research. However, the predominant view among stakeholders we spoke to was that SCBEMs should be seen as complementary to embryo research, not a replacement.[61] For example, as fertilisation and the earliest stages of embryonic development cannot currently be replicated in SCBEMs, the study of embryo failure or developmental issues that arise at these stages still require human gametes and embryos.[62] We heard that the use of some SCBEMs might be just as likely to drive increased use of human embryos and non-human animal models, for example to validate or test hypotheses arising from SCBEM research.[63]

Scientific challenges and bottlenecks

A current challenge for research is the ability to generate and sustain the development of some structures or cell lineages, such as extra-embryonic tissue lineages.[64] These tissue types do not only play a role in facilitating implantation, but are also thought to drive patterning and cell differentiation processes within the epiblast during gastrulation. Some studies have compensated for this by modifying some cells or adding extra-embryonic tissue stem cells which have been derived separately, to generate **assembloids**, albeit with low reproducibility. However, we also heard that due to their 'modular' nature, the scientific utility of post-implantation models such as

58 Interview with Peter Rugg-Gunn.

59 One example our working group considered was an imagined scenario in which an embryo from a couple is used to derive pluripotent stem cells (PSCs) – which could be genetically altered to address a particular problem such as recurrent miscarriage or early embryo arrest – that could then be used to derive one or more SCBEMs for uterine transfer. Such an approach might be relevant if it is shown that genetically altering PSCs is more efficient and safer than manipulating the embryo directly. In future, such PSCs might also be used to perform gametogenesis in vitro.

60 Savulescu J, Labude M, *et al.* (2022) Two kinds of embryo research: four case examples *Journal of Medical Ethics* **48(9)**: 590-6.

61 This view is also reflected in Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode

62 Boiani M, MHR-ISSCR guidelines working group (2024) The future of embryoids from a reproductive science perspective *Molecular Human Reproduction* **30(2)**: gaae009.

63 This possibility was raised during our evidence gathering meeting with interdisciplinary experts, see Appendix **Methods of evidence gathering**.

64 Dupont C (2024) A comprehensive review: synergizing stem cell and embryonic development knowledge in mouse and human integrated stem cell-based embryo models *Frontiers in Cell and Developmental Biology* **12**: 1386739.

gastruloids might not require the presence of all extra-embryonic tissues.[65]

Reproducibility and efficiency are key challenges for current SCBEM research. However, we heard that this might be expected to improve as the research field matures. In many published studies, methodologies used are mostly described and reproducible across research groups. However, many studies rely on commercially-produced culture media, the composition of which is proprietary and not made public.[66]

We heard that there is a need for a range of ancillary technologies to develop alongside stem cell science to support SCBEM development in the longer term. Appropriate culture media was highlighted as a field where supply is lagging behind demand. It was posited that supply chain issues may be resolved as the field becomes more established and commercial providers increase investment. Laboratories may also begin in-house production of the materials needed (assuming the culture media for SCBEM research will not be subject to the same strict requirements as those developed for clinical embryology).[67]

Ultimately, the value of SCBEM research will greatly depend on the extent to which it can be validated. This in turn will depend on expanding knowledge of how human embryos develop, including greater understanding of 'normal' variation in the timing and characteristics of healthy embryonic development.[68] As we discussed in the previous section, it was clear from what we heard that there is no current prospect of SCBEMs being considered equivalent to, or having the potential to replace, the use of human embryos in research. However, efforts are underway to establish criteria for the evaluation of SCBEMs with respect to their reproducibility and their fidelity to natural embryos (see **Box 2**). According to Martinez Arias *et al.*:

> **"These models of mammalian embryogenesis need not generate an exact replica of natural embryos to warrant their utility in research. However, they should be sufficiently close to their in vivo counterparts, such as comprising the correct constituent cell types and displaying the structural organization of the natural embryo, as well as being amenable to experimentation, to provide informative and actionable new knowledge of development."** [69]

65 Martinez Arias A (2024) *Gastruloids: a pluripotent stem cell model of gastrulation and body plan engineering in development and disease*, presentation at ESHRE Annual Meeting 2024, abstract available at: https://academic.oup.com/humrep/article/39/Supplement_1/deae108.202/7703589; Turner DA and Martinez Arias A (2024) Three-dimensional stem cell models of mammalian gastrulation *BioEssays* e2400123 (Epub ahead of print).

66 Rugg-Gun P, Mori N and Tam PLP (2023) Technical challenges of studying early human development *Development* **150(11)**: dev201797.

67 See for example Turner DA and Martinez Arias A (2024) Three-dimensional stem cell models of mammalian gastrulation *BioEssays* e2400123 (Epub ahead of print).

68 Discussed at our roundtable on scientific developments, see appendix **Methods of evidence gathering**.

69 Martinez Arias A, Rivron N, Moris N *et al.* (2024) Criteria for the standardization of stem-cell-based embryo models *Nature Cell Biology* **26(10)**: 1625-8.

Box 2: Criteria for evaluating the fidelity of human stem cell-based embryo models

In a 2024 paper, a group of developmental biologists proposed a set of benchmarking criteria for the evaluation of SCBEMs:

- the cellular composition and cellular states, as determined by transcriptome and, where appropriate, additional modalities (for example, proteome, metabolome);
- the spatial organisation of cell types in the modelled structure and, where relevant, sub-structures (for example, somites, neural tube);
- the morphology of the complete structure and, where relevant, its components (for example, individual organ primordia);
- the spatiotemporal sequence of morphogenetic events; and
- the matching of developmental stages to the target on the basis of these criteria.

Martinez Arias A, Rivron N, Moris N, et al. (2024) Criteria for the standardization of stem-cell-based embryo models *Nature Cell Biology* **26(10)**: 1625-8.

The scientific context

Notwithstanding the challenges described in the section above, the scientists we spoke to were clear that SCBEM research is advancing rapidly and that the pace is likely to accelerate as experience and interest builds.[70] The field is international, with prominent research groups based in Austria, France, the Netherlands, Spain, Israel, China, Japan and the US, as well as the UK.

We heard of extensive collaboration across research groups, and efforts to establish joint principles and research standards.[71] However, we also heard concerns about competition and pressure to publish. Some felt that this could drive the premature publication of work before the reproducibility and robustness of the findings are fully established, potentially contributing to a degree of sensationalism in some media coverage of the research.[72] Many scientists working in this field have a keen

70 Discussed at our roundtable on scientific developments, see appendix **Methods of evidence gathering**.

71 See for example Rivron NC, Martinez Arias A *et al.* (2023) An ethical framework for human embryology with embryo models Cell 186(17): 3548-57; Martinez Arias A, Rivron N, Moris N *et al.* (2024) Criteria for the standardization of stem-cell-based embryo models *Nature Cell Biology* **26(10)**: 1625-8. We note that this is not unique to the field of SCBEM research. In other research areas, international committees have emerged to produce guidelines on minimal information required for acceptable research; for example, minimal information for studies of extracellular vesicles (MISEV), see International Society for Extracellular Vesicles (2023) *MISEV 2023*, available at: https://www.isev.org/misev; and minimum information for biological and biomedical investigations (MIBBI), see Digital Curation Centre (2024) MIBBI – *minimum information for biological and biomedical investigations*, available at: https://www.dcc.ac.uk/resources/metadata-standards/mibbi-minimum-information-biological-and-biomedical-investigations

72 Rivron NC, Martinez Arias A, *et al.* (2023) Changing the public perception of human embryology. *Nature Cell Biology* **25**:1717–9.

awareness of the potential impact (opportunity and threat) of wider perceptions of this technology.[73] We have seen this reflected within scientific forums, where the need to communicate clearly and accurately, in order to encourage public trust in science and ensure that public discourse is well-informed, is prominently and widely discussed.[74]

The conditions for this research to flourish also depend on a facilitative governance regime with respect to emerging technologies generally, the governance of ESCs, and the legal status of SCBEMs (see '**Legislative application and gaps**' and '**The legal status of SCBEMs**'). Whether SCBEMs are defined as human embryos, and subject to the same or similar restrictions, clearly has a significant impact on what type of research is possible and where it takes place. It can also affect funding. Public funding programmes in the US and the EU (including Horizon Europe) exclude any research from their eligibility criteria that involves the destruction of human embryos (though privately-funded research in the US is not so restricted).[75] Internationally, insofar as SCBEMs are considered to fall outside the definition of embryos and the regulatory frameworks that govern embryo research, it appears that scientists are nevertheless approaching any SCBEM research which may be perceived as crossing lines applicable to embryo research with caution, such as legal limits on embryo culture.

The public context

Public perceptions of SCBEM research are likely to be influenced by the ways in which it is communicated.[76] Media reporting of SCBEM research raises public awareness and can enhance collaboration and public science literacy, and boost investment by attracting attention from funders and investors.[77] However, if claims are exaggerated, it can also lead to misconceptions and misinterpretation, which can erode public trust. Scientists have an important role to play in improving public understanding.[78]

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73 See for example Zernicka-Goetz M and Hyun I (2024) Embryo models need consistent ethical oversight *Nature* **630**: 305; Nicolas P, Etoc F and Brivanlou AH (2021) The ethics of human-embryoids model: a call for consistency *J Mol Med* **99**, 569–79; Rivron NC, Martinez Arias A, Sermon K, *et al.* (2023) Changing the public perception of human embryology *Nature Cell Biology* **25(12)**: 1717–19.

74 Rivron NC, Martinez Arias A, Sermon K, et al. (2023) Changing the public perception of human embryology *Nature Cell Biology* **25(12)**: 1717–19.

75 Matthews KRW, Morali D (2022) Can we do that here? An analysis of US federal and state policies guiding human embryo and embryoid research *Journal of Law and the Biosciences* **9(1)**: lsac014; and 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, available at: https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en

76 Rivron NC, Martinez Arias A, *et al.* (2023) Changing the public perception of human embryology. *Nature Cell Biology* **25**:1717–9.

77 Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: https://www.nuffieldbioethics.org/publications/emerging-biotechnologies

78 Rivron NC, Martinez-Arias A, Sermon K, *et al.* (2023) Changing the public perception of human embryology *Nature Cell Biology* **25(12)**: 1717–19.

Public perceptions of SCBEMs inform strategies for governance. While wider public discussion of SCBEM research has so far been limited, a small number of studies have explored public perceptions of SCBEMs:

- A Dutch study conducted in 2020-2021 by Ana M Pereira Daoud *et al*. consisted of a focus group with health law and ethics professionals, three focus groups with a representative selection of lay citizens, and five in-depth interviews to consider different religious and humanist perspectives.[79]
- A 2023 Human Developmental Biology Initiative (HDBI) public dialogue on human embryo research, co-funded by the UK Research and Innovation (UKRI) programme Sciencewise, engaged with participants broadly reflective of the UK population and those with relevant lived experience.[80]
- A January 2024 public dialogue on the governance of research involving stem cell-based embryo models (hereafter referred to as the 'UK G-SCBEM public dialogue') commissioned by Cambridge Reproduction and co-funded by UKRI Sciencewise. This followed from the HDBI dialogue, with around 38 of the previous 70 members of the public participating, and was aimed at informing the development of the UK SCBEM Code of Practice.[81]

These initiatives offer valuable initial insights, which we have referred to at various points in this report.

The commercial context

The Patents Act 1977 was amended to implement the European Directive 98/44/EC on the patentability of biotechnological inventions in UK law. Article 6(2)(c) of the Directive renders inventions unpatentable "where their commercial exploitation would be contrary to *ordre public* or morality". The *Brüstle* decision of the Court of Justice of the European Union[82] ruled that Article 6(2)(c) of the Directive prevents human embryos – defined as organisms "capable of commencing the process of development of a human being" – from being patented for commercial purposes. Following this decision, the UK has made clear that the Intellectual Property Office will not patent uses of human embryos for commercial purposes, or inventions that require the destruction of human embryos. It will, however, allow patents of human stem cells not derived from human embryos, including iPSCs and inventions for clinical purposes, such as treatment and diagnosis.[83]

79 Pereira Daoud AM, Dondorp WJ, Bredenoord AL and de Wert GMWR (2022) Dutch perspectives on the conceptual and moral qualification of human embryo-like structures: a qualitative study *Humanities & Social Sciences Communications* **9(1)**: 151.

80 HDBI (2023) *Public dialogue on early human embryo research*, available at: https://hdbi.org/public-dialogue

81 Hopkins Van Mil (2024) *Addressing the governance gap: a public dialogue on the governance of research involving stem cell-based embryo model*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

82 *Oliver Brüstle v Greenpeace* [2011] Case C-34/10.

83 Intellectual Property Office (25 March 2015) *Statutory guidance: inventions involving human embryonic stem cells: 25 March 2015*, available at: https://www.gov.uk/government/publications/inventions-involving-human-embryonic-stem-cells-25-march-2015/inventions-involving-human-embryonic-stem-cells-25-march-2015

Jonathan Lewis and Søren Holm note that "if medical technologies were to be developed in future that required or involved the distribution of embryo models then ... the question of the patentability of such technologies in the EU/EEA may be considered as turning on whether these human embryo models are deemed to be human embryos".[84] Though patentability of related medical technologies may be some way off, we later consider arguments for a regulatory distinction between SCBEMs and embryos, coupled with a reinforcement in law of the scientific intention that SCBEMs will not for the foreseeable future be developed for reproductive purposes (see '**A proposal for a regulatory classification**' below). Together these proposals have the potential to stabilise the classification of SCBEMs and encourage investment in them.

Previous Nuffield Council on Bioethics (NCOB) work has highlighted the need for patent protections to be sufficiently long to allow innovators in emerging biotechnologies to recover the costs of developing their successful products – and offsetting the costs of those that failed – without providing overly-broad protection that could stifle competing research and innovation.[85]

The UK G-SCBEM public dialogue noted that:

> **"Misuse of embryo models was a concern voiced frequently and a term used when participants described their concerns about the research being used for profit rather than public benefit."** [86]

> **"Some participants assume that the research will inevitably, over time, involve those with commercial as well as public sector interests. This gives rise, in their view, to a potential harm from a profit motive. They see a risk in commercial interests, for example private clinics offering enhanced IVF techniques developed through research involving embryo models for a higher fee, private medical practices treating cancer, or private research laboratories dominating the research agenda because they have the funds. They see this as potentially undermining a public sector research ethos focused on addressing key issues for all society by making the discoveries from research involving embryo models available only to those who can afford them."** [87]

84 Lewis J and Holm S (2024) *HYBRIDA Project D6.2: Regulating organoid and organoid-related activities: proposals to address regulatory gaps and areas of over-regulation*, available at: https://hybrida-project.eu/deliverables/, and Durham CELLS blog (pre-publication) *Patents & stem cell based embryo models in Europe: The need for nuanced bioethics scrutiny?*, available at: https://www.durham.ac.uk/research/institutes-and-centres/ethics-law-life-sciences/about-us/news/cells-blog/

85 Nuffield Council on Bioethics (2013) *Emerging biotechnologies: technology, choice, and the public good*, available at: https://www.nuffieldbioethics.org/publications/emerging-biotechnologies

86 Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

87 Ibid.

A careful balance is required between social costs and benefits of commercialisation.[88] Patents limit access to, and place restrictions on, the practice of protected inventions, but they also promote investment that can make development possible. Later, we recommend measures that will help achieve this balance by establishing a clear regulatory dividing line between embryos and SCBEMs, governed by bespoke and targeted measures (see '**A proposal for a regulatory classification**' below).

88 See McMahon A (2022) The 'ethical' regulation of 'novel being' technologies: the potential role for patents and ethical drivers, blockers and guiders? In *Novel beings: regulatory approaches for a future of new intelligent life*, Morley S and Lawrence DR (Editors) (Cheltenham: Edward Elgar Publishing), chapter 7.

II. Ethical considerations

In this section, we set out a range of ethical considerations drawn from discussion in the literature and from our engagement with ethicists and scientists, to inform how SCBEMs should be treated and used.

SCBEM research: what matters?

Ethical debate about the moral status of the embryo at different stages of development, combined with the varied extent to which the embryo is emulated in SCBEM research and speculation as to the concerns that might arise as the research advances, make consensus on the ethics of SCBEM research difficult to achieve. In this subsection, we focus on 'what matters' or, more accurately given uncertainties around future development, 'what *might* matter'. We apply these factors in the subsequent section to guide our approach to the governance of SCBEMs.

Public interest, transparency and accountability

As we've explored, SCBEMs are thought to be valuable research tools with the potential to increase knowledge about early human development and may result in findings or applications that improve human health and wellbeing (see '**Contribution and potential uses**' above). The potential utility of SCBEMs provides an ethical argument in favour of developing them – albeit in a carefully controlled and regulated environment – for reasons we set out in the sections that follow.[89]

Nevertheless, it is important to note that there is considerable uncertainty about the range of possible outcomes of SCBEM research and the likelihood that they will arise. There is a risk that over-promise and hype may raise expectations both of benefits and harms that may never materialise.[90]

89 For example, akin to what Savulescu *et al.* call a "moral imperative", see Savulescu J, Labude M, Barcellona C, *et al.* (2022) Two kinds of embryo research: four case examples *Journal of Medical Ethics* **48(9)**: 590-6.

90 For a discussion of the characteristics of emerging biotechnologies, see Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: https://www.nuffieldbioethics.org/publications/emerging-biotechnologies

We have noted above that SCBEMs include a diverse range of models with varying features. Current guidelines for SCBEM research assume that some types of SCBEM are more ethically concerning than others and therefore require greater levels of oversight.[91] However, if the categories on which oversight mechanisms are based are (or become, due to unforeseen developments) ill-defined, the consequence could be that some research is subject to disproportionate levels of oversight. The costs of this might include inefficiency in the governance system and lost opportunities if research is disincentivised. It could also mean that research which might raise significant ethical concerns 'flies under the radar'.

Increased transparency about all types of SCBEM research should contribute to a better technical understanding of different types of SCBEMs, their features and potential applications. This in turn could form the basis for a more robust, ongoing appraisal of the benefits, risks and costs of both the research and how it is (or is not) governed.[92]

Notwithstanding current uncertainty about what types or features of model might raise greater or lesser moral concern, there are features of SCBEMs as a field of research which might be of public interest. An obvious example is the public interest in the potential benefits that SCBEM research might bring, as discussed earlier (see '**Contribution and potential uses**' above). Another consideration is that the creation of SCBEMs relies on public systems that facilitate donation and access to donated human tissue, and on the extent to which people are prepared to donate. Individuals' motivations to donate to research vary, but research has identified the importance of communal values, such as altruism and solidarity, as well as trust in research and research governance systems.[93]

SCBEM research also involves the control or manipulation of natural processes (i.e. those involved in early human development) and could raise questions of the kind highlighted in a previous NCOB report with respect to emerging biotechnologies more generally, for example:

> **" (...) questions about who exercises such control, their motives, and the quality of their judgment. There may be questions of accountability and vested interest concerning the motives of particular scientists, private firms or public research sponsors, advisors or governments".**[94]

Such questions were raised by participants in the UK G-SCBEM public dialogue. For example, some expressed concerns about commercial interests and profit motives,

91 Lovell-Badge R, Anthony E, Barker RA *et al.* (2021) ISSCR Guidelines for Stem Cell Research and Clinical Translation: The 2021 update *Stem Cell Reports* **16(6)**: 1398-1408.

92 Spyrakou E and Stavridi V (2022) *HYBRIDA Project D8.4: Embedding a comprehensive ethical dimension to organoid-based research and relating technologies*, available at: https://hybrida-project.eu/deliverables/

93 Nuffield Council on Bioethics (2011) *Human bodies: donation for medicine and research*, available at: https://www.nuffieldbioethics.org/publications/human-bodies-donation-for-medicine-and-research

94 Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: https://www.nuffieldbioethics.org/publications/emerging-biotechnologies

and about potential uses of the SCBEMs for unacceptable purposes or to bring about an undesirable future.[95]

Given the potential costs and benefits involved, there is arguably a public stake in SCBEM research and an ethical case for both accountability and oversight of those involved, and for oversight and accountability mechanisms to be informed by open and inclusive public discussion about the research.

Potential

The question of 'potential' – the extent to which, in the right conditions, SCBEMs have the capacity to develop into a human being or to develop other morally significant features – is a key point of debate in the ethical discourse around this research.

Potential for reproductive use

We have not seen evidence of any research with the explicit purpose of developing SCBEMs for procreative use, nor of any attempts to transfer SCBEMs to the reproductive tract of a person to test their potential for onward development *in vivo*. Such an experiment would fall under the category of prohibited research activities in the 2021 ISSCR guidelines on the basis that they "lack a compelling scientific rationale and are widely considered to be unethical".[96] There appears to be broad consensus that even if it became theoretically possible for SCBEMs to implant and develop *in vivo*, this would necessitate extensive and highly risky clinical testing, which would be considered unjustified and unacceptable.[97] Should the significant issues concerning safety and risk be resolved in the future, wide and inclusive societal debate about the justification and ethical acceptability of SCBEMs as a reproductive technology would be important.

The significance of developmental potential in vitro

The working group noted that a distinction can be drawn between reproductive potential (for example, the potential for transfer and onward development *in utero*) and potential to develop (for example, in terms of what is possible longer term in culture), whilst noting that full ectogenesis – if possible and permitted – would collapse the distinction.

The extent to which potential to develop is relevant for appraising the moral status of SCBEMs is subject to debate.[98] Some argue that the theoretical potential of

95 Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

96 International Society for Stem Cell Research (2021) *ISSCR guidelines for stem cell research and clinical translation*, available at: https://www.isscr.org/guidelines

97 Nicolas P, Etoc F, and Brivanlou AH (2021) The ethics of human-embryoid model: a call for consistency *Journal of Molecular Medicine* **99(4)**: 569-79; Anifandis G, Sutovsky P, Turek PJ, *et al.* (2022) Bioethics in human embryology: the double-edged sword of embryo research.

98 Devolder K and Harris J (2005) The ambiguity of the embryo: ethical inconsistency in the human embryonic stem cell debate. *Metaphilosophy* **38(2-3)**: 153-69; Pereira Daoud AM, Dondorp WJ, Bredenoord AL, *et al.* (2024) Potentiality switches and epistemic uncertainty: the Argument from Potential in times of human embryo-like structures *Med Health Care and Philos* **27(1)**: 37-48; Piotrowska M (2020) Avoiding the potentiality trap: thinking about the moral status of synthetic embryos. *Monash Bioethics Review* **38(2)**: 166-80, at page 175.

developing into a human being confers moral status similar to embryos' status and protections in research.[99] As we discuss in the section '**International guidance**' below, this argument has been influential in some countries in aligning certain SCBEMs and embryos for governance purposes. It has been pointed out that the potential to develop into a human being is often not realised even in implanted embryos, which often do not develop to term.[100] However, an argument could also be made that embryos considered as a *cohort* have the potential to develop to term, whereas SCBEMs (until evidence suggests otherwise) do not. Not all embryos develop into human beings, but all human beings have developed from embryos.

Others argue that SCBEMs, embryos and stem cells alike are dependent on the right environment to develop into a human being, rendering potentiality irrelevant in its own right.[101]

The significance of the potential capacity of some SCBEMs to develop in a manner *similar* to embryos is reflected in the 2021 ISSCR guidelines, which recommend a higher level of oversight for SCBEMs that "could potentially achieve the complexity where they might realistically manifest the ability to undergo further integrated development if cultured for additional time *in vitro*." [102]

As we've explored, the potential of SCBEMs to develop is both varied and variable (see '**Challenges for the categorisation and definition of SCBEMs**' above). It is varied in that most SCBEMs model only elements of the embryo yet some models are more complex and complete. It is variable in that embryo models are modular and easy to adapt. There are ways in which science can limit or prevent this potential, for example, by excluding features from the model that are necessary for onward development (see '**Amendment of the UK SCBEM Code of Practice**' below).[103] As we later propose, regulation can also be used to prevent reproductive potential from being realised by placing an upper limit on SCBEM development and prohibiting the transfer of SCBEMs to the reproductive tract of a human or other animal.

Capacities and features

Aside from reproductive or developmental potential, we found reference to certain capacities or features in SCBEMs that could raise concerns or confer moral status, and could therefore justify a precautionary approach to the research.[104]

99 Wilger K (2020) *Gaps in embryo model ethics* (Ethics & Medics: The National Catholic Bioethics Center)

100 Piotrowska M (2020) Avoiding the potentiality trap: thinking about the moral status of synthetic embryos. *Monash Bioethics Review* **38(2)**: 166-80, at page 175.

101 Ibid.

102 International Society for Stem Cell Research (2021) *ISSCR guidelines for stem cell research and clinical translation*, available at: https://www.isscr.org/guidelines

103 Such as by incorporating genetic switches leading to programmed cell death, see Rivron N, Pera M, Rossant J, *et al.* (2018) Debate ethics of embryo models from stem cells. *Nature* **564(7735)**: 183-5.

104 A similar argument is made in relation to embryos in Birch J (2024) *The edge of sentience: risk and precaution in humans, other animals, and AI* (Oxford: Oxford University Press); Pereira Daoud AM, Dondorp WJ, Bredenoord AL and de Wert GMWR (2022) Dutch perspectives on the conceptual and moral qualification of human embryo-like structures: a qualitative study *Humanities & Social Sciences Communications* **9(1)**: 151.

All stakeholders we heard from considered it undesirable to develop SCBEMs with the capacity to experience pain.[105] This is generally accepted to occur in the **fetus** at 24–28 weeks when the cerebral cortex (which becomes responsible for processing thought) develops and the mechanisms for experiencing pain are analogous to those of the mature adult.[106] Stuart Derbyshire and John Bockmann argue that we should not rule out the relevance of other experiences of pain that might be possible before the 24-week mark, but after the development of neural activity in the subplate (one of the first zones to develop in the cerebral cortex) at 12 weeks.[107] All stakeholders also suggested that it would be undesirable for the SCBEM to achieve a level of awareness or consciousness, were that to become scientifically feasible. Anna Ciaunica *et al*. consider that the traditional view of consciousness is adult-centric and vision-based;[108] that is, we report what we see and understand from our own experience of consciousness. A relevant alternative view, they suggest, focuses on the nature of subjective experiences. The ability to make anticipatory, goal-directed actions is observable in fetuses from between 12 and 14 weeks. At this stage, the fetus is capable of isolated movements of different parts of its body that could suggest a sensory understanding of its environment and the onset of awareness, albeit an awareness that is quite different to the experience of adults.[109]

In the UK G-SCBEM public dialogue, features that were considered to raise 'red flags' for research included: the capacity to feel pain, having an established nervous system, consciousness, feeling, sensitivity to touch, resembling a fetus and existence of the brain.[110] The Dutch focus groups referred to above also found that chief considerations were: "(1) 'are these organisms capable of feeling pain?', and (2) 'are these organisms capable of more complex forms of self-awareness?'".[111]

While in practice it might be difficult to prove whether such abilities are present, observable features – such as the development of the **primitive streak** – have been suggested as proxies for their capacity to develop. The Warnock Committee took this approach, acknowledging that while "biologically there is no one 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

105 We note discussion of the significance of features between SCBEMs and embryos, for example in Pereira Daoud A, Popovic M, Dondorp WJ, *et al*. Modelling human embryogenesis: embryo-like structures spark ethical and policy debate *Human Reproduction Update* **26(6)**: 779-98.

106 Royal College of Obstetricians and Gynaecologists (2010) *Fetal awareness: review of research and recommendations for practice*, available at: https://www.rcog.org.uk/media/xujjh2hj/rcogfetalawarenesswpr0610.pdf; see also Birch J (2024) *The edge of sentience: risk and precaution in humans, other animals, and AI* (Oxford: Oxford University Press).

107 Derbyshire SW and Bockmann JC (2020) Reconsidering fetal pain *Journal of Medical Ethics* **46(1)**: 3-6.

108 Ciaunica A, Safron A and Delafield-Butt J (2021) Back to square one: the bodily roots of conscious experiences in early life *Neuroscience of Consciousness* **2021(2)**: niab037.

109 Ibid.

110 Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

111 Pereira Daoud AM, Dondorp WJ, Bredenoord AL and de Wert GMWR (2022) Dutch perspectives on the conceptual and moral qualification of human embryo-like structures: a qualitative study *Humanities & Social Sciences Communications* **9(1)**: 151.

must be taken, in order to allay public anxiety." [112]

Over time, a more accurate picture will emerge of what models could potentially be achieved and the capacities of the SCBEMs that might result. Indeed, one of the purposes of developing SCBEMs is to better understand early human development. As the science develops, there is potential for increasingly accurate assessment of embryonic and fetal capacities. This in turn can be used to inform public discourse and the specific and targeted governance of SCBEMs.

Dignity

Human dignity is often cited as the underlying justification for the set of rights to which all humans are entitled. It plays a prominent role in our legal system, from international conventions to common law development. It upholds the idea that human beings should never be used as a mere means to an end and has been extended to debates about early human development.

An issue with relying on the concept of dignity is that it has more than one conception and this can impact on who or what is considered deserving of dignity. Christian readings consider that dignity results from human beings having been made in the image of God.[113] A Kantian conceptualisation considers that dignity is based on rationality.[114] Deryck Beyleveld and Roger Brownsword contrast conceptualisations of dignity as empowerment and constraint.[115] Conceptualised as 'empowerment', it is applied in a liberal manner, upholding agency and extending the ambits of individual choice. On this view, for example, commodifying human tissue would not be incompatible with dignity.[116] An alternative, more conservative conception sees dignity as 'constraint' on individual choice. The UN Declaration on Human Cloning, for example, refers to the need to prohibit human reproductive cloning due to its incompatibility with respect for human dignity.[117] Contextual changes around what is safe and what benefits a technology can bring, for example, will influence the debate about what is compatible with human dignity. An example of this is the reference to dignity in the historical calls to ban surrogacy,[118] a position now widely considered to

112 Department of Health and Social Security (1984) *Report of the committee of inquiry into human fertilisation and embryology*, available at: https://www.hfea.gov.uk/media/2608/warnock-report-of-the-committee-of-inquiry-into-human-fertilisation-and-embryology-1984.pdf, at page 65.

113 Müller S (2020) Concepts and Dimensions of Human Dignity in the Christian Tradition *Interdisciplinary Journal for Religion and Transformation in Contemporary Society* **6(1)**: 22-55.

114 See discussion in Prainsack B and Buyx A (2011) *Solidarity: reflections on an emerging concept in bioethics*, available at: https://www.nuffieldbioethics.org/assets/pdfs/Solidarity-report.pdf, at section 4.3.

115 Beyleveld D and Brownsword R (2001) *Human dignity in bioethics and biolaw* (Oxford: Oxford University Press).

116 Ibid, at page 218.

117 United Nations (2005) United Nations Declaration on Human Cloning, available at: https://digitallibrary.un.org/record/541409?ln=en&v=pdf

118 See Department of Health and Social Security (1984) *Report of the committee of inquiry into human fertilisation and embryology*, available at: https://www.hfea.gov.uk/media/2608/warnock-report-of-the-committee-of-inquiry-into-human-fertilisation-and-embryology-1984.pdf, at paragraph 8; and Hansard HL Deb (31 October 1984) **456**, c541, available at: https://api.parliament.uk/historic-hansard/lords/1984/oct/31/human-fertilisation-warnock-report-1#column_541

be outdated.[119]

Because of the conceptual disagreements about what dignity entails, it will not provide an uncontested answer to questions about the appropriate governance of SCBEMs. Reference to dignity does, however, demonstrate what Roger Brownsword refers to as a shared concern "to try to do the right thing".[120] As such, dignity arguably has an important role in the debate about the governance of SCBEMs and underlines the notion that there will be different conceptions of what actions are compatible with dignity that should be taken into consideration when drawing governance lines.

The relationship between human dignity and SCBEMs will differ according to various factors, including the model's complexity and completeness and the cells from which it is derived. David Kirchhoffer and Kris Dierichx[121] argue that non-embryonic human tissue, such as that from iPSC lines, cannot be said to have human dignity as it has no moral agency and lacks personhood. Nonetheless, they argue that dignity is implicated in its *use*, not in relation to the moral status of the tissue itself, but out of respect for the tissue donors (see '**Consent**' above). They call for 'dignity-driven reflection' given that

> **"A person has 'entrusted' an aspect of his or her dignity to us, both in terms of his or her genetic identity (absolute) and in terms of the values that may have motivated his or her donation in the first place (contingent)."**

Use of embryonic stem cell lines that involve destruction of an embryo in research elevate concerns around human dignity. In the UK, special rules and approvals apply, as we explore later (in '**Legislative application and gaps**').

For the more complete or integrated SCBEMs, the extent to which SCBEMs are considered similar or equivalent to embryos might give rise to additional considerations. Whilst some hold the view that human dignity is relevant to the legal protections that apply to embryos, the extent to which it applies and the implications of this are contested.[122]

Associations with embryos and the value of human life

Insofar as SCBEMs are perceived to share features with the embryo, and embryos are associated with human life, some restrictions on their use may be justified, subject to the relative value and importance of other compelling societal interests.

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119 Law Commission of England and Wales and the Scottish Law Commission (2023) *Building families through surrogacy: a new law. Volume 1: core report*, available at: https://lawcom.gov.uk/project/surrogacy/

120 Brownsword R (2015) Human dignity from a legal perspective, in *The Cambridge handbook of human dignity* Düwell M, Braarvig J, Brownsword R and Mieth D (Editors) (Cambridge, UK: Cambridge University Press), at page 21.

121 Kirchhoffer DG and Dierickx K (2011) Human dignity and human tissue: a meaningful ethical relationship? *Journal of Medical Ethics* **37(9)**: 552-6.

122 See, for example, the European Convention on Human Rights and Biomedicine 1997 (the 'Oviedo Convention') Article 18, which aims to protect the dignity of all human beings, and prohibits the creation of human embryos for research purposes. The UK did not sign or ratify the Convention, and always had the option of entering a reservation to the Article 18 restriction under Article 36.1.

However, there are also features which some feel clearly distinguish SCBEMs from embryos. Some of the participants of the Dutch lay focus group drew on notions of *artificiality*:

> **"When we asked whether this participant would think differently if hELS [human embryo-like structures] could grow into human beings, the answer was still 'no' because the resulting clone would be an artefact: '... even then, it would not be a real human being in my view, because it originates from an existing DNA'. Similarly, a professional who accorded the highest ranking to 'everything that is or can become a human being' did not reason that hELS – if capable of growing into a human being – should be on the same level. Instead, the professional placed such hELS still 'somewhat (...) lower because they are more artificial'."** [123]

Another factor that is perceived as relevant in distinguishing the societal value placed on SCBEMs from the value attributed to embryos, is the explicit research focus of SCBEMs.[124] In their 2023 report, the Conseil d'orientation of the French Agence de la biomédecine took the position that SCBEMs may never be equivalent to human embryos, even if some SCBEMs may in time look very similar to them, because unlike SCBEMs, "embryos are conceived as part of an original parental project" even if they are eventually donated to research.[125] The Conseil refers to this as 'intentionality,' in that there is never an intention for SCBEMs to be part of a parental project.[126]

This position debatably has less relevance in the UK where, with the appropriate licence, embryos *can* be created explicitly for use in research. Furthermore, not everyone will agree that the intention is morally relevant. For example, if two organisms A and B were identical in all relevant respects except that A was *intended* to be or become a companion animal, and B was *intended* to be or become a research subject animal, would it follow that A had a different (higher) moral status? It could also be countered that not all conceptions which result in human babies are intentional. However, it is still arguable that SCBEMs might be perceived as having a purely research-oriented value that differentiates them from embryos.

We might care about how some SCBEMs are treated in research because of what they might be considered to represent, or because of their association with things that we value, such as respect for human life. And this might apply even if there are grounds upon which to differentiate even the more complete or complex SCBEMs from embryos. For example, the UK G-SCBEM public dialogue reported that:

123 Pereira Daoud AM, Dondorp WJ, Bredenoord AL and de Wert GMWR (2022) Dutch perspectives on the conceptual and moral qualification of human embryo-like structures: a qualitative study *Humanities & Social Sciences Communications* **9(1)**: 151.

124 Ibid.

125 Agence de la Biomédecine (2023) *Opinion of the Conseil d'orientation: stem cell-based embryo models*, available at: https://www.agence-biomedecine.fr/IMG/pdf/22-06_avis_du_co_embryoi_des_eng-2.pdf (Note: this is a translation).

126 Ibid.

> **"...most participants increasingly felt that embryo models, particularly those that are less complete, are different from human embryos, or different enough that they pose fewer ethical concerns than human embryo research."** [127]

It seems fair to assume that the range of views expressed in the public engagement exercises cited above would be reflective of a diversity of values and potential views among the wider public. It is also likely that there will be a broadly shared view that there are lines that should not be crossed, and that some research might be seen to push against these lines. We suggest that such research might include the more complex or complete models at later stages of embryonic development – in particular, those which bear resemblance to a fetus,[128] those which have capacity for pain or awareness, and models which are and appear complex but which are engineered specifically to prevent them from developing capacities for pain or awareness.

Consent

As Lewis and Holm note, there are reasons why the relationship between the donor and the model can have moral value. SCBEMs are created from cells donated by individuals.[129] This means that they will have a biological link to individual donors (for example by sharing their unique genetic material) or couples (with a parental link to donated embryos), as well as a personal connection, including the experience of those individuals in creating and donating embryos or tissue. As genetic sequencing technology improves and becomes more widely available, donor anonymity may be less secure, raising new issues of data protection and confidentiality.[130]

The importance donors place on these connections might vary considerably, as might their expectations of control over possible future uses of the tissue they have donated. A previous NCOB report concluded that it is meaningful and ethical to seek generic consent for future research uses, but that there is value in recognising donors' onward interest in the donated material.[131] This does not mean that donors should expect to direct how their tissue is used in research but, for example, that consent processes ensure that donors are informed of the range of possible uses of their tissue and allow them to place limits on certain uses.[132]

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127 Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

128 See Richardson MK and Reiss MJ (1999) What does the human embryo look like and does it matter? *The Lancet* **354(9174)**: 244-6.

129 Lewis J and Holm S (2024) *HYBRIDA Project D6.2: Regulating organoid and organoid-related activities: Proposals to address regulatory gaps and areas of over-regulation*, available at: https://hybrida-project.eu/deliverables/

130 See Bentzen HB (2025) Human organoids: things or data? In *Confidentiality, and data protection in biomedicine: international concepts and issues*, Dove ES (Editor) (Abingdon and New York: Routledge); see also Nuffield Council on Bioethics (2015) *The collection, linking and use of data in biomedical research and health care: ethical issues*, available at: https://www.nuffieldbioethics.org/publications/biological-and-health-data

131 Nuffield Council on Bioethics (2011) *Human bodies: donation for medicine and research*, available at: https://www.nuffieldbioethics.org/publications/human-bodies-donation-for-medicine-and-research

132 Jackson E (2024) Regulating embryo models in the UK *Journal of Law and the Biosciences* **11(2)**: lsae016.

However, the pace of developments in stem cell and SCBEM research can mean that it is more difficult to predict future research uses. Many cell lines currently in use were created when current uses might not have been predicted.[133] We note that, while current regulations stipulate that *embryo* donors can only consent to donation for specific research projects, this can be a significant barrier to research and the HFEA is, at the time of writing, seeking an amendment to the law to allow generic consent in this context. We can see a case for wider dialogue to better understand views on the use of donated stem cells for the creation of SCBEMs, and to explore the role of consent processes and engagement in facilitating research that is of public interest. An aim should be to foster solidarity, creating an environment in which people from all sections of society feel able to trust tissue banks and researchers with their bodily material, and are motivated to donate so that SCBEMs reflect diversity within the population.

133 Isasi R and Bentzen HB, *et al*. (2024) Dynamic governance: A new era for consent for stem cell research *Stem Cell Reports* **19(9)**: 1233-41.

III. Governance mechanisms

Overview

In the UK, proactive regulatory oversight over contentious areas of research has achieved success in balancing the concerns of moral harms with the potential for benefit.[134] Public trust, and relatedly institutional trustworthiness, are seen by many as foundational to this success, both instrumentally and because governance should reflect public interests. We heard the suggestion that public confidence itself is an important ethical consideration, facilitated by public trust and institutional trustworthiness.[135]

In this section, we make recommendations as to what **governance** and **regulatory** measures are appropriate to SCBEMs. We differentiate between broad 'governance' and narrower 'regulation', which is a subset of governance involving oversight by regulatory bodies, often based on legal authority. We also differentiate between '**hard law**' by which we mean binding legal obligations, and '**soft law**' which means principles, guidelines and codes which are not legally binding but have strong influence. Finally, we differentiate between voluntary and legal measures, the former being 'voluntary' in the sense that they are not mandated in law, though this is not to say that there cannot be strong incentives to comply.

One of the aims of governance of scientific endeavours is to build public trust.[136] A loss of public trust in a science or scientists can have damaging consequences, as we have witnessed in relation to genetically modified food[137] and vaccine hesitancy.[138] Diverse public perspectives should feed into discussions about how an ethically and clinically appropriate governance scheme might look. Accountability is enhanced

134 Discussed in '**Comparative positions on the status of the SCBEM**' below.

135 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode, at page 18.

136 See, for example, R Sturmey (2024) Guidelines on lab-grown embryo models are strong enough to meet ethical standards – and will build trust in science *Nature* **632(8023)**: 9. See also McCrea R, Coates R, Hobman EV et al. (2024)Responsible innovation for disruptive science and technology: The role of public trust and social expectations *Technology and Society* **79**: 102709.

137 House of Lords Select Committee on Science and Technology (2000) *Third report. Science and society*, available at: https://publications.parliament.uk/pa/ld199900/ldselect/ldsctech/38/3802.htm

138 See, for example, UK Health Security Agency press release (29 August 2024) *UKHSA warns of back to school measles surge*, available at: https://www.gov.uk/government/news/ukhsa-warns-of-back-to-school-measles-surge

when researchers and policymakers are required to justify their decisions to an informed public. Transparency is fostered through open discussions that shed light on the scientific process and potential implications of SCBEM research. Community participation ensures that diverse voices and perspectives are heard and considered, leading to more inclusive decision making. Finally, justice and fairness are promoted by giving all stakeholders, including marginalised groups, an opportunity to influence the direction of research and its regulation. In this section, we suggest a staged approach to governance, which would present opportunities to inform, engage and discuss potential solutions with both the public and stakeholders, in order to help ensure that governance is fit for purpose.

We start by examining the governance gap that exists around SCBEMs and recent initiatives to address it, and then make recommendations for approaches going forward. We propose a model of governance that provides scientists with clarity as to what is expected of them, and reassurance to the public and government that research will be conducted in an ethically and scientifically robust manner to the potential benefit of society.

This balance is not easy to achieve, not least because the science is in flux and developing at pace. There are many advantages to a soft law model of governance, including its adaptability to develop alongside the science. Nevertheless, we highlight risks associated with this approach in the longer term, chief among them being:

1. There is potential under current law for some or all SCBEMs to be reclassified as embryos. Doing so would impose strict limitations on research, particularly as SCBEMs are very difficult to categorise effectively in a future-proofed manner. As such, it would likely be disproportionately restrictive of some SCBEMs. Moreover, the very existence of this risk may limit investment in the infrastructure needed to realise the potential benefit of SCBEMs in the shorter term.
2. Soft law guidelines and oversight mechanisms take time to embed and the penalties for non-compliance may be insufficient, or perceived as insufficient, to prevent unethical practices if the science continues to develop at pace.

We propose a three-stage response, allowing learning and reflection at each stage that seeks to mitigate these two risks:

- Gradual strengthening of voluntary measures to incorporate an upper threshold for the culture of SCBEMs and to empower the Oversight Committee proposed in UK SCBEM Code.
- Legislative change to enforce the ban on the transfer of human SCBEMs to an in vivo human or non-human animal reproductive tract to prevent harm and secure the research-focused intent of SCBEM use.
- Powers set out in **primary legislation** to make **secondary legislation**, in order to facilitate incorporation of SCBEMs and other stem cell-based models under a collaborative, agile and adaptable form of regulation called a

'**regulatory sandbox**', which we define and discuss later (see '**Amendment to the UK SCBEM Code of Practice**' below). The 'sandbox' is a testbed which should have clear exit pathways that will categorise SCBEMs according to the risks and benefits they pose, and subject them to proportionate controls.

There are parallels between this approach and the approach taken in the regulation of embryos. Before the Human Fertilisation and Embryology Act 1990 established the HFEA, the Voluntary (later Interim) Licensing Authority for Human In-vitro Fertilisation and Embryology was set up by the Medical Research Council and the Royal College of Obstetricians and Gynaecologists.[139] Similarly, we propose that the UK SCBEM Code of Practice, which is a voluntary form of governance in the sense that it is not mandated in law, is strengthened by proportionate and bespoke regulation that targets those SCBEMs that are likely in the future to require increased oversight.

After establishing the need for governance, the forms it might take, and its challenges and goals, we set out the governance context and make recommendations as to the status of SCBEMs as a separate entity to the embryo. Building on these foundations, we set out proposals for a way forward to effect a Warnock-style consensus that aims to balance the needs of researchers, government and society.

Establishing the need for governance

SCBEMs have the potential to benefit society by affording a better understanding of human development and offering future therapeutic applications, but their use can pose risks. On the one hand, the risks include unethical development, research misconduct and the collapse of public trust. On the other, they include disproportionate control and lack of investment, which could prevent developments that serve the public interest. Regulation is a mechanism to manage risks and support ethical scientific development. It involves rules or expected behaviours set out to achieve a public policy goal, and often involves a regulator or regulators influencing compliance.[140]

John Harris and David Lawrence lament the tendency for regulation to "act in arrears" and call for a proactive approach as new morally significant technologies become reality.[141] There is no single formula to determine what governance arrangements are optimal and when they should be imposed. The HYBRIDA project, a three-year HORIZON 2020 project, developed proposals for a regulatory framework for organoid and related research, including SCBEMs.[142] It concluded in

139 MacNaughton M (2005) Regulation before the HFEA *Human Fertility* **8(2)**: 61-62; and Gunning J and English V (1993) *Human in vitro fertilization: a case study in the regulation of medical innovation* (Brookfield, VT: Dartmouth).

140 National Audit Office (2021) *Principles of effective regulation* (2021), available at: https://www.nao.org.uk/wp-content/uploads/2021/05/Principles-of-effective-regulation-SOff-interactive-accessible.pdf, at page 3.

141 Harris J and Lawrence DR (2022) Newer technologies, older attitudes, and retrograde regulation. In *Novel beings: regulatory approaches for a future of new intelligent life*, Morley S and Lawrence DR (Editors) (Cheltenham: Edward Elgar Publishing), chapter 5.

142 See HYBRIDA Project (2024), available at: https://hybrida-project.eu

2024 and recommended that ethical concerns are addressed proactively, ensuring continuous ethical engagement among stakeholders, scientists and society so that research practices can be responsive to ethical considerations and societal expectations.[143]

A range of governance measures exists, from prescriptive rules set out in legislation, to principle-based guidance and codes of practice. Risks are apparent at both ends of the scale of permissiveness. Over-regulation could impose disproportionate limits on research contrary to the public good. Under-regulation could lead to research breaching ethical boundaries of permissibility, which could cause harms and undermine public trust. The National Audit Office advises that formal regulation should only be used when it is the best and most cost-effective method to achieve policy objectives.[144] Less authoritative styles of governance may be a viable alternative or a stepping stone to more formal regulation and a mechanism by which the principles of governance can be tested and honed.

It would be erroneous to assume that SCBEM scientists want unfettered freedom that others seek to constrain. In many emerging technologies, the existence of a governance gap can undermine researcher and funder confidence and deter both public and commercial investment. This in turn can undermine the duty to support ethically and scientifically robust research that has the potential to benefit society. Proportionate governance will serve researchers as well as the public, reducing the risks of physical, social or moral harms and contributing to an environment in which research can advance safely and ethically.

This was clear to the Warnock Committee's Inquiry into Human Fertilisation and Embryology in 1984, which recommended a 14-day limit on the culturing of human embryos for research. This recommendation, along with other prohibitions and restrictions on embryo research, was accepted and written into the Human Fertilisation and Embryology Act 1990, and is influential internationally. It resulted in what Sarah Franklin and Emily Jackson term the "Warnock consensus".[145] This persuaded "an often sceptical public, as well as adamantly opposed parliamentarians, to accept a workable and enforceable framework for the regulation of embryo research which ... enabled a high degree of public trust to support innovative translational research".[146] The result is a social contract: a prospect of societal benefit in return for precise and controlled permissions to carry out research.

In the case of SCBEMs too, governance should aim to promote scientifically and ethically robust research that reflects public values and interests. Even where, as is

143 Andreescu I, Baertschi B, Chneiweiss H, et al. (2024) *Executive summary of HYBRIDA's operational guidelines*, available at: https://hybrida-project.eu/wp-content/uploads/2024/05/HYBRIDA-executive-summary-OGLs-final-02052024-.pdf

144 National Audit Office (2021) *Principles of effective regulation* (2021), available at: https://www.nao.org.uk/wp-content/uploads/2021/05/Principles-of-effective-regulation-SOff-interactive-accessible.pdf, at page 8.

145 Franklin S and Jackson E (2024) *The 14 day rule and human embryo research: a sociology of biological translation* (Abingdon and New York: Routledge).

146 Ibid, at page 29.

inevitable, there is disagreement as to the moral status of SCBEMs and the ethical and legal protections that should be bestowed on them, there is contemporary evidence of agreement that some governance is better than none.[147] What engenders public trust in science has been the subject of recent scrutiny by the British Academy, which highlights the importance of:

- framing policy and the role of science within it;
- recognising the public's desire for nuance and transparency; and
- deepening engagement with different publics to build trust in science in a way that preserves the integrity and independence of the scientific process.[148]

In the introduction to her report, 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."** [149]

We consider this sentiment, which related to "new techniques" rather than embryo research specifically, to also be relevant to SCBEMs. As such, governance can enhance trust of researchers, funders, and investors in the research environment, and enhance public confidence that a proportionate response is taken to minimise risks and that ethical considerations have been taken into account. There are distinct advantages in starting to address this now while the science is in its infancy, but there is also an imperative to advance the implementation of regulation in the sector incrementally to limit the risk of disproportionate regulation.

Governance dilemmas

Agreement that governance of some sort is needed gets us only so far. Agreeing the model and content of governance is made difficult by several confounding factors, set out in **Figure 1** below.

147 See Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

148 The British Academy (2024) *Public trust in science-for-policymaking*, available at: https://www.thebritishacademy.ac.uk/publications/public-trust-in-science-for-policymaking/

149 Department of Health and Social Security (1984) *Report of the committee of inquiry into human fertilisation and embryology*, available at: https://www.hfea.gov.uk/media/2608/warnock-report-of-the-committee-of-inquiry-into-human-fertilisation-and-embryology-1984.pdf, at paragraph 5.

Figure 1. Governance dilemmas

The uncertainty of the risks	**This includes uncertainty as to whether one day a complex SCBEM could be capable of transfer to a human or non-human uterus and onward development.**
The uncertainty of benefits	**This includes the potential to over-promise in a manner that downplays difficulties and complexities.**
The global nature of scientific advances	**This is in contrast with the largely national organisation of regulatory measures.**
The nature of the UK regulatory system	**The system was not designed with SCBEMs in mind.**
The evolving and diverse nature of SCBEMs	**These are difficult to categorise given their different features and capabilities, and the pace of development.**

This, in turn, raises the following overarching questions which we return to in subsequent subsections:

1. **How to effectively balance governance and regulation.**
   Whilst principle-based governance is often preferred to rule-based regulation for emerging technologies due to its flexibility, a combination of hard and soft measures is almost inevitable.[150] When new soft law fills a gap, it must operate within the existing regulatory environment. Rule-based regulation "should be carried out in a way that is transparent, accountable, proportionate and consistent" and "targeted only at cases in which action is needed." [151]
2. **What to regulate now and what to defer to the future, when more will be known about SCBEMs' potential uses and risks.**

150 Nuffield Council on Bioethics (2013) *Emerging biotechnologies: technology, choice, and the public good*, available at: https://www.nuffieldbioethics.org/publications/emerging-biotechnologies, at paragraph 8.31.

151 See section 2(3) of the Legislative and Regulatory Reform Act 2006.

The pace of development is uneven and pipeline development is currently poorly understood. An important part of the governance regime will be creating the flexibility to, if possible, anticipate and respond appropriately to future developments. Governance should also improve transparency to make those developments more predictable.

3 **When to focus on technology-specific governance and when to collectively govern a range of technologies posing similar issues.** Some other stem cell-based technologies, including neural organoids and *in vitro*-derived gametes,[152] present overlapping ethical and governance issues which may in time warrant shared governance responses.[153] Governing by technology rather than the characteristics of the product can lead to overlapping and inconsistent governance.

The governance goal

The working group considers that the governance goal is to produce a framework that facilitates scientific progress, upholds ethical standards and reflects public interests. We take the view that governance should create an environment in which there is clarity as to the morally relevant considerations and legal status of SCBEMs to encourage responsible investment and stability, whilst guarding against potential adverse outcomes, and creating structures to anticipate developments and sufficient flexibility to respond appropriately to them.

To this end, the next subsections recommend the incremental development of a mix of substantive and procedural tools that aim to forge and sustain a consensus. This should balance caution, in light of potential risks, against societal interests in realising benefits from the development of this emerging technology. The procedural tools should seek to record, monitor and facilitate learning. The substantive tools – which can flow from primary and secondary legislation,[154] delegation to regulatory bodies and self-governance – should operate to guard against actions or events that would be detrimental to society and the advancement of science.

The governance context

Successes in UK biotechnological research innovation flow from both its strong base of researchers and from policymaking and the regulatory environment. For example, the potential of stem cell research, cell nuclear replacement,[155] and human admixed embryos[156] was unforeseen when the Human Fertilisation and Embryology Act 1990

152 Detailed consideration of these technologies is beyond the scope of the report.

153 See Ravn T, Falkenberg M and Sørensen MP (2023) *HYBRIDA Project D4.4: Report on the expert interviews and co-creation workshops*, available at: https://hybrida-project.eu/deliverables/, at section 5.3.1.

154 Secondary legislation is law created by ministers under powers set out in an Act of Parliament (primary legislation).

155 Transfer of the nucleus from an adult cell into a donated egg from which the nucleus has been removed. see Glossary.

156 An embryo that contains human and non-human animal material.

was debated, and yet regulatory mechanisms have been forged, adapted and amended to facilitate ethical scientific development. These examples suggest that a regulatory regime that guards against known and foreseeable adverse outcomes, whilst maintaining sufficient flexibility to respond to scientific developments and foster beneficial innovation, will garner public trust.

Legislative application and gaps

As we have seen, stem cells can be obtained from a variety of sources, including from human embryos, aborted fetuses, umbilical cord blood and adult somatic cells. Regulation has responded incrementally to the developing science and also to the special status of the embryo and ESCs.

The different regulatory regimes governing human pluripotent stem cells (ESCs and iPSCs) and stem cell lines from which SCBEMs can be generated are summarised in **Table 1**. Unsurprisingly given their novelty, SCBEMs are not explicitly referred to in legislation. Furthermore, there is currently no licensing structure that applies to the use of human stem cell lines in research. A Code of Practice developed by the UKSCB Steering Committee was issued by the Medical Research Council in 2010;[157] it sets out the governance structure for ESCs and principles relating to access, quality assurance and donor consent.

The governance of human stem cell cultures from which SCBEMs are derived takes two forms, both of which recognise the importance of donor informed consent and proportionate ethical review:

1. The Human Fertilisation and Embryology Act 1990 (as amended) governs research on embryos, but governance ceases when the ESCs are made into stem cell lines – a group of cells grown in culture outside the human body that can be expanded for prolonged periods by making more copies of themselves and have the potential to give rise to any cell type in the human body. At this point, the lines must be banked at the UKSCB which then oversees research, including research generating SCBEMs from ESCs. The UKSCB, set up in 2003 and funded by the National Institute for Health Research, is the sole public repository for UK ESC lines. It undertakes research to enhance their quality and facilitates research and development. The independent UKSCB Steering Committee governs approvals for UK human ESC research based on principles set out in the 2010 Code of Practice. Like the 2024 UK SCBEM Code of Practice, the 2010 Code is a 'voluntary' policy. In the case of human ESC lines, compliance with the 2010 Code is reinforced by virtue of being an HFEA licensing requirement.[158] Additional approval from an NHS Research Ethics

157 UK Research and Innovation (2010) *Code of practice for the use of human stem cell lines: version 5*, available at: https://www.ukri.org/wp-content/uploads/2021/08/MRC-0208212-Code-of-Practice-2010-use-of-human-stem-cell-lines.pdf

158 See the Foreword in UK Research and Innovation (2010) *Code of practice for the use of human stem cell lines* v5, available at: https://www.ukri.org/wp-content/uploads/2021/08/MRC-0208212-Code-of-Practice-2010-use-of-human-stem-cell-lines.pdf

Committee (REC) is not required.[159] Extra-embryonic stem cells – cells which give rise to structures that support embryonic development such as the placenta – are not subject to regulation by any official body.

2 The Human Tissue Act 2004 (applicable in England, Wales and Northern Ireland) and the Human Tissue (Scotland) Act 2006 govern the use and storage of tissue and cells that come from the human body. This is relevant to iPSCs, which are skin, blood or other body cells that have been reprogrammed into an embryonic-like pluripotent state. The Human Tissue Authority (HTA) issues licenses under the Human Tissue Act 2004 and performs certain tasks on behalf of the Scottish government. Consent is central to both statutes. With consent, tissue can be used to create a stem cell line. Once the stem cell line is established, the Acts and licensing regimes do not apply. Research tissue banks can apply for Health Research Authority (HRA) approval of their arrangements for collection, storage, use and distribution on a voluntary basis. The UKSCB and UKSCB Steering Committee's remit does not extend to iPSC lines, but the 2010 Code of Practice sets out ethical principles relevant to all human pluripotent stem cell lines. Ethical approval can be provided by institutional, and in some cases NHS, RECs.

Whilst our report focuses on SCBEMs derived from human stem cell lines, it is important to acknowledge the potential to involve non-human animals in the study of human SCBEMs and *vice versa*. There is currently no legal prohibition preventing transfer of a human SCBEM into the *in vivo* reproductive tract of a non-human animal.

Most of the current research on SCBEMs is basic research; that is, it is aimed at of generating knowledge and understanding of the underlying mechanisms of early human development. As discussed previously, there is also the potential in future to apply this research to improve pregnancy outcomes (see '**Contribution and potential uses**' above). A well-established regulatory regime governs clinical research, and this would apply to any clinical research involving SCBEMs. The Medicines and Healthcare products Regulatory Agency (MHRA) regulates research outputs from stem cell research for medicinal use. The Gene Therapy Advisory Committee (GTAC) advises the government and provides ethical oversight of proposals to conduct trials involving gene therapy or stem cell therapies derived from stem cell lines.

Table 1 below reveals two important issues with the current governance framework. Firstly, the regulatory landscape is complex, which can be a source of burden to researchers. Secondly, there is regulatory oversight of the processes by which the cells become a stem cell line and regulatory oversight if the SCBEMs are later used for medicinal application; however, there is a governance gap between those two points. As such, there are limited legislative or governance mechanisms controlling the research processes that develop the SCBEMs themselves.

159 UK Research and Innovation (2010) *Code of practice for the use of human stem cell lines* v5, available at: https://www.ukri.org/wp-content/uploads/2021/08/MRC-0208212-Code-of-Practice-2010-use-of-human-stem-cell-lines.pdf, at section 7.1.3.

Table 1. The regulatory mechanisms and gaps governing the production of SCBEMs

Regulated activity	Approval required	Legislation	Regulator
Primary cell cultures			
Storage and use of human tissue (not including embryos outside the human body), some fetal tissue[160] and some chimeric non-human animals without using cell lines	Licence to store and Research Ethics Committee (REC) approval to use tissue from licensed tissue bank	Human Tissue Act 2004 and Human Tissue (Scotland) Act 2006 Human Tissue (Quality and Safety for Human Application) Regulations 2007	Human Tissue Authority (HTA) (England & Wales and Northern Ireland and certain tasks performed for Scottish government)
Use of human embryos or human admixed embryos	Research licence	Human Fertilisation and Embryology Act 1990 (as amended)	Human Fertilisation and Embryology Authority (HFEA) (UK)
Use of human gametes	–	Human Fertilisation and Embryology Act 1990 (as amended) regulates treatment using eggs and sperm ('permitted' gametes)	HFEA
Use of 'protected animals'	Licence and inspection	Animals (Scientific Procedures) Act 1986	Home Office
Stem cell lines			
Research on human embryonic stem cell (ESC) lines	Cell lines generated from human embryos under HFEA licence must be deposited in UK Stem Cell Bank	–	UK Stem Cell Bank Steering Committee which reports to the Medicines and Healthcare products Regulatory Agency (MHRA)
Research on human inducted pluripotent stem cell (iPSC) lines	–	–	Health Research Authority (HRA) REC approval for new tissue donations Institutional REC approvals
Use of cell lines for human application or therapeutic use	Establishment needs licence to store/import	The Human Tissue (Quality and Safety for Human Application) Regulations 2007	HTA (England & Wales and Northern Ireland)
Clinical research – human application			
Clinical trials and master cell banks with reasonable utility[161] expectation of clinical	HRA approval Marketing authorisation	Medicines for Human Use (Clinical Trials) Regulations 2004	HRA MHRA
Other research (non-clinical trials)	REC approval	–	HRA

160 See Human Tissue Authority (2020) Code of practice *A: guiding principles and the fundamental principle of consent*, available at: https://www.hta.gov.uk/guidance-professionals/codes-practice-standards-and-legislation/codes-practice, at paragraphs 141-143 on the requirements for research on fetal tissue under 24 weeks, stillbirths and neonatal deaths. The HTA provides guidance on disposal of pregnancy remains, which is not directly addressed in the Human Tissue Act 2004.

161 See Human Tissue Authority (2024) *Regulating human embryonic stem cell lines for human application*, available at: https://www.hta.gov.uk/guidance-professionals/regulated-sectors/human-application/regulating-human-embryonic-stem-cell

International guidance

The ISSCR, a global non-profit independent organisation, issued guidelines in 2021[162] supportive of SCBEM research and distinguishing current SCBEMs from embryos. It recommends that SCBEM research is subject to review, approval and monitoring through a specialised oversight process. It does not prescribe the form of oversight but recommends that its purpose should be to assess the scientific rationale and merit of the research and its ethical permissibility. The ISSCR recommends that non-integrated SCBEMs should be reported but not necessarily reviewed, and integrated SCBEMs should be both reported and reviewed. In 2023, the ISSCR issued a statement supporting SCBEM research and compliance with the 2021 guidance.[163]

The European Society of Human Reproduction and Embryology (ESHRE) Ethics Committee writing group has recently set out ethical guidance relying on the distinction between integrated and non-integrated SCBEMs.[164] One of its recommendations is that non-integrated SCBEMs should be used whenever it is expedient to do so given the objectives of the research, because integrated models have a higher moral status. Another recommendation is that integrated SCBEMs should not currently have the same moral or legal status as embryos, but should in the future if they become sufficiently similar.

The ISSCR's distinction between integrated and non-integrated SCBEMs represented a helpful attempt to categorise the developing models to ensure that oversight would be specific and proportionate, but for the reasons we have explored, this categorisation is becoming increasingly difficult to sustain (see '**Challenges for the categorisation and definition of SCBEMs**' above). This salutary lesson speaks to the value in establishing categories so that governance and oversight can be tailored to risks and benefits posed by each type, but also the dangers and difficulties of establishing categories that can remain fluid as the research develops at pace. In this report, we do not attempt a new categorisation but instead propose mechanisms that will allow the science to develop safely to the point where categorisations are likely to be sustainable in the medium to long term.

The ISSCR guideline is under review at the time of writing.[165] There are advantages to achieving international consensus on aspects of the oversight and governance of SCBEMs. Without it, there is a risk of international research being carried out that does not meet high ethical and scientific standards; this in turn could impact on the national public perception of risk, leading to a more risk-averse approach that

162 International Society for Stem Cell Research (2021) *ISSCR guidelines for stem cell research and clinical translation*, available at: https://www.isscr.org/guidelines

163 International Society for Stem Cell Research press release (26 June 2023) *The ISSCR statement on new research with embryo models*, available at: https://www.isscr.org/isscr-news/isscr-statement-on-new-research-with-embryo-models

164 Writing Group of the ESHRE Ethics Committee, Pennings G, Dondorp W, Popovic M, *et al.* (2024) Ethical considerations on the moral status of the embryo and embryo-like structures *Human Reproduction* deae228 (Epub ahead of print).

165 See International Society for Stem Cell Research press release (17 June 2024) *The ISSCR forms embryo models working group*, available at: https://www.isscr.org/isscr-news/the-isscr-forms-embryo-models-working-group

hinders responsible scientific development. Moreover, a degree of harmonisation will improve international collaboration and help to advance the science. However, there are also limits to what can be achieved given the divergence of normative views on the status of the embryo and the SCBEM, and variations in regulatory frameworks, including legal definitions of 'embryo'. Some countries, such as Austria, Germany and Italy, ban embryo research.[166] Some, like the UK, allow licensed research up to 14 days, and others do not set out a limit. These positions are likely to impact on the perceived acceptability of SCBEM research in different countries. International consensus on SCBEMs might therefore focus on procedural oversight mechanisms and red lines, but detailed frameworks are likely to be left to each state.

The HYBRIDA project outputs provide another useful international resource.[167] It focused on organoids but also included SCBEMs. In 2024, it set out operational guidance and a Code of Conduct for researchers. This differentiates between organoids that do not require ethical review and those that will always require it (including blastoids and other 'complex assembloids'). It also sets out prohibitions, including gestating human SCBEMs. A practical guide for ethics committees – where they are willing to review SCBEM research proposals – includes a checklist and tools to enhance transparency.

UK SCBEM Code of Practice

A UK SCBEM Code of Practice was produced in 2024 in a partnership between Cambridge Reproduction and Progress Educational Trust.[168] The *Code of Practice for the Generation and Use of Human Stem Cell-Based Embryo Models* has the potential to form the basis for soft law governance of SCBEMs in the UK. To do so, it will need to be adopted by relevant organisations, institutions and funders. With those endorsements in place, the UK SCBEM Code could increase confidence in research whilst retaining flexibility to respond to scientific developments.

The UK SCBEM Code builds on the ISSCR guidance but does not adopt the distinction between integrated and non-integrated models.[169] The Code advises that all SCBEMs should be subject to ethical review. It sets out fundamental research principles, including the requirement that SCBEMs are only as 'complex' or 'integrated' as needed to achieve the research objectives, and that they are researched for the minimum time necessary.

In compliance with ISSCR guidance, the Code recommends that an Oversight Committee should be established, and a register maintained to record studies and make basic details available to the public. The Oversight Committee will need high standards of governance and transparency in constitution, funding and decision

166 Matthews KRW and Morali D (2020) National human embryo and embryoid research policies: a survey of 22 top research-intensive countries *Regenerative Medicine* **15(7)**: 1905-17.

167 See HYBRIDA Project (2024), available at: https://hybrida-project.eu

168 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode

169 Ibid, at page 5.

making to allay concerns as to its independence and legitimacy.[170] It is not clear at the time of writing how the committee and register will be funded, how the composition of the committee will be determined, and whether there will be a close relationship with relevant regulators, as called for by the Code's authors.[171]

Those complying with the Code must not transfer a SCBEM (whether human or non-human) "to the *in vivo* reproductive tract of a human host" or transfer a human SCBEM "to the *in vivo* reproductive tract of a non-human animal host".[172] The Code does not, however, set fixed limits for keeping SCBEMs in culture.[173] The Chair of the Code working group, Roger Sturmey, argues that this approach avoids "oversimplified limits" and the impracticability of applying "unified limits to all types of embryo model."[174] Instead, the Code advises that limits should be set on all research projects on a case-by-case basis. This will be imposed by the Oversight Committee, based on a reasoned case that it is the minimum time needed to achieve the scientific objective proposed, and subject to the Oversight Committee's approval of that objective.[175] We support both the prohibitions and the case-by-case limits, but make cases for both putting the prohibitions on a statutory footing to give them legal force, and working towards a fixed upper limit for the most complex models to apply in conjunction with the case-by-case limits (see '**Governance options**' below).

Søren Holm has raised concerns that the Code does not set out relevant ethical principles that researchers and the committee would need to apply to assess the ethical justifications for the research. He concludes: "What will be provided is, therefore, likely not to be governance or regulation, but (merely?) legitimation".[176] We note that Annex 3 to the Code proposes that the Oversight Committee would be responsible for developing guidance and online tools to support the application and

170 See Mallapaty S (2024) Lab-grown embryo models: UK unveils first ever rules to guide research. *Nature* **631(8020)**: 259-60; and see Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

171 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode, Appendix 3 says "The Committee should include members with a range of expertise, including in relevant scientific and legal fields, in ethics, and in the regulation of scientific research, as well as lay members or patients with lived experience relevant to research involving SCBEMs."

172 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, 5.4 available at: https://www.repro.cam.ac.uk/scbemcode

173 See the discussion in Mallapaty S (2024) Lab-grown embryo models: UK unveils first ever rules to guide research. *Nature* **631(8020)**: 259-60; and see Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

174 Sturmey R (2024) Guidelines on lab-grown embryo models are strong enough to meet ethical standards – and will build trust in science *Nature* **632(8023)**: 9.

175 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode, at section 5.1.

176 Holm S (27 August 2024) Regulating SCBEMs without reviewing standards – Akin to selling elastic by the metre? *PET BioNews* **1253**, available at: https://www.progress.org.uk/regulating-scbems-without-reviewing-standards-akin-to-selling-elastic-by-the-metre/; and see in reply Hitchcock J (30 September 2024) Embryo models and governance – the honest measurement of elastic *PET BioNews* **1258**, available at: https://www.progress.org.uk/embryo-models-and-governance-the-honest-measurement-of-elastic/

reporting processes.[177] We return to matters of oversight later on (see '**Creating the flexibility for collaborative regulation**').

Legitimacy and accountability will be key to the success of the UK SCBEM Code. There are important mechanisms built into it to account for scientific development. One is that it should be subject to regular review and update.[178] Another is that, if SCBEMs develop so that they have "the potential to develop fully within a human host, it would no longer be appropriate to refer to it as a 'model', rather, it should then be viewed as an 'embryo', and would be governed as such." [179] A risk inherent with this approach is that it will be difficult to control when that potential is considered sufficient, and which models should be accommodated within the definition of 'embryo'. We consider below why that risk is disruptive and how it might be mitigated.

The UK G-SCBEM public dialogue that fed into the UK SCBEM Code reported support for a voluntary code but also wide agreement that legislation would be necessary in the medium to long term, and that the UK SCBEM Code might provide a valuable stepping stone to its development.[180] More broadly, whilst some participants considered that the fast-paced development of SCBEMs was a reason for flexible voluntary governance, others considered it a strong indicator that legislation was needed to exercise sufficient control of what should be permitted and restricted.[181] We make recommendations later on how the Code might be strengthened and what forms the subsequent stages in the governance of SCBEMs should take (see '**Amendment of the UK SCBEM Code of Practice**').

We believe that the Code responds to the governance gaps in a timely and flexible manner. It fills an immediate gap in advance of the legal changes that we propose, which are likely to take some years to come about. In the sections that follow, we suggest a staged approach to governance in which the UK SCBEM Code – if well executed and supported – will provide immediate support and reassurance whilst also serving as a valuable learning mechanism.

The legal status of SCBEMs

'SCBEM' is an umbrella term that incorporates models of varying degrees of complexity and which are derived from stem cells from different origins. In Australia, some SCBEMs are encompassed in their statutory definition of 'embryo' and as a result are subject to the same regulatory framework. Elsewhere, however, there is broad consensus that SCBEMs are not currently embryos and, as such, a bespoke governance response is needed that balances a precautionary approach to risk and the **public benefits** that

177 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode, page 21.

178 Ibid, at page 4.

179 Ibid, at page 7.

180 Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

181 Ibid.

might flow from the research (see '**Contribution and potential uses**' above).

Comparative positions on the status of the SCBEM

Partial embryo models emulate elements of embryonic tissue or structures. **Gastruloids**, for example, are three-dimensional structures that model aspects of the gastrula stage equivalent to 14 to 21 days after fertilisation. However, they do not mimic the dynamic linear developmental timelines of the embryo, and they model only some of the embryo's features. These models do not resemble complete embryos but at some point in the future might develop morally relevant features and could potentially be developed into more complex models.[182]

Although more complex and integrated SCBEMs model the embryo more completely, even the most complex models are currently structurally dissimilar to the human embryo and also differ in terms of their origins and the researcher's intention for their use and development. However, it is also the case that some forms of SCBEMs will gain scientific value if they can mimic aspects of early embryonic development in as complete a manner as possible. We have heard that the field is moving towards more complex models at later stages of development. As such, whilst some predict the SCBEMs will always be 'incomplete',[183] it is possible that in the medium to long term the similarities between embryos and some forms of SCBEM will be meaningful and significant. At some point in the future, it is possible that SCBEMs could reach a 'tipping point' at which they become indistinguishable from embryos, either because SCBEMs go through the same steps of embryogenesis or because they, or their derivatives, result in capacities commensurate with the potential for live birth.[184] However, it might be difficult to recognise that this moment has arrived or indeed that it is imminent. We do not, at the time of writing, have an effective means of tracing and monitoring developments, though the UK SCBEM Code proposes to establish a register that would go some way to improving transparency. Moreover, the science may not develop incrementally, and signs of advancement in non-human animal models – such as a pregnancy initiated and sustained in a non-human primate (NHP) by an NHP-derived blastoid – may not provide accurate indicators.

The regulatory landscape is complicated by the fact that there is international variation as to the definition of an embryo, what the definition entails in terms of restrictions on research, and whether SCBEMs would fall within that definition. There would undoubtedly be benefit to an international consensus on these matters, but even if that were possible given differing views on the moral status of the embryo, it is unlikely to be achieved quickly. Meanwhile, the need to fill the governance gap at a national level grows more pressing.

182 Zernicka-Goetz M and Hyun I (2024) Embryo models need consistent ethical oversight *Nature* **630**: 305.

183 See, for example, Bristows (21 June 2023) *Governing models of human development* blog, available at: https://inquisitiveminds.bristows.com/post/102iho5/governing-models-of-human-development

184 Rivron NC, Martinez-Arias A, Pera MF, Moris N and M'hamdi HI (2023) An ethical framework for human embryology with embryo models *Cell* **186(17)**: 3548-57.

The HFEA is currently of the opinion that their licensing regime does not extend to SCBEMs.[185] The Human Fertilisation and Embryology Act 1990 is concerned with the creation of an embryo outside the human body. It sets out three levels of control: prohibition; powers vested in the Secretary of State for Health to make regulations for particular purposes; and powers vested in the HFEA to grant, revoke, suspend or deny a licence or to give binding directions. The Act prohibits licences that authorise the keeping of an embryo beyond 14 days or the appearance of the primitive streak; placing an embryo in a non-human animal; and keeping or using it in circumstances which secondary legislation prohibits. The Act also prohibits placing in a woman a live embryo other than a permitted human embryo or any live gamete other than permitted human gametes.

The term 'embryo' is defined in section 1(1) of the HFE Act 1990 as "a live human embryo". Whilst this might seem an unhelpfully circular description, the broad definition has resulted in a degree of flexibility to accommodate emerging technologies within the Act's licensing scheme. The 1990 Act originally regulated IVF; the use of donated eggs or sperm in treatment; the storage of embryos, sperm or eggs; and the use of human embryos in research. It has since been modified to extend the purposes for which research can be licensed beyond reproductive purposes, to include purposes such as increasing knowledge about serious disease or to better understand the development of embryos. Further amendments allowed research to advance cell nuclear replacement for therapeutic purposes, and Regulations in 2015 allowed mitochondrial donation techniques as part of IVF.

That flexibility could, in theory, lead to incorporation of some SCBEMs within the definition of 'embryo'. This could be happen if either a court were to decide that they fall within the ordinary meaning of the term[186] or the Secretary of State were to incorporate, via **secondary legislation**, some SCBEMs within the meaning of the term 'embryo' by virtue of section 1(6) of the HFE Act 1990. This is unlikely at present, if only because it would strain the ordinary meaning of 'embryo'. However, unless legislation is reformed to make clear that SCBEMs are distinct from embryos, it remains a possibility in the future, especially if SCBEMs become more difficult to distinguish from embryos. We discuss later why we consider that the incorporation of SCBEMs within the definition of embryos would be problematic, and propose statutory reform to protect against this change (see '**A proposal for a regulatory classification**').

In Australia, the Research Involving Human Embryos Act 2002 and the Prohibition of Human Cloning for Reproduction Act 2002 have been interpreted to apply to entities that have the potential to develop to, or beyond, the stage where the primitive streak appears. This is so even if those entities do not follow the normal stages of embryonic development, form a primitive streak, or pass through the gastrulation stage. Where that is the case, the entity is defined as an embryo and research can only proceed under

185 Human Fertilisation and Embryology Authority (2023) *Modernising fertility law*, available at: https://www.hfea.gov.uk/about-us/modernising-the-regulation-of-fertility-treatment-and-research-involving-human-embryos/modernising-fertility-law/

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

licence and would be subject to the 14-day rule.[187] The Embryo Research Licensing Committee has set out guidance to determine which SCBEMs are defined in Australian law as embryos.[188] The guidance provides two case studies: a 2022 blastoid model that met the criteria for embryo and could only proceed under licence, and a 2023 gastruloid model that did not demonstrate "organised development of a biological entity" because it lacked the full parts of a normally developing embryo and so did not constitute an embryo (though this does not rule out some gastruloids falling within the definition).

Australia is an outlier in this regard, but application of the law there demonstrates the potential to accommodate some SCBEMs within the definition of 'embryo', thereby setting an upper limit on its culture. It also demonstrates the impact that doing so can have on scientific development, and we are persuaded that these restrictions would not constitute a proportionate or targeted approach if applied in the UK.

The Health Council in the Netherlands is, as far as we are aware, the only body in a European country with proposals to revise legislation (the Dutch Embryo Act 2002) to define limits on culture time and define both embryos and SCBEMs. The proposals recommend a 28-day culture limit for both embryo research and integrated SCBEMs that might one day have the potential to develop into a human being. These models would be designated "non-conventional embryos". It is the Health Council's contention that the knowledge gap between 14 and 28 days makes the SCBEM a particularly relevant tool, but that thereafter the gains do not outweigh the risks.[189]

In their 2023 report on SCBEMs, the Conseil d'orientation of the French Agence de la biomédecine differentiates between three ways of viewing the status of SCBEMs (or 'embryoids' as the Conseil translation prefers), and mapped these onto different appropriate regulatory responses:

1. "restrictive position: embryoids are not embryos, but techniques will improve and the goal is to achieve equivalence. Consequently, research on embryoids should already be regulated in the same way as research on embryos.
2. permissive position: embryoids are not embryos, they are cultured cells. No special framework should be provided, but the same rules should apply as for all research on cell lines.
3. intermediate position: embryoids are not embryos, but they model early embryonic development and enable scientific and medical advances. Therefore, they deserve a specific framework that should be more flexible

187 On the restrictive impact of this position on SCBEM research in Australia, see Mallapaty S (2024) Human embryo models are getting more realistic – raising ethical issues *Nature* **633(8029)**: 268-71.

188 National Health and Medical Research Council. *Determining whether an embryo model is regulated by the ERLC*, available at: https://www.nhmrc.gov.au/research-policy/embryo-research-licensing/commonwealth-and-state-legislation/determining-whether-embryo-model-regulated-erlc

189 Health Council of the Netherlands (2023) The 14-day rule in the Dutch Embryo Act, available at: https://www.healthcouncil.nl/binaries/healthcouncil/documenten/advisory-reports/2023/10/31/the-14-day-rule-in-the-dutch-embryo-act/16e_The-14-day-rule-in-the-Dutch-Embryo-Act_advisory-report.pdf; and Van Kerckvoorde M (6 November 2023) Health Council of the Netherlands recommends doubling the 14-day limit on embryo research *PET BioNews* **1214**, available at: https://www.progress.org.uk/health-council-of-the-netherlands-recommends-doubling-the-14-day-limit-on-embryo-research/

than that for embryo research, but more stringent than that for research on traditional cell lines." [190]

The Conseil d'orientation, in common with the ISSCR, supports the intermediate position. The Conseil concludes that even if non-human animal models acquire properties that make them impossible to distinguish from embryos, the human SCBEM can be distinguished from the human embryo because the SCBEM originates from stem cells rather than fertilisation and SCBEMs are at no point intended to serve the goal of procreation.[191]

In France, all embryos available for research are initially considered by the Conseil to be part of a 'parental project', even if they are later used for research. That is not the case in the UK where embryos can be created purely for research purposes (see '**Sources of human stem cells**'). Nonetheless, as we discuss in the next section, we see value in making clear that SCBEMs cannot now, and should not in the future, be developed for purposes of *in vivo* implantation in the reproductive tract of a human or non-human animal with reproductive intent.

Two potential classifications of the SCBEM

The similarity of SCBEMs to embryos points in two potential directions.

1 As the science develops it is possible to imagine a future when some SCBEMs would be effectively indistinguishable from embryos in the opinion of experts, insofar as they share features that reliably indicate potential for onward development.[192] We note that SCBEMs may always retain the hallmarks of prolonged culture that on close inspection would render them distinguishable. At present, this results in differences, such as higher mutation rates and unusual epigenomic marks.[193] It is possible that even if culture methods improve, these differences will persist. Assuming, however, that a '**Turing test**' of equivalence is passed, it might be argued that those SCBEMs should at that point be regulated as *embryos*.[194] The ESHRE Ethics Committee writing group recommends that the 14-day rule that applies to embryo research is extended to 28 days, and that integrated SCBEMs that pass a test of equivalence to embryos are subject to the same upper time limit, though based on

190 Agence de la Biomédecine (2023) *Opinion of the Conseil d'orientation: stem cell-based embryo models*, available at: https://www.agence-biomedecine.fr/IMG/pdf/22-06_avis_du_co_embryoi_des_eng-2.pdf (Note: this is a translation).

191 Ibid.

192 On which, see Jackson E. Regulating embryo models in the UK (2024) *Journal of Law and the Biosciences* **11(2)**: lsae016.

193 Epigenomic marks refer to compounds and proteins that attach to the genome, thought to modify their expression and turn genes on or off; See, for example, Wang S, Wang Z, Su H, et al (2021) Effects of long-term culture on the biological characteristics and RNA profiles of human bone-marrow-derived mesenchymal stem cells *Molecular Therapy Nucleic Acids* **26**: 557-74.

194 Named after Alan Turing, who in 1950 set out a mathematical test of a machine's ability to exhibit intelligent behaviour equivalent to that of a human. On the relevance of the Turing test to SCBEMs, see Rivron NC, Martinez Arias A, Pera MF, *et al.* (2023) An ethical framework for human embryology with embryo models *Cell* **186(17)**: 3548-57.

morphological development rather than time elapsed.[195] The UK SCBEM Code also relies on the concept of equivalence insofar as it suggests:

"... 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 to refer to it as a 'model'; rather, it should then be viewed as an 'embryo', and would be governed as such." [196]

As such, assuming agreement that the equivalence criteria have been satisfied, the licensing regime set out in the Human Fertilisation and Embryology Act 1990 would be invoked and its strict prohibitions applied. As we have seen, based on current UK laws some SCBEMs could in future potentially be incorporated within the definition of 'embryo' if the HFEA changed its current position, or if the Act was amended by secondary legislation, or through a judicial decision.

There are risks inherent in an approach where the regulatory response is predicated on the concept of equivalence. The ESHRE writing group consider that equivalence would occur when the SCBEM goes through the same steps of embryogenesis as embryos and once there have been "live births in several mammalian species".[197] The steps, however, can potentially be manipulated, and there is nothing to say that human SCBEMs would necessarily lag behind the development of other mammalian species.[198] As such, both the point at which equivalence occurs, and reliance on it, are likely to be contentious. In the UK, where some groups might consider that equivalence is achieved well before that point or that regulatory action is justified ahead of equivalence, an approach that relies on equivalence to embryos risks under-regulation if it is judged to occur too late, and over-regulation if it is judged to occur too early.

2 Alternatively, if it is accepted that there are relevant factors that justify separate classifications of the embryo and a SCBEM, then their similarity or points of overlap might form the justification for governance or regulation, albeit *different* governance or regulation.

Some groups might consider some SCBEMs to be sufficiently equivalent to justify classification as an embryo, and the number who hold this view may increase if/as the models develop in complexity. We have discussed previously the 'Warnock

195 Writing Group of the ESHRE Ethics Committee, Pennings G, Dondorp W and Popovic M, *et al.* (2024) Ethical considerations on the moral status of the embryo and embryo-like structures *Human Reproduction* deae228 (Epub ahead of print).

196 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode, at page 7.

197 See Rivron NC, Martinez-Arias A, Pera MF, et al. (2023) An ethical framework for human embryology with embryo models *Cell* **186(17)**: 3548-57.

198 Points made by Søren Holm during the HYBRIDA Project final conference, held on 15 May 2024. https://hybrida-project.eu/2024/05/16/hybrida-final-conference-in-brussels/

consensus', reached to allow embryo research but impose clear limits on its ambits (see '**Establishing the need for governance**'). We consider that the best way to achieve a governance consensus that allows researchers a clear and protected space, affords society the potential benefits of research developments, and guards against the development of unethical models, is to maintain separate classifications and separate governance tools to govern SCBEMs and embryos.

A proposal for a regulatory classification distinguishing SCBEMs and embryos

As such, we prefer the second direction referred to in the previous section, whereby, for *governance purposes*, the SCBEM is considered to be distinct from the embryo even if a time may come when, for *scientific purposes*, the two could become indistinguishable in terms of their capacity for onward development, as evidenced by the reliable detection of certain molecular and cellular proxies.

How is this defensible? In *Matadeen v Pointu*, Lord Hoffmann famously stated that "treating like cases alike and unlike cases differently is a general axiom of rational behaviour." [199] The case concerned laws designed to protect people from discrimination. He went on to say

> **"The very banality of the principle must suggest a doubt as to whether merely to state it can provide an answer to the kind of problem which arises in this case. Of course persons should be uniformly treated, unless there is some valid reason to treat them differently. But what counts as a valid reason for treating them differently?"** [200]

Our proposal is that there are sufficient reasons to justify differential treatment. We consider that bespoke governance of SCBEMs as a separate entity would be more robust, predictable, consistent and coherent than governing them all (or a subsection of them) as embryos.[201] Two pragmatic problems would flow from the governance of SCBEMs as embryos:

1. The change in status would disrupt scientific development. This is not problematic if the disruption is proportionate and justified, but, as we will go on to discuss, there are reasons to doubt that that would be the case. The undue disruption of scientific development has ethical implications insofar as it would prevent advances that have the potential to benefit society. Reclassification of SCBEMs as 'embryos' would have a radical impact on what research can be undertaken in the UK and the way models are protected nationally and internationally. We consider there to be a risk that

199 *Matadeen v Pointu* [1999] 1 AC 98, 109.

200 Ibid.

201 As supported by section 2(3)(a) of the Legislative and Regulatory Reform Act 2006: "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*, available at: https://www.nao.org.uk/wp-content/uploads/2021/05/Principles-of-effective-regulation-SOff-interactive-accessible.pdf

this would be disproportionate and disruptive, either because the categorisation is too crude and SCBEMs that are not like embryos are included, or because the reclassification happens at some point before the equivalence stage is reached. The former is possible because, for reasons we have explored above, the categorisation of different models to allow targeted governance has so far proved to be difficult (see '**Challenges for the categorisation and definition of SCBEMs**'). The latter is possible because it is unclear both when equivalence is achieved, and whether it is the appropriate point at which to act. In the UK context, case law, Regulations or a regulatory change of position could result in a reclassification of SCBEMs in advance of evidence of equivalence. Assuming that a more permissive environment exists internationally, researchers would likely relocate. Even the potential for this change and the uncertainty that surrounds it is likely to impact on patentability and investment.

2 The regime governing embryos would make for a poor fit, even for those SCBEMs that most closely resemble the embryo. 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 do so to incorporate SCBEMs is, we consider, an indicator of the lack of equivalence from a governance perspective. A bespoke governance solution would be better suited to protecting against inadvertent breaches and to ensure that loopholes are not pursued to evade the purpose of governance.

We recommend that SCBEMs and embryos are considered different entities for governance purposes. The governance position we propose is proactive rather than reactive. It neither denies nor resolves the moral dilemma as to whether a SCBEM is, or could one day be, *scientifically* very similar to an embryo. Rather, it provides a justification for differential treatment in law based on the pragmatic ground that governance as a separate entity will be safer and more proportionate.

The issue of whether SCBEMs should be governed as embryos is distinct from the question of whether SCBEMs should be subject to governance and, if so, what such governance should look like. As such, recognising the SCBEM as a separate entity is not to deny that governance could be justified, and we turn to this issue later (see '**Governance options**').

Our conclusion, then, is that notwithstanding the theoretical potential in the future for SCBEMs to pass a 'Turing test' of equivalence with embryos, our preferred solution is to govern embryos and SCBEMs separately. This is in recognition of the different origins and intentions associated with SCBEMs and, given the current framework for

the regulation of embryos, the pragmatic advantages of separate governance which would facilitate targeted, proportionate, effective and bespoke oversight.

Hard and soft law approaches

One of the challenges of proportionate governance is finding the right combination of hard and soft law options (see **Figure 2** below).

Soft law and self-governance are frequently methods of choice for emerging technologies, as they can readily incorporate strategies for dealing with uncertainty.[202] This is advantageous in terms of flexibility, relevance and buy-in from those who will be subject to the relevant governance framework.[203] However, as the name implies, soft law is not binding but voluntary. That is not to say that soft law inevitably lacks sanctions. The UK SCBEM Code, for example, will rely on relevant institutions to help enforce the Code, in the hope that funding (for example) is conditional on compliance with the Code. Soft law measures do, however, rely heavily on trust of the group that makes and applies the rules to which it is then subject.

Hard law, on the other hand, is precise, binding and violations often result in sanctions. However it is slow to come about, difficult to change and can have unintended consequences if unanticipated developments occur.[204] For example, as we have previously discussed, the definition of 'embryo' used in Australia has led to some SCBEMs being incorporated within the legislation, which has had a restrictive impact on research (see '**Comparative positions on the status of the SCBEM**'). In the context of SCBEMs, the ISSCR has advised that "publicly accountable regulatory oversight is preferable to proscriptive legislation that could have unintended negative consequences in the future." [205]

Delegation comes in various forms but generally involves ground rules set out in hard law, delegating responsibility for governance in the application and/or development of the law to third parties. Sometimes a principle is set out in law and a regulatory body is tasked with its interpretation. Sometimes third parties are given powers to make certain decisions in an iterative process of learning, adapting and responding.

The various mechanisms are not necessarily antagonistic and can be used in combination. In emerging technologies, soft law is sometimes a stepping stone to hard law. In relation to SCBEMs, the UK SCBEM Code is a form of **soft law**, but it recognises the relevance of **hard law** as a backup position if some SCBEMs become

202 Note, for example, the concept of technology readiness levels used to measure the maturity of a technology and match it to appropriate funding opportunities. See UK Research and Innovation (2022) *Activities associated with different technology readiness levels*, available at: https://www.ukri.org/publications/activities-associated-with-different-technology-readiness-levels/

203 The UKRI Code of Practice for the use of Human Stem Cell Lines (2010), discussed above in the 'Legislative application and gaps' section, is an example of a successful soft law mechanism.

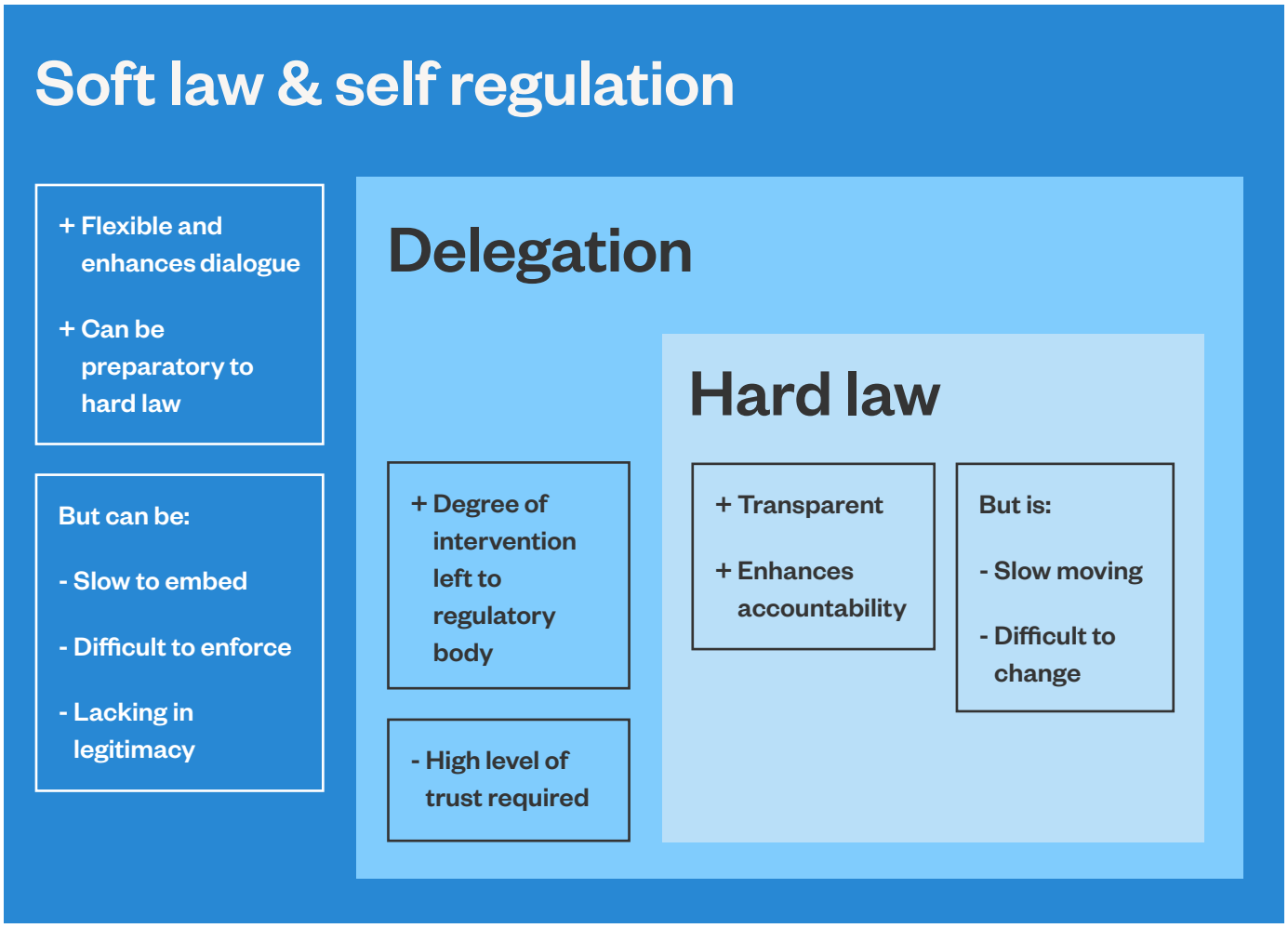
204 International Society for Stem Cell Research (2021) *ISSCR guidelines for stem cell research and clinical translation*, available at: https://www.isscr.org/guidelines

205 International Society for Stem Cell Research (2021) *ISSCR guidelines for stem cell research and clinical translation*, available at: https://www.isscr.org/guidelines

equivalent to embryos, saying that it is "sensible, periodically, to reassess whether SCBEMs fall within the definition of 'embryo' under the HFE Act".[206]

Both soft law and hard law mechanisms have cost implications both for the governing or regulatory body and those subject to regulation. When compared with a hard law *prohibition*, soft law mechanisms and delegation can be relatively time-consuming and expensive, though much depends on the costs of enforcing the prohibition. When compared with delegated oversight of a regulator, soft law mechanisms may be less expensive, but monitoring may also be less rigorous. We have not undertaken a cost analysis as part of this project, but we consider that a process of learning and development towards a governance system to be important in working out the true benefits and costs associated with governance and regulatory action.

Figure 2. Hard law and soft law approaches



206 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode, at page 18.

Governance options

We referred earlier to the acceptance by the French Conseil d'orientation of the intermediate governance position that SCBEMs "are not embryos, but they model early embryonic development and enable scientific and medical advances. Therefore, they deserve a specific framework that should be more flexible than that for embryo research, but more stringent than that for research on traditional cell lines" (see **International guidance**).[207]

Several governance options fit into this intermediate approach. The most permissive is self-governance as set out in the UK SCBEM Code. A more restrictive approach would be to enforce certain prohibitions in legislation or delegate certain matters to a regulatory body to oversee.

In the current climate, we consider self-governance a proportionate response. Provided the register and Oversight Committee prove effective, and provided the soft law mechanisms prove sufficient to ensure compliance within a reasonable timeframe, the Code will offer significant advantages over the current governance gap. Crucially, there would be enhanced transparency about what research is being undertaken, allowing greater foresight about the speed and direction of advancements. We are confident that compliance with the UK SCBEM Code would ensure high standards and reassure the public and researchers.

We recognised earlier the voluntary nature of the Code and its dependence on endorsement from institutions, organisations and funders for it to be effective (see '**UK SCBEM Code of Practice**'). This will require a coming together of different groups and will inevitably take time and a degree of good will. We have four additional concerns at the time of writing. These concerns do not constitute criticism of the model or question its relevance and value; on the contrary, we believe the UK SCBEM Code to be a sound basis for the longer-term development of SCBEM governance. Rather, our approach is to consider how proportionate governance can be future-proofed by proactively laying foundations now for the likely development of the field.

Whilst we are assured that compliance with the UK SCBEM Code will improve research and investor confidence in the short term, we consider that there are risks to its potential to do so in the longer term. **We recommend that future governance should be proactively designed rather than reactive to a particular development or event, risking a disproportionate and disruptive response.**

1 With regard to the proposed Oversight Committee and register, it is not yet clear precisely how the Oversight Committee will be funded, who will sit on it, and how decisions will be monitored and enforced. We are heartened by

207 Agence de la Biomédecine (2023) *Opinion of the Conseil d'orientation: Stem cell-based embryo models*, available at: https://www.agence-biomedecine.fr/IMG/pdf/22-06_avis_du_co_embryoi_des_eng-2.pdf (Note: this is a translation).

reports of the Oversight Committee being developed in the near future.[208] One option is to situate the Committee within an existing structure. A small number of RECs could potentially be highlighted as specialist SCBEM RECs and develop expertise in this regard. Alternatively, an entirely new committee might be established. The UK SCBEM Code calls for involvement of relevant regulators in the Oversight Committee.[209] An option we explore below is **for the committee to be allied to a regulatory body, but with representation from across other relevant regulators** (see '**Creating the flexibility for collaborative regulation**'). In particular, the UKSCB Steering Committee, HTA and HFEA have expertise and oversight capabilities that could enhance effectiveness and legitimacy. Together with the MHRA, the HTA and HFEA have issued a joint statement on ESC lines for human application that, whilst brief, demonstrates overlapping remits and the intention to work collaboratively.[210] **For researchers and society to benefit from regulatory involvement, and for the regulators to avoid reputational risk, some powers would need to accompany their involvement.** We consider below how that might be achieved proportionately and flexibly.

We consider that an Oversight Committee might develop scientific and ethical expertise that could in time be useful in a wider range of research models, potentially incorporating some organoid models and *in vitro*-derived gametes, for example. The committee might also have a useful role in advising the Government on developments. In time, as we recommend later, it may be advantageous to put an Oversight Committee on an independent and potentially statutory footing, increasing its status and powers, and establishing routes for monitoring performance of the committee (see '**Amendment of the HFE Act 1990**').

2 A longer-term risk is that a reactive regulatory response could render the UK SCBEM Code redundant in relation to some SCBEMs. The UK SCBEM Code recognises that a time may come when a SCBEM could be considered to have the potential to develop fully within a human host.[211] At this point, the Code considers it would be appropriate to regulate the SCBEM as an embryo. A risk in this approach is that the questions of when this point is reached, and which models are included, will be highly contentious. The UK's current definition of an embryo, existing powers in the HFE Act 1990 and judicial precedent combine to create the potential for a decision to change the classification of SCBEMs in a manner that is

208 Sturmey R (2024) Guidelines on lab-grown embryo models are strong enough to meet ethical standards – and will build trust in science *Nature* **632(8023)**: 9.

209 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode, at page 21.

210 Human Tissue Authority, Human Fertilisation and Embryology Authority and Medicines and Healthcare Products Regulatory Agency (2022) *Regulating human embryonic stem cells lines for human application*, available at: https://www.hta.gov.uk/guidance-professionals/regulated-sectors/human-application/regulating-human-embryonic-stem-cell

211 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode, at page 7.

disproportionate and that radically alters the research landscape to its detriment. This risk is not current: the judicial route, for example, would depend on establishing that the SCBEM falls within the ordinary meaning of the term 'embryo'.[212] The evidence suggests that this point is some way off. The point is that it is difficult to predict when the argument will be raised and on what evidence, and whether it will be successful. We consider below that proactive measures to make this less likely, in tandem with regulatory assurances of barriers that must not be crossed, would future-proof the scientific development of SCBEMs in the longer term, enhance investment in SCBEM research, and thereby improve the prospect of societal benefit.

3 We consider there to be benefit in reinforcing the prohibition on transfer of any SCBEM to the *in vivo* reproductive tract of a human or non-human animal[213] that is set out in the UK SCBEM Code, in hard law. This would serve to future-proof the 'SCBEM' as a research model and provide reassurance to the public that the prohibition is binding.

4 We support the Code's perspective that the case-by-case limit might be viewed as a 'holding position' pending clearer categorisation that would make a single fixed culture limit feasible.[214] We recommend a step towards that limit in the form of a revision to the UK SCBEM Code that would set out an upper threshold to be applied by the proposed Oversight Committee. We set out where the threshold should sit, for what purposes, and how it might be applied. An aim should be to test and develop the threshold with a view to establishing a clear upper limit in future.

How might this be achieved?

Amendment of the UK SCBEM Code of Practice to introduce an upper threshold

The UK SCBEM Code sets out a case-by-case limit that will be applied by the proposed Oversight Committee to ensure that SCBEMs are maintained "for the minimum time needed to achieve the scientific objective proposed".[215] The Code recognises that there would be value in a fixed upper limit in the longer term and proposes that the case-by-case limit is a 'holding position'.[216] Indeed, there are strong pragmatic reasons to consider an upper limit, which has the potential to enhance public trust.[217]

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

213 We are also supportive of the UK SCBEM Code of Practice prohibition on transfer of a non-human SCBEM to the *in vivo* reproductive tract of a human host, but have focused in this report on human SCBEMs.

214 Cambridge Reproduction and Progress Educational Trust (2024) *Code of practice for the generation and use of human stem cell-based embryo models*, available at: https://www.repro.cam.ac.uk/scbemcode, at page 8.

215 Ibid, at section 5.1

216 Ibid, at page 8.

217 See Mallapaty S (2024) Lab-grown embryo models: UK unveils first ever rules to guide research. *Nature* **631(8020)**: 259-60.

As Mary Warnock argued in 1984 when proposing the '14-day rule' that was subsequently applied to embryo research:

> **"There must be *some* barriers that are not to be crossed, *some* limits fixed, beyond which people must not be allowed to go."** [218]

The 14-day rule, which describes the maximum time an embryo can be kept in culture for research purposes, coincides with the point around which human embryos develop the primitive streak. As Sarah Franklin and Emily Jackson explain, it balanced the risk of the limit appearing arbitrary with the risk of having no limit at all. It did this by finding a scientific, ethical and sociological compromise that enough people would find acceptable so that it would provide a workable basis for governance.[219]

Three reasons are given in the UK SCBEM Code for not setting out a fixed upper limit on SCBEMs at this point. One is that a cautious approach is needed, given the paucity of knowledge about SCBEMs and how they might develop. The second is that the Code aims to guide best practice and does not have authority to set out a single fixed limit. The third is that it is not yet needed because SCBEMs are not approaching the point where pain perception is possible, which the Code – citing the Royal College of Obstetricians and Gynaecologists[220] – considers to be around 28 weeks.

While we accept that caution is required so that valuable and ethical research is not obstructed by an upper limit, we consider that, even now when the science is advancing quickly, this can be accommodated through careful framing and sufficient discretion in its application. This is made possible precisely because of the Code's soft law status, which facilitates a process of reflection, learning and amendment as the science develops. The third reason is troublesome because, as we discussed in the section '**Capacities and features**', there is disagreement about when a fetus can experience capacity and consciousness, with some positing that this can happen from as early as 12 weeks. Whilst there is no evidence that we are approaching a point in the scientific development of SCBEMs where they could attain either capacity, we consider that there is ethical justification for taking a cautious approach by setting out clear guidance in the UK SCBEM Code that some research objectives are not ethically justifiable.

We recommend a first step towards a fixed upper limit that would initially function as a guide to researchers and the proposed Oversight Committee in the application of the case-by-case limit. This should be refined and strengthened as the

218 Department of Health and Social Security (1984) *Report of the committee of inquiry into human fertilisation and embryology*, available at: https://www.hfea.gov.uk/media/2608/warnock-report-of-the-committee-of-inquiry-into-human-fertilisation-and-embryology-1984.pdf, at paragraph 5.

219 Franklin S and Jackson E (2024) *The 14 day rule and human embryo research: a sociology of biological translation* (Abingdon and New York: Routledge), at page 112.

220 Royal College of Obstetricians and Gynaecologists (2022) *Fetal awareness evidence review*, available at: https://www.rcog.org.uk/media/gdtnncdk/rcog-fetal-awareness-evidence-review-dec-2022.pdf, see section 6 'Conclusions and implications for clinical practice', at page 9.

categorisations of SCBEMs becomes clearer and more stable, and more targeted application becomes possible. In future, a fixed upper limit on SCBEM culture could potentially be incorporated into the regulatory regime we propose below. It may be that, as categorisations improve, and as the proposed Oversight Committee learns from its application of the case-by-case limit, different upper limits are applied to distinct categories. Those SCBEMs that most closely resemble embryos might be permitted to develop to a different stage from complex models that have no capacity for onward development but could potentially develop morally relevant features. Other SCBEMs that do not resemble the embryo in a meaningful way might not be subject to an upper limit at all because the case-by-case limit is considered sufficient. **In advance of the scientific developments, learning and public dialogue that would make fixed upper limit/s reliable, an interim threshold is proposed.**

We recommend that section 5.2 of the UK SCBEM Code on 'Limits for culture' is revised to include guidance to the proposed Oversight Committee when applying the case-by-case limit on SCBEM research. The Code currently states that:

> **"All SCBEMs shall be subject to a limit for *in vitro* culture to be determined during the course of application to the SCBEM Oversight Committee, as below. This limit must not be breached without further review by the SCBEM Oversight Committee. ...the models shall only be cultured *in vitro* for the minimum time needed to achieve the scientific objective proposed."**

A guiding principle in the Oversight Committee's imposition of "the minimal time needed to achieve the scientific objective" in each case should be that:

No SCBEM should be developed with features consistent with Carnegie Stage 23 or beyond if:

(i) the SCBEM has the potential to develop capacities for pain or awareness;
(ii) the purpose of the research is to explore the feasibility of reproductive purposes; or
(iii) the SCBEM has been genetically altered to avoid the capacities referred to in (i) and (ii), resulting in a SCBEM that would diminish public confidence in research if the model were to proceed beyond this threshold.

We elaborate on each of the three research purposes shortly, but turn first to the justification for the threshold.

Identifying a justifiable threshold

We have seen that, in the Warnock Report, a consensus on the point at which embryos should be allowed to develop *in vitro* for research purposes was impossible to achieve and a compromise was successfully adopted.[221] The compromise was a practical time

221 And, as we note above, is currently being reconsidered.

limit rather than a moral boundary, but it was also a limit that would have resonance with most people. We recommend a similar approach with SCBEMs, recognising two complicating factors. Firstly, a temporal (time) limit is not feasible for reasons we will come to shortly. Secondly, unlike embryos, SCBEMs are not a consistent entity but a range of entities with markedly different features and capacities. An upper limit that is justifiable in relation to a complex model that closely resembles an embryo, for example, would be disproportionately restrictive if it is applied to a model of just one part of the embryo, such as certain cell structures or tissue.

As we explored earlier, there *is* broad consensus as to the sort of capacities and features that researchers should not develop in a SCBEM model (see '**Capacities and features**' above). We propose that instead of aligning an upper limit for SCBEMs with the limit set for embryos,[222] the initial focus in setting an upper threshold for SCBEMs should be on ensuring that researchers do not develop SCBEMs with those features and capacities.

An added complication is that an upper limit on SCBEMs cannot effectively focus on temporal limits (i.e., how many days old it is) because SCBEMs can develop at different rates and in different ways to embryos and there is no clear 'day zero'. By way of example, Hyun et al. have noted that "human pluripotent stem cells grown in 3D microfluidic devices can form structures resembling the early primitive streak stage within 48 h of culture".[223] In an embryo, the primitive streak takes around 14 days to form. The Carnegie staging system is a series of points in embryonic development starting at fertilisation and ending at 56 days (or 8 weeks). It was developed in 1914 by Franklin P Mall and later George L Streeter at the Department of Embryology of the Carnegie Institution of Washington DC. It is particularly useful in this context because it is based on various morphological features rather than chronological age or size.[224]

In natural human development, the final embryonic stage before the embryo becomes a fetus is CS23.[225] This occurs in an embryo at days 56–60. We consider that an upper threshold of CS23 is a relevant point in development, *insofar as it would prevent development of the capacities in SCBEMs that many agree would be concerning*. As such, models that come within the three research purposes we have identified should not be developed beyond this stage.

None of this is to assume that it would justifiable, now or in the future, to develop a 'complete' embryo model to CS23. The Oversight Committee case-by-case

222 See, for example, Writing Group of the ESHRE Ethics Committee, Pennings G, Dondorp W and Popovic M, *et al.* (2024) Ethical considerations on the moral status of the embryo and embryo-like structures *Human Reproduction* deae228 (Epub ahead of print).

223 Hyun I, Munsie M, Pera MF, Rivron NC and J Rossant (2020) Toward guidelines for research on human embryo models formed from stem cells. *Stem Cell Reports* **14(2)**: 169-74.

224 O'Rahilly R, and Müller F (2010) Developmental stages in human embryos: revised and new measurements *Cells Tissues Organs* **192:2**: 73-84. See also HDBR Atlas (2024) *Carnegie staging criteria*, available at: https://hdbratlas.org/staging-criteria/carnegie-staging.html

225 The distinction between embryonic and fetal material is not always clear in the scientific literature.

consideration will ensure that models are only cultured for the minimal time required. The limit we propose is not designed to allow researchers to develop complex embryo models *up* to CS23, but to serve as a clear indication for researchers and the proposed Oversight Committee of what research objectives are justifiable, and apply a recognisable threshold that would work towards that aim.

An earlier upper limit, at 28 days for example, might justifiably be imposed following public and stakeholder dialogue, but to impose such a threshold at this stage would open it to criticism that it is arbitrary and that it could potentially disrupt research that would not involve the development in the SCBEM of controversial capacities and features. CS23, on the other hand, is significant because it represents the point at which the embryo is widely considered to become a fetus. At this stage in natural human development, the vital formations of the body plan are complete, and the chances of miscarriage are considerably lower.[226] Post CS23, the focus is on growth and maturation of structures that were formed in the embryonic period. In line with the protections afforded the embryo and fetus in UK law, some complex models of the post-CS23 stage could invoke different ethical and potentially also legal considerations, that do not apply to the embryo model. As such, it is not arbitrary, and it would prevent complex or complete SCBEMs that have features and capacities that could confer on them the same moral status as a fetus. On that basis, it would serve as an initial threshold that could be developed as categorisation of SCBEMs improves.

CS23 is not considered a *moral* boundary, rather, it would serve as a *practical* boundary, and one that is widely recognised as an important marker, in advance of the wider debate that is needed to settle fixed upper boundaries for the culture of certain categories of SCBEM.

Why not impose the upper threshold on all SCBEMs?

The working group notes that numerous current research programmes are using stem cell-based approaches to examine human biology and disease processes, including the use of organoids. Such organoids may not only model adult tissue; organoids modelling embryonic and fetal stages may shed light on key developmental processes required for normal function of organs, such as the heart, kidneys, etc., and explore disease processes that have their origins during this period. They may also be an important source of cells for therapeutic use. The working group was clear that such important research should not be obstructed in any way by the imposition of an upper limit for the culture of SCBEMs. Additionally, the working group considered that an upper limit should not result in inconsistent application by imposing limits on simple or partial SCBEMs that do not (and would not justifiably) apply to organoids. Rather, when considering an upper limit, the

226 As seen in foundational biological education texts; for example, Moore KL, Persaud TVN and Torchia MG (Editors) (2015) *The developing human: clinically orientated embryology*, 10th Edition (Philadelphia, PA: Elsevier Health Sciences), and supported by patient information websites; for example, NHS (2021) *You and your baby at 8 weeks pregnant*, available at: https://www.nhs.uk/pregnancy/week-by-week/1-to-12/8-weeks/#:~:text=By%20the%20time%20you're,The%20legs%20are%20getting%20longer

working group's focus was on SCBEMs that would represent attempts at more holistic development of the embryo, perhaps yielding recognisably intact, complex or complete models of the earliest stages of fetal development.

Research objectives

We turn now to our justification for this recommendation, which the working group considers should guide the Oversight Committee in exercising discretion in its approval of SCBEM research objectives on a case-by-case basis. The upper threshold would have three aims:

Aim 1: Prevent development to explore the feasibility of reproductive purposes

In our recommendations that follow, we consider that the SCBEM and embryo are sufficiently different to warrant separate legal statuses and that it should be made unlawful to transfer a human SCBEM to the *in vivo* reproductive tract of a human or non-human animal host. Both recommendations rest on an assumption that it would be unethical now and in the foreseeable future to develop a SCBEM for reproductive purposes. We recommend that the upper threshold focuses on supporting and upholding this rationale.

A potential means by which the SCBEM could in future be developed for reproductive purposes is transfer of SCBEMs to an **artificial uterus** for development outside a human or animal reproductive tract.[227] 'Complete' or 'full' ectogenesis, which would involve the whole process of conception, gestation and development taking place outside the human body, remains a considerable way off, but may in the future become possible through the convergence of research on IVF and embryo viability and the treatment of very premature babies.[228] There is wide agreement that ahead of meaningful societal debate, attempts at complete ectogenesis would be unethical. An upper threshold would support its prohibition.

Aim 2: Preventing models that can experience pain or consciousness

As we've set out above, at CS23 the embryo is not capable of either consciousness or pain perception on even the most conservative estimations of when those capacities might begin (see '**Capacities and features**'). The upper threshold would prevent the development of models that could, if the science should develop to make it possible, attain these features.

Aim 3: Maintain confidence in SCBEM research

The first two grounds focus on certain morally relevant features of the SCBEM that an upper threshold could make clear should not be the focus of

227 We note that the UK SCBEM Code at section 5.4 proposes to prohibit "full ectogenesis … to viability". Our suggestion is that this is maintained and reinforced by the upper threshold.

228 See Alghrani A (2018) *Regulating assisted reproductive technologies: new horizons* (Cambridge, UK: Cambridge University Press), at chapter 4.

research. The third ground focuses on the potential to genetically alter SCBEMs to avoid those particular features. If researchers can constrain or enhance the potential of SCBEMs to develop certain features,[229] a SCBEM might in future be developed that is genetically modified to thwart its reproductive potential or capacity to feel pain, but that nonetheless is sufficiently human-like to cause significant public concern. For example, it could become possible to develop a model that has all the features of a fetus, but by virtue of a genetic 'switch' introduced at the stem cell stage – such as one leading to programmed cell death in certain tissues at certain stages – could not reach viability. Whilst this would thwart its active potential for personhood, we recognised earlier that by sharing features with the fetus, such a model would diminish public confidence in SCBEM research and in science (see '**Dignity**'). We consider that the CS23 upper threshold would help reassure the public that integrated or complete models incapable of viability, pain or consciousness, but which nevertheless were able to develop fetal characteristics, would not be produced ahead of public and stakeholder engagement.

Conclusion

We recommend that an upper threshold would have utility in directing scientists as to what we have identified as unsuitable research goals for SCBEMs, and reassuring the public that the proposed Oversight Committee would be mindful of the potential for SCBEMs to develop certain features which we set out above (see '**Capacities and Features**'). There we discussed public concerns that SCBEMs should not be allowed to develop capacity to feel pain or experience consciousness.[230] Whilst a case-by-case limit might well prevent such research, an upper threshold would provide additional clarity and transparency.

We have also set out reasons why, for now at least, the threshold should be applied at the discretion of the Oversight Committee. The categories and indeed definitions of SCBEMs lack clarity, which means that a hard law upper limit could prevent valuable research that in no way engages with the three aims we have set out and which does not raise ethical concerns. An additional consideration is that compliance will be difficult to monitor. Molecular or other features of CS23 might be developed unwittingly and revealed only after culture has ceased. Even with fluorescent tagging for live imaging, mistakes could occur. As such, the focus, at least initially, should be on 'soft law' enforcement mechanisms which are sufficiently agile and flexible to adapt to new categorisations of SCBEMs.

229 Rivron N, Pera M and Rossant J, et al. (2018) Debate ethics of embryo models from stem cells. *Nature* **564(7735)**: 183-5.

230 Hopkins Van Mil (2024) *Addressing the governance gap: A public dialogue on the governance of research involving stem cell-based embryo models*, available at: https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf

Amendment of the Human Fertilisation and Embryology Act 1990

When considering whether and how to regulate SCBEMs, an alternative to starting afresh with a bespoke regulatory body and system, which would likely be disproportionate not least in terms of cost, is to look for fit with existing regulatory bodies and mechanisms. The HFEA has proposed that the HFE Act 1990 is opened for debate and amendment, and has recognised that any reform could incorporate SCBEMs in some as yet unspecified form.[231] Whilst much of the Act remains fit for purpose, the HFEA has called for its modernisation, so as to meet today's challenges and future-proof the Act for the foreseeable future. This may present an opportunity to make changes to substantive rules that achieve the consensus we have called for to support robust and ethical research whilst managing risk.

Reform of the 1990 Act is not the only possible route to legislative change, and if legislation on human tissue is revisited in the future then there may be potential changes that could usefully be made to the Human Tissue Act 2004. Because we are not aware of any such intention, we have focused on potential changes to the 1990 Act.

We note that changes brought in via the 1990 Act would not necessarily restrict regulatory oversight of SCBEMs to the HFEA. In the following section, we propose a collaborative endeavour that would ensure that the oversight of SCBEMs represents a range of regulatory interests. The UKSCB Steering Committee, for example, has particularly relevant experience and expertise that it has developed in overseeing the use of human ESC lines in the UK.

We consider that legislative amendments should be set out that will perform three interlinked and simultaneous tasks:

Distinguish embryos from SCBEMs

Reinforce red lines

Create flexibility for regulatory oversight

The first task is to make clear that SCBEMs are not embryos and so limit the risk that the Secretary of State by Regulations, or the courts by judicial decision, could extend the term 'embryo' to include some SCBEMs and thereby unduly disrupt investment and research. The second is to reinforce key prohibitions set out in the UK SCBEM Code to make the limits of what is acceptable clear to scientists, and to give confidence to the public and parliament that lines will not be crossed. The third task is to create flexibility for regulatory oversight and an environment in which proportionate regulation can be co-developed.

231 Human Fertilisation and Embryology Authority (2023) *Modernising fertility law*, available at: https://www.hfea.gov.uk/about-us/modernising-the-regulation-of-fertility-treatment-and-research-involving-human-embryos/modernising-fertility-law/

In the subsequent sections, we briefly explore the three proposed legislative amendments, recognising that any substantive change would require consultation and deeper consideration of wider implications and acceptability to the public and stakeholders than we can provide in this report.

Distinguishing SCBEMs and embryos

We considered previously the risk that the HFEA, a court case or secondary legislation could incorporate some or all SCBEMs within the definition of 'embryo' (see '**Comparative positions**'). Whilst this is unlikely at present, the potential may grow, particularly if some SCBEMs become more 'complete' models of the embryo. We have suggested that, **provided regulatory safeguards ensure that the SCBEM is constrained as a model of an embryo, we do not consider that it should be regulated as an embryo.** As such, we consider the potential for incorporation of the SCBEM within the definition of embryo to be potentially disruptive to research, its oversight, and investment in the technology.

We consider two potential changes that would differentiate SCBEMs and embryos. The first is to define the term 'embryo' so that SCBEMs are excluded. We consider this problematic. The second, which we think has greater potential, is to exclude SCBEMs from the term 'embryo'.

Taking them in order, the first option would be to amend the HFE Act 1990 to clarify the definition of 'embryo'. Defining the SCBEM is difficult, not only because the science is evolving, but also because the definition of the *embryo* that it models is itself unclear and contested. This leads to uncertainty as to whether SCBEMs do, or could in the future, come within its terms. One approach, then, would be to define the term 'embryo' more clearly to legislatively differentiate the embryo from SCBEMs.

The Human Fertilisation and Embryology Act 1990 defines the embryo as "a live human embryo".[232] The House of Lords viewed this as a deliberate attempt to specify the *type* of embryo that requires regulation rather than to provide a definitive definition of the umbrella term.[233] The focus in the Act, then, is on 'live' and 'human' embryos, terms which are to be given a 'purposive' rather than literal meaning, so that the fact that a type of embryo was not envisaged in 1990 will not subsequently be fatal to its inclusion within the definition. This prevents a 'free for all'.[234]

The advent of IVF challenged the notion that the embryo could be defined by reference to the natural reproductive process that brought it about. In the future, it might become possible to generate sperm and eggs from stem cells in the laboratory (a process known as *in vitro* gametogenesis), fertilisation of which could result in an embryo.[235]

232 Human Fertilisation and Embryology Act 1990, s.1(1)(a).

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

234 Ibid.

235 National Academies of Sciences, Engineering, and Medicine (2023) *In vitro-derived human gametes as a reproductive technology: scientific, ethical, and regulatory implications: proceedings of a workshop*, available at: https://nap.nationalacademies.org/read/27259/chapter/1

Is fertilisation of an egg and sperm the key to a definition? Several emerging technologies suggest not. **Somatic cell nuclear transfer** (SCNT) involves an enucleated oocyte, for example.[236] Focusing on the potential of the embryo to develop into a fetus is also problematic as we recognise and legally protect embryos that lack this potential.

Conceptually, we might work towards a dual definition of the embryo, distinguishing between relevant features that flow from fertilisation and features that flow from other processes.[237] In the former case it is possible to rely on developmental markers such as the point at which the fertilised embryo develops its own genome, or the appearance of the primitive streak at 14 days which was so crucial to the Warnock Committee's deliberations. Another definition is arguably needed to encompass embryos resulting from other methods.[238] This definition might relate to intrinsic potential, but potential can change.

We conclude that it would be problematic, for our purposes, to refine the current statutory definition of 'embryo'. There is utility in the current approach, which gives the term its ordinary language meaning and allows regulation the flexibility to encompass scientific developments.

Instead of re-defining the term 'embryo', the HFE Act 1990 might be amended to limit the likelihood of any claim that the SCBEM is for legal purposes a human embryo requiring an HFEA licence and subject to the restrictions that currently apply to the embryo. Our working group considered this to have greater potential.

How might it be achieved? One option would be to amend the Act to expressly exclude SCBEMs from the definition of embryo. Whilst we do not presume to say how this *should* be achieved, we are interested in whether it is feasible to do it and in that spirit would suggest that section 1(1)(a) could potentially be amended along the following lines:

"1 Meaning of "embryo", "gamete" and associated expressions.
(1) In this Act (except in section 4A or in the term "human admixed embryo")—
(a) embryo means a live human embryo and does not include a human admixed embryo (as defined by section 4A(6)) **or a stem cell-based embryo model (as defined by section X) …"**

Another option would be to incorporate a new section 1(8) to restrict the Secretary of State's powers to designate a SCBEM as an embryo:

236 See somatic cell nuclear transfer (SCNT) in Appendix **Glossary**.

237 Findlay JK, Gear ML, Illingworth PJ, *et al.* (2007) Human embryo: a biological definition. *Human Reproduction* **22(4)**: 905-11.

238 Ibid.

"1 Meaning of "embryo", "gamete" and associated expressions.

...

(6) If it appears to the Secretary of State necessary or desirable to do so in the 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.

(7) Regulations made by virtue of subsection (6) may not provide for anything containing any nuclear or mitochondrial DNA that is not human to be treated as an embryo or as eggs, sperm or gametes.

(8) Regulations made by virtue of subsection (6) may not provide for a human stem cell-based embryo model (as defined by section X) to be treated as an embryo.

A difficulty with both options is that they would require a clear statutory definition of SCBEMs which, as we have seen, includes a range of organised structures. Broadly, they are self-organised three-dimensional models of aspects of early human development. The process of refining this definition during parliamentary debate would benefit from further stakeholder and **public engagement**.

Reinforcing red lines

We consider that our proposed amendment to exclude SCBEMs from the definition of 'embryo' should be made in conjunction with a prohibition on transferring a human SCBEM to the *in vivo* reproductive tract of a human or non-human animal.

There are two reasons for this recommendation. The first is that legal prohibition is justified given the level of harm that could result from breach of a softer ban. SCBEMs are currently used in basic research with the potential for beneficial clinical research applications. We found no evidence in our discussions with scientists of reproductive intent and no evidence that transfer to an *in vivo* reproductive tract of a human or non-human animal would be possible in the medium term, the longer-term potential being impossible to predict. However, we heard concerns that the emphasis on originality and significance in publishing is such that similarities between the SCBEM and the embryo could be pursued to an extent that is not justified by the research aims and subsequent data. There have been recent examples outside the UK and in other areas of science, of similar ambitions leading to unethical practices that explicit and binding legal rules could arguably have prevented.[239]

As such, we consider that the prohibition would have utility. The ISSCR categorisation of stem cell research put the transfer of human SCBEMs to the

239 Chen Q, Ma Y, Labude M, *et al.* (2021) Making sense of it all: Ethical reflections on the conditions surrounding the first genome-edited babies. *Wellcome Open Research* **5**: 216.

reproductive tract of a human or non-human host in its most restrictive category. It recommended in 2021 that some practices should be "currently not permitted" whereas transfer of a SCBEM to a host is firmly prohibited due to "broad international consensus that such experiments lack a compelling scientific rationale or are widely considered to be unethical".[240] The UK SCBEM Code expressly prohibits such transfer. A legislative ban would make it legally enforceable.

A related consideration is that transfer of a human SCBEM to an *in vivo* reproductive tract is currently considered dangerous due to the extent to which the human cells have been manipulated and the impact this manipulation could have on the recipient, any future child and its descendants. The progression of SCBEM development is uneven and unpredictable and it is not implausible for there to be leaps rather than steps forward. There is a case then that the prohibition set out in the UK SCBEM Code is insufficient in terms of its enforceability, given the potential for harm. We considered that there may one day be the potential for reproductive use of SCBEMs. As such, we do not deny that a ban on implantation could one day potentially limit therapeutic use or that the ban might at some future point need to be revisited. We consider the ban to be justified on the basis of current risk.

The second reason is more pragmatic. Current law would only prohibit transfer of a SCBEM to the *in vivo* reproductive tract of a person if either SCBEMs were incorporated within the definition of 'embryo' (which we consider to be problematic) or, as we recommend, a new prohibition is set out on transfer of a SCBEM to the reproductive tract of a host. This is because s.3(2) of the Human Fertilisation and Embryology Act 1990 only prohibits placing certain 'embryos' in a woman. In the event that transfer of a human SCBEM to the *in vivo* reproductive tract of a human or non-human animal host might be put to the test, a court might currently find that the SCBEM in question came within the ordinary meaning of "a live human embryo" under the HFE Act 1990, in which case it would be a criminal offence because the embryo is "unpermitted".[241] We accept that even if the SCBEM was not found to come within the ordinary meaning 'embryo', a clinician overseeing the transfer could face other ramifications, such as breach of the General Medical Council's guidance that could lead to sanctions, including possible erasure from the medical register. Nonetheless, we consider that the current potential to reconceptualise the SCBEM as an embryo in law offers a safety net that should be retained in some other form if our recommendation to clearly distinguish embryos and SCBEMs in law is taken up.

A hard law prohibition would provide pragmatic reassurance that even if, as we propose, SCBEMs and embryos are clearly distinguished in law, there would be clear penalties attached to developing SCBEMs for human reproductive use. It would additionally serve to support the notion that the SCBEM is purely a research model, should transfer to the reproductive tract of a living human or non-human animal ever become theoretically feasible.

240 International Society for Stem Cell Research (2021) *ISSCR guidelines for stem cell research and clinical translation*, available at: https://www.isscr.org/guidelines

241 As defined in the Human Fertilisation and Embryology Act 1990, section 3ZA.

In conclusion, we recommend that consideration is given to amending the HFE Act 1990 to make clear that transfer of a human SCBEM to the reproductive tract of a human or non-human animal is prohibited. How this might be achieved will depend on other potential amendments, but several possibilities exist:

- One would be to amend section 3 of the 1990 Act which sets out prohibitions. This might simply state, in line with the UK SCBEM Code, that no person shall transfer a SCBEM to the reproductive tract of a human host and no person shall transfer a human SCBEM to the reproductive tract of a non-human animal. However, we think that in order to avoid definitional quandaries and risk unintended consequences, it could be preferable that revisions focus instead on controlling *actions*. This might involve amending section 3(2) which currently reads: "No person shall place in a woman - (a) an embryo other than a permitted embryo .... (as so defined)" to clearly prohibit the placing in a **human reproductive tract** anything *except* a permitted embryo, permitted eggs or permitted sperm.
- In relation to the placing of a human SCBEM in a non-human animal, the proscription could potentially be listed in the section 4A prohibitions in connection with genetic material not of human origin.

Creating the flexibility for collaborative regulation under a statutory scheme

We recommend amendment to the Human Fertilisation and Embryology Act 1990 to make provision for regulatory oversight of SCBEMs. At this early stage in their development it would be inadvisable to dictate the precise form that this should take. As such, the Act should set out delegated powers that can be activated by making **secondary legislation (Regulations)**. That way, the timing and extent of regulatory control can be responsive to the ways in which this emerging technology develops. The powers are generally delegated to the Secretary of State for Heath, but in some circumstances are delegated to a regulatory body. The powers to make Regulations should take three forms:

1. Powers to regulate SCBEMs under a regulatory sandbox

2. Powers to develop from the sandbox a bespoke and targeted regulatory scheme

3. Powers to put the SCBEM Oversight Committee on a statutory footing

Subject to analysis of the cost and time burdens this would involve, which is beyond the scope of this report, we propose a governance scheme in three incremental stages:

STAGE 1: Embed voluntary code

STAGE 2: Set up regulatory sandbox

STAGE 3: Settled regulation of relevant SCBEMs

We consider that this approach would enhance compliance with the National Audit Office's recommendation that a learning cycle is crucial to effective regulation.[242] It also exemplifies several of the Regulatory Horizon Council's focal points in its report *'Closing the gap': getting from principles to practices for innovation friendly regulation*,[243] including that regulatory design and implementation should consider the full range of regulatory tools.

Stage 1: Embed the UK SCBEM Code

Stage 1 involves *governance* rather than regulation. This stage focuses on implementation of the UK SCBEM Code. We call upon regulators to support its application, and scientists and the proposed Oversight Committee to work with regulators collaboratively with a view to the subsequent stages we propose. Regulators should use this period to develop clear regulatory objectives for Stage 2. One objective should be to learn during this period about the potential risks, benefits and capabilities of SCBEMs through public and stakeholder engagement, taking advantage of the increased transparency that is likely to flow from the register proposed in the UK SCBEM Code. The ultimate objective should be to co-develop proportionate regulation that does not stifle beneficial innovation.

Stage 2: Enhance regulatory control

Stage 1 will continue until it is possible to bring about the legislative change that is required for Stage 2. Whilst we recognise that this may not happen for some years from the publication of this report, we recommend both that change is expedited and that preparations begin in our proposed Stage 1. Primary legislation should create powers to issue secondary legislation, which can then be used to set up a 'regulatory sandbox'.

Regulatory sandboxes – effectively 'testbeds' – are a relatively new model that allows

242 National Audit Office (2021) *Principles of effective regulation*, available at: https://www.nao.org.uk/wp-content/uploads/2021/05/Principles-of-effective-regulation-SOff-interactive-accessible.pdf, at page 4.

243 Department for Science, Innovation and Technology, Regulatory Horizons Council Independent Report (2022) *'Closing the gap': getting from principles to practices for innovation friendly regulation*, available at: https://assets.publishing.service.gov.uk/media/62ab5a668fa8f5356c35bb61/closing-the-gap-regulation-full-report.pdf

innovation in a controlled environment, usually in a time-limited fashion, under the supervision of regulators. It has been used in the financial industry to trial small-scale live testing of new products under guidance[244] in challenging areas, such as artificial intelligence (AI). More recently it has been used in a healthcare setting. The Care Quality Commission piloted a regulatory sandbox scheme to develop regulation for innovative services. It found that co-production and collaboration were key to effectiveness.[245] The MHRA has adopted a similar approach to regulate AI as a medical device and found it to be "proactive, collaborative, agile".[246] The HFEA has proposed that regulatory sandboxes could be used "to support innovation in treatment and research" and future-proof suggested revisions to the HFE Act 1990.[247]

By this method, development of SCBEMs would not be a licensed activity but the regulator, in collaboration with stakeholders, would be able to develop guidelines (potentially by adopting and adapting the UK SCBEM Code) and monitor compliance whilst the science develops. The sandbox would only extend to activities that are lawful and, as such, this method would be of limited value if SCBEMs were brought within the definition of 'embryo' by secondary legislation or a court case – something we consider legislation should aim to prevent as outlined above.

The form the sandbox takes should be dictated by learning during the Stage 1 period. We propose that the simplest and least disruptive form would be to bring the Oversight Committee established in Stage 1 within the oversight of a single regulator so that scientists benefit from a 'one stop (regulatory) shop', but that the committee facilitates collaboration between relevant regulators. On this model, as the UK SCBEM Code proposes, the Oversight Committee will review all SCBEMs, but the least complex will require only light review. The more scientifically and ethically complex SCBEMs will require a higher level of oversight and our proposal is that the sandbox will be used to explore and develop how that can be proportionately and effectively achieved. As such, the Oversight Committee would evolve from the body proposed in the UK SCBEM Code to one in which key regulatory bodies collaborate under the authority of the regulatory sandbox, so providing enhanced legitimacy and control.

There are several options for where to situate the Oversight Committee in the sandbox stage. We discuss them briefly, noting that our focus here is on regulatory functions in the first instance, rather than their potential executors. One option is to extend the remit of the UKSCB Steering Committee, which currently subjects

244 See Jeník I and Duff S (2020) *How to build a regulatory sandbox: a practical guide for policy makers*, available at: https://www.cgap.org/sites/default/files/publications/2020_09_Technical_Guide_How_To_Build_Regulatory_Sandbox.pdf

245 See Care Quality Commission (2022) *Evaluation of CQC's regulatory sandboxing pilot*, available at: https://www.cqc.org.uk/what-we-do/how-we-work-people/evaluation-cqcs-regulatory-sandboxing-pilot

246 See Medicines and Healthcare Products Regulatory Agency (2024) *AI Airlock: the regulatory sandbox for AIaMD*, available at: https://www.gov.uk/government/collections/ai-airlock-the-regulatory-sandbox-for-aiamd

247 Proposal 14 in Human Fertilisation and Embryology Authority (2023) *Modernising fertility law*, available at: https://www.hfea.gov.uk/about-us/modernising-the-regulation-of-fertility-treatment-and-research-involving-human-embryos/modernising-fertility-law/

SCBEMs and other models originating from human ESC lines to ethical oversight, to also include scrutiny of iPSC-derived entities. A benefit is that they have experience and scientific expertise to oversee the stepwise development of sophisticated SCBEMs and have reviewed projects and considered relevant research on complex organoids, therapeutic use of stem cells in regenerative medicine, and directed differentiation from embryonic to adult tissues, all of which are relevant to the future of SCBEM research. A drawback is that the UKSCB Steering Committee's focus on ESCs reflects the special status conferred on them by parliament. Another option is to extend the remit of the HTA, which has experience of receiving donations of 'pregnancy remains', including both embryonic and fetal tissue. A third option is the HFEA, which has expertise regulating research of embryos created *in vitro* that will have relevance to the most complex SCBEMs which, in the proportionate model we propose, will require more sophisticated transparency and accountability mechanisms than simple, non-integrated SCBEMs. However, we heard concerns in our evidence gathering that the HFEA's largely clinical focus and lack of experience governing stem cell research may limit their suitability, and their current focus on licensing might not prove an appropriate model for SCBEMs.

The working group recognises that no single regulator is a perfect fit. Our preference for a collaborative model would bring in the expertise of the HFEA, UKSCB Steering Committee, HTA, MHRA and HRA. This should be facilitated by a lead regulator. A relevant consideration is that the changes we propose will require legislation to bring the SCBEMs within the remit of an existing regulator. Whilst the HFEA could currently choose to bring some SCBEMs within their remit if it considered them sufficiently alike to embryos to bring them within that definition, we are proposing that SCBEMs and embryos are distinguished in law which would remove that potential. Pragmatically, the strongest case for a review of legislation focuses on the Human Fertilisation and Embryology Act 1990 (as amended). As we discussed above, the HFEA has proposed that the 1990 Act is opened for debate and amendment regarding a number of important updates, including the potential to respond to new scientific advances with more agile sandbox regulation. If supported, this would create the potential to debate the changes we propose, in a timely manner.[248] A viable option may therefore be to enact primary legislation that gives powers to make Regulations that would bring the regulatory sandbox under the remit of the HFEA as a collaborative endeavour with other regulators. This model would not involve regulating SCBEMs as embryos but as entities requiring a bespoke regulatory response. We propose that one of the exit strategies from the sandbox would be to remove the Oversight Committee from the remit of the regulators and put it on an independent *statutory* footing, potentially with a wider remit that covers other stem cell-based research. This would require legal change, provision for which should be set out in primary legislation setting out powers to make Regulations to this effect.

248 Human Fertilisation and Embryology Authority (2023) *Modernising fertility law*, available at: https://www.hfea.gov.uk/about-us/modernising-the-regulation-of-fertility-treatment-and-research-involving-human-embryos/modernising-fertility-law/

Collaboration will be crucial to effectiveness. The HFEA and HTA have shown that they can work together effectively on overlapping areas[249] and this is promising for the potential future regulatory adoption of SCBEMs. The National Audit Office in its *Principles of Effective Regulation* recognises that the identification of a regulatory gap that does not fit neatly within an existing regulatory structure is neither unusual nor insurmountable:

> **"Many areas of regulation involve one or more main regulators with specific powers and duties to enforce or otherwise influence compliance with rules and standards. These regulators can be at national and local level, and sometimes there is not a clear boundary between regulators' remits, requiring them to work closely together."** [250]

The SCBEM regulatory sandbox should have clearly articulated milestones, success criteria and a clear funding stream. It should also be time-limited, with an exit strategy setting out the potential routes for Stage 3. The timing for exit from the sandbox to stage 3 should be clear enough so that the sandbox has a defined end point, but flexible enough that so it can respond to what is learned, as well as to scientific developments.

Stage 3: Settle the regulatory scheme for SCBEMs

Stage 3 should set out ongoing regulatory controls for different categories of SCBEM that are graded according to the risks and benefits they pose. As we have discussed, it is not possible for us to set out these categories at this time given the pace at which the science is developing, but we envisage that this will become increasingly feasible as the potential and focus of the science become clearer. Our working group is clear that the more 'integrated' or 'complete' models will require greater oversight and monitoring than 'non-integrated' or 'partial' models because they pose a greater risk of encroaching on the boundaries of societal acceptance.

The proportionate regulatory scheme should differentiate between models that come under the SCBEM umbrella. As such, we propose that:

- Minimal-risk categories of SCBEM might be deregulated if the sandbox period reveals that regulatory burdens are disproportionate. They would still be subject to *governance* depending on the review requirements that apply to the stem cell line type utilised, but outside of a formal regulatory system. As the ISSCR and UK SCBEM Code recognise, this would not currently be appropriate. As such, even the least complex SCBEMs should currently be subjected to light touch review. However, the time may come when this is no

249 See, for example, the HFEA and HTA joint statement on ovarian and testicular tissue storage, available at: https://www.hta.gov.uk/guidance-professionals/guidance-sector/human-application/hfea-and-hta-joint-statement-ovarian-and

250 National Audit Office (2021) *Principles of effective regulation*, available at: https://www.nao.org.uk/wp-content/uploads/2021/05/Principles-of-effective-regulation-SOff-interactive-accessible.pdf, at page 4.

longer considered necessary or proportionate.

- Low-risk categories might be subject to regulatory oversight by expedited (streamlined) review of the Oversight Committee.
- Medium- to high-risk categories might be subjected to a higher level of regulatory oversight, as we set out below.

An aim of the sandbox should be to test and develop a suitable regulatory regime that would apply to the medium- to high-risk category. It would be premature to recommend the precise form(s) this should take. Our focus is on the importance of preparing for possible future eventualities rather than predicting them with confidence. We consider that review of applications by the Oversight Committee and registration of research will remain important features. Additional monitoring functions may also be required. We merely set out some of the options (broadly in order of their restrictiveness), noting that they could be set up individually or in conjunction:

- Establish a scheme of inspections whereby SCBEM researchers could be visited periodically to ensure that they are complying with the red-line prohibitions we have proposed. An example of this model is the Food Standards Agency's food safety inspections. There, local authorities visit premises to check compliance with relevant laws, with the level and type of inspection based on the type of business and previous record.
- Require (rather than request) registration. Combined with a requirement to submit research proposals for approval to the Oversight Committee and (if considered relevant) to report at the end of projects and potentially also annually, this would provide an additional incentive to comply with the UK SCBEM Code. An example of this model is the Charity Commission for England and Wales register.[251] This makes certain details available to the public, including the name of the charity, its registration status and whether the report was received on time. Where a report is overdue, the reporting column is highlighted in red, recording the number of days by which the report is late. This potentially cost-effective method could be used by the Oversight Committee so that reporting delays or other infractions are taken into consideration in future applications.
- Issue a scheme of voluntary certification with standards set by the Oversight Committee.
- Issue a bespoke licensing regime with separate licensing conditions to those applying to embryos, but which sets out monitoring, oversight and clear sanctions for breach.

The choice between these alternatives should be guided by the principles of effective regulation set out by the National Audit Office.[252] We do not restate that

251 See the Register of the Charity Commission for England and Wales, available at: https://register-of-charities.charitycommission.gov.uk/en/about-the-register-of-charities

252 National Audit Office (2021) *Principles of effective regulation* (2021), available at: https://www.nao.org.uk/wp-content/uploads/2021/05/Principles-of-effective-regulation-SOff-interactive-accessible.pdf

advice here beyond recognising that proportionate and risk-based regulation must balance innovation and public trust, fostering transparency in how SCBEMS are developed and accountability for misuse.

The working group consider that primary legislation should make provision for Regulations to this effect, and also to put the Oversight Committee on a statutory footing as a new and independent entity so that this option is available as an exit strategy from the sandbox. The latter measure would be particularly useful if the options at the more restrictive end of the scale are preferred. We have recognised the potential overlap of ethical and regulatory issues between SCBEMs and other technologies. A statutory committee would facilitate the incorporation of those technologies within the newly constituted committee's remit if that was considered expedient. The statutory committee, which we propose could be named the Committee on Stem Cell-based Research Models (CSRM), could take over review, registration and oversight and provide advice to the government. A successful example of this model is the GTAC which was set up in 1993 and put on a statutory footing in 2004.[253] As we have noted, the HFEA too began on a voluntary, non-statutory footing.

As such, we propose that the Oversight Committee could change its constitution and powers in each of the three stages we set out:

Stage 1: Embed the UK SCBEM Code	Stage 2: Regulatory sandbox	Stage 3: Settled regulation
Voluntary Oversight Committee	**Voluntary collaborative regulatory Oversight Committee**	**Statutory Committee on Stem Cell-based Research Models (CSRM)**

This three-stage strategy has several benefits over current governance arrangements. Firstly, it facilitates an incremental and collaborative response allowing learning and reflection that we identified as valuable in this context. Additionally, commitment to the process has the potential to result in a tailored and proportionate solution that would give stability to scientists, satisfy the public that research would be effectively governed and stimulate technological advancement in the public good. Finally, it provides the opportunity to strengthen and future-proof oversight of SCBEMs by building incrementally on the foundations set out in the UK SCBEM Code of Practice. A legal duty to register research and submit to ethical approval is likely to be more effective more quickly than a voluntary approach, and a formal body with statutory backing is more likely to be able to effectively monitor compliance, secure funding and establish independence.

253 See NHS Health Research Authority – Gene Therapy Advisory Committee (2020), available at: https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/gene-therapy-advisory-committee/

It is important to also acknowledge risks in our proposed strategy. One, which we discuss above, is that the Stage 1 reliance in the UK SCBEM Code could lack effectiveness. This is particularly likely if the proposed Oversight Committee and register are insufficiently resourced or slow to form and embed. Without these crucial elements the UK SCBEM Code will have limited value. Another risk is that the legislation our proposals depend on will be slow to take form or rejected in parliamentary debate. We have focused in this document on the value of our approach for scientists and the public, but we note the importance of technology in the government's vision for growth[254] and have argued that stability as to the status of SCBEMs and their governance would enhance investment, and with it the capacity for the UK to play a key role in realising their potential.

254 See DSIT (2024) 'Government backs UK R&D with record £20.4 billion investment at Autumn Budget' 31 October at https://www.gov.uk/government/news/government-backs-uk-rd-with-record-204-billion-investment-at-autumn-budget'

Conclusion

Returning to the three governance dilemmas

This report recommends approaches to resolve three governance dilemmas:

1 **How to effectively balance governance and regulation.**

We consider that soft law principle-based governance is better equipped than hard law to adapt to the emerging development of SCBEMs, but also recognise the benefits certainty and clarity can bring. We propose an incrementally imposed balance of soft and hard law approaches moving from governance to regulation, to enhance certainty for researchers and provide public reassurance through hard law prohibitions on reproductive use.

2 **What to regulate now and what to defer to the future when more will be known about SCBEMs' potential uses and risks.**

Primary legislation takes time to develop and apply. We call on government, researchers, institutions and funders to support the UK SCBEM Code as a first regulatory step. Simultaneously, considering the direction of travel and the potential for some SCBEMs to become more similar to the embryo, we consider it expedient to set out legislative prohibitions and lay foundations for future agile legislative responses. The latter element can be achieved by setting out powers in primary legislation to make Regulations.

3 **When to focus on technology-specific governance and when to collectively govern a range of technologies posing similar issues.**

SCBEMs are not the only stem cell-based models to raise ethical concerns. We consider it useful to build adaptability into the structure and remit of the Oversight Committee that is planned for SCBEMs, so that it might in future oversee and advise on the governance or regulation of other entities.

Lessons from the Warnock Committee

In 1984, Mary Warnock set out a consensus by which embryo research was permitted to develop within constraints that satisfied broad sections of the public that the research would be robust and ethical. Though there are now reasonable calls to reconsider the boundaries of that consensus, it has proved reliable and successful for 40 years, permitting embryo research to advance in a respected and trusted regulatory environment.[255]

We have recommended that a model of consensus is also utilised to govern SCBEMs. Researchers are currently operating in an environment in which the legal status and thus the regulatory consequences of their research are uncertain. A court case or secondary legislation could bring some SCBEMs under the definition of 'embryo' if public trust in the current mechanisms was diminished, and especially if an alternative, more proportionate, governance measure was not readily available. This would potentially impact on the patentability of products or medicines that could in the future be developed as a result of SCBEM research and otherwise impact adversely on research infrastructure.

Clarity as to the legal status of the SCBEM would strengthen investment in research.[256] But in return, the governance system must provide reassurances to Parliament and the public that the research is rigorous and ethical.

The UK SCBEM Code of Practice is a valuable first step in this process. But going forward, we consider that there is a risk that, without reinforcement, the principles and procedural safeguards it sets out will not provide adequate reassurance to the research community as to the legal status of SCBEMs and will not alone provide adequate reassurance to the public that red lines will not be crossed.

As such, we recommend action to enforce and future-proof effective governance by building on these foundations to form a distinct governance framework for SCBEMs and counsel that the foundations of public and stakeholder engagement laid in the UK G-SCBEM public dialogue are built upon as the science progresses.

255 See Franklin S and Jackson E (2024) *The 14 day rule and human embryo research: a sociology of biological translation* (Abingdon and New York: Routledge). And see Cave E (2023) The Warnock Report on Human Fertilisation and Embryology (1984) in Fovargue S & Purshouse C (Eds.), Leading Works in Health Law and Ethics. Routledge.

256 Durham CELLS blog (pre-publication) *Patents & stem cell based embryo models in Europe: The need for nuanced bioethics scrutiny?*, available at: https://www.durham.ac.uk/research/institutes-and-centres/ethics-law-life-sciences/about-us/news/cells-blog/

Appendices

Glossary

This glossary provides clarifying definitions and examples of terms as used in this report. *Note: given the early stage of the field, we anticipate terminology may change as science progresses.*

Key terminology

Carnegie stages – a standardised system used to describe human embryonic development in 23 stages by observable, **morphological** (physical) features. The stages were initially developed, and named, through work with a collection of human embryos at the Carnegie Institute of Washington.

Conceptus – the products of all stages of human development from fertilisation to birth. These include the **embryo proper**, the placenta and all extra-embryonic membranes, and the fetus. The **embryo proper** refers to parts of the conceptus that will form the new body and excludes the extra-embryonic tissues.

Embryo – the term embryo is defined and used differently across biological, legal, and social contexts. In this report, embryo refers generically to all to the stages of human development after the zygote's first cell division to the fetal stage at nine weeks post fertilisation, and includes the placenta and other extra-embryonic membranes.

Extra-embryonic – describes the cells and tissues that develop from the zygote and support development but do not form part of embryo proper or future fetus, for example, the placenta, yolk sac, and amnion.

Fetus – refers to the post-embryonic stages of human prenatal development, after major structures have formed. In humans, this period is from eight to nine weeks after fertilization (or Carnegie Stage 23) until birth.

Stem cell-based embryo model (SCBEM) – an umbrella term for organised, multicellular structures that recapitulate features of early human development, which may or may not contain extra-embryonic tissue. SCBEMs vary greatly in their

level of complexity and the extent to which they mimic 'complete' embryos versus particular parts or stages of embryonic development. Some alternative terms include embryo-like structures, embryoids, or embryo models for short.

Model – a biological system, structure, and/or organism which replicates aspects of a more complex biological entity, process, or function. An embryo model is a structure derived from stem cells which replicates some processes and features of the developing embryo, but is not an embryo itself.

Embryogenesis

Gamete – a reproductive cell, for example a human sperm or egg, that only carries one copy of each chromosome. Their combination, through called fertilisation and then **syngamy** (fusion), results in a cell with chromosomes from two biological parents called the **zygote**, which can then develop into an embryo.

Pre-implantation stage – refers to the period of early human development after fertilisation and before the embryo attaches to and invades the endometrial tissue, usually seven to eight days after fertilisation. This includes the zygote, cleavage, morula and blastocyst stages. Before implantation, the embryo is a relatively simple cellular structure with minimal cell differentiation.

Zygote – the single cell resulting from the combination of a sperm and egg, which gives rise to the entire organism. This is referred to as day one of embryonic development.

Blastocyst – the embryo, around five to six days after fertilization, which consists of a spherical layer of **trophoblast** cells that form a cavity around the **inner cell mass**. The **trophoblast** cells will attach to the endometrium during implantation and gives rise to a large part of the placenta. In late blastocyst, the **inner cell mass** develops into two flattened layers, the:

> **Primitive endoderm**, which gives rise to extra-embryonic membranes such as the yolk sac and **amnion**, and
>
> **Epiblast**, which gives rise to the embryo proper (defined above).

Blastoids – a term for SCBEMs which recapitulate aspects and processes of the blastocyst stage of embryonic development.

Post-implantation stage – refers to the period of early human development following the implantation of the embryo to uterine tissues, which concludes around 9 days after fertilisation. Soon after implantation, the embryonic development irreversibly commits to the development of more complex and specialised tissues via the process of gastrulation.

Gastrulation – a key process of embryonic development beginning around 14 days after fertilisation which prepares the embryo for organ formation (**organogenesis**) and establishes directionality so the body plan can begin to develop. This includes the processes of **patterning** and **cell differentiation**, where the epiblast develops from a symmetrical layer of identical cells into a multilayered structure of lineage-specific cells, called primary germ layers (described below).

Germ layers – three primary, lineage-specific cell layers formed during gastrulation that each give rise to certain types of differentiated cells and tissues of the future body.

Gastruloids – a term for SCBEMs which recapitulate aspects and processes of the gastrulation stage of embryonic development.

Primitive streak – a groove that forms in the epiblast layer which establishes bilateral symmetry in the embryo and marks the beginning of gastrulation. In humans, the primitive streak appears around 14 days after fertilisation and serves as the maximum limit for culturing human embryo *in vitro*.

Wider science

Artificial uterus – technologies, systems, and/or processes which provide a supportive environment and functions that seek to mimic the normal conditions of gestation.

Assembloid – a term used to describe an *in vitro* system of two or more organoid models together, such as a SCBEM and an endometrial organoid.

Culture media – the substance which provides necessary nutrients and environment to support cell growth and direct cell development *in vitro*.

Differentiate – the process by which cells to develop or mature into a more specialised form of cell.

Ectogenesis – a process enabling the partial or full development of an entity (e.g. an embryo and/or fetus) in an environment that mimics conditions of gestation outside of a reproductive tract, typically by using an 'artificial uterus'. In the context of embryo models, the UK SCBEM Code of Practice defines full ectogenesis as development to viability of an organism entirely outside a host organism.

Efficiency – the proportion of successful end products or results from initial attempts in an experiment.

Embryoid body – simpler, semi-organised stem cell aggregates that can model some aspects of early blastocyst-stage embryonic development through the spontaneous differentiation of stem cells.

Endometrium – the tissue that lines the uterus *in vivo*, where implantation of the embryo occurs.

Fidelity – the degree of similarity between two entities i.e. between an embryo model and the features and/or processes of the embryo.

Human reproductive tract – the internal organs and tissues involved in supporting reproduction *in vivo* and which are contained within the pelvis.

***in vitro* culture** – cells grown and developed in a clinic or laboratory for research, such as in a dish or flask, as opposed to in the body (*in vivo*).

Organoid – a three-dimensional, stem cell-based structure that self-organises and differentiates into specialised cell types, which model aspects of an organ or tissue *in vitro*, such as the placenta, liver, or neural tissue.

Pluripotent stem cells – cells with the unique ability to divide and/or differentiate into any type of cell of the future body, including other stem cells. Unlike somatic cells, pluripotent stem cells have the ability to self-organise into 3-D structures mimicking embryonic development. SCBEMs are made from pluripotent stem cells, either:

> **Embryonic stem cells (ESCs)** – derived from the inner cell mass of a blastocyst-stage embryo, or
>
> **Induced pluripotent stem cells (iPSCs)** – derived from specialised cells of various kinds (such as skin cells) by a process of transformation into pluripotent stem cells through the introduction of 'reprogramming' factors found to be active in embryonic stem cells.

Reproducibility – the ability to independently repeat an experiment and achieve the same results in a consistent manner.

Self-organisation and self-assembly – the unique ability of stem cells to spontaneously form complex multicellular structures and to change their positions over time.

Somatic cell – all the body's cells that are not gametes or pluripotent stem cells, i.e. the various kinds of specialised cells that form an organism's tissues, organs, and bodily structures.

Somatic cell nuclear transfer (SCNT) – involves removing a human egg cell's nucleus (enucleation) to replace it's genetic information with the nuclear genetic information from a patient's adult cell. When the egg (also called an **oocyte**) is stimulated to begin dividing, it produces an embryo from which embryonic stem cells can be derived. These can be used to treat and replace diseased tissues without being rejected by a patient's immune system – also referred to as therapeutic cloning. Therapeutic cloning by SCNT is legal in the UK under a license from the HFEA.

Turing Test – a test of equivalence. In this context, it is a process by which an evaluator could not distinguish between a SCBEM and an embryo without having information about their origins. The classical thought experiment was designed by Alan Turing and is traditionally used in the context of evaluating a machine's ability to 'think' equivalent to a human. The Turing Test for evaluating SCBEM equivalence was set out in a 2023 paper which suggested that certain 'tipping points' of functionality would make SCBEMs sufficiently similar to be considered embryos, which the authors defined as "a group of human cells supported by elements fulfilling extraembryonic and uterine functions that, combined, have the potential to form a fetus." [257]

Governance

Hard law and soft law – two approaches to governance, used separately or in conjunction. Hard law is legally binding and enforceable. Soft laws, such as agreements, codes of practice and guidelines, are 'voluntary' in the sense that they are agreed standards that are not legally binding.

Governance – in this report, governance is an umbrella term to describe soft and hard law mechanisms that control how SCBEM research is conducted (e.g. overseen, permitted, monitored, and/or evaluated).

Regulation – a subset of governance involving oversight by regulatory bodies, often based on legal authority.

Regulatory sandbox – an agile form of regulation that gives researchers access to regulatory expertise and a degree of oversight without the burdens of full regulation.

Primary and secondary legislation – primary legislation, also referred to as Acts or statues e.g. *set out in statute*, are the laws passed by Parliament, which can only be amended by Parliament. The Human Fertilisation and Embryology Act 1990 (as amended) is primary legislation. Primary legislation can delegate powers to ministers or public bodies so that specific detail can be laid out in **secondary** (subordinate) **legislation**, such as Regulations.

Public engagement and dialogue – public engagement is an umbrella term for the variety of ways an organization may involve members of the public in two-way information sharing for mutual benefit. **Public dialogue** involves the participation of a broad cross-section of people in deliberation around issues of public relevance. The process brings members of the public together with specialists in the field over a series of workshops to give careful thought and discussion to a given topic to inform policy and decision-making through understanding participants' values and preferences.

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Abbreviations

CS23	Carnegie stage 23
ESC	embryonic stem cell
ESHRE	European Society of Human Reproduction and Embryology
EU/EEA	European Union/ European Economic Area
HDBI	Human Developmental Biology Initiative
GTAC	Gene Therapy Advisory Committee
HFEA	Human Fertilisation and Embryology Authority
HFE Act 1990 or 1990 Act	Human Fertilisation and Embryology Act 1990 (as amended)
HTA	Human Tissue Authority
hELS	human embryo-like structure
iPSC	induced pluripotent stem cell
ISSCR	International Society for Stem Cell Research
IVF	*in vitro* fertilisation
MHRA	Medicines and Healthcare products Regulatory Agency
MIBBI	Minimum Information for Biological and Biomedical Investigations
MISEV	Minimal Information for Studies of Extracellular Vesicles
NHS	National Health Service
NHP	non-human primate
REC	Research Ethics Committee
UKSCB	UK Stem Cell Bank
UKRI	UK Research and Innovation
UK	United Kingdom

Methods of evidence gathering

Background

The Nuffield Council on Bioethics initiated this rapid review in January 2024 to explore the ethical and governance issues raised by research involving human stem cell-based embryo models in the UK. A working group with interdisciplinary expertise was appointed in March 2024 (a full list of members can be found **above**), with the following terms of reference:

Aim

To deliver credible and well-informed analysis and robust, evidence-based recommendations for the governance of research involving human stem cell-based embryo models in the UK.

Specific project aims

1. To identify and review the most up-to-date evidence and analysis of:
   - Current and potential near future capabilities and applications of stem cell-based embryo models in research.
   - A diverse range of views on the ethical issues raised by human stem cell-based embryo models.
   - The suitability of possible regulatory or other oversight models.
2. To develop robust and proportionate recommendations for relevant decision-makers and audiences.
3. To inform future policy and practice in relation to stem cell-based embryo model research.

Evidence gathering and deliberation

- Across June 2024 we hosted three roundtable meetings in London, bringing together expertise around the current science, law and governance, and ethical issues.
- Two smaller online roundtable discussions were held on 03 and 04 July to explore the experience of and views on regulatory approaches in Australia and the Netherlands.
- A number of one-to-one interviews carried out online with individual experts in the UK and internationally.
- Two final roundtable discussions:
  1. A meeting on 24 July to discuss emerging themes and remaining questions with a multidisciplinary panel of external experts
  2. A roundtable discussion on 24 September with relevant UK regulators to discuss and test proposed recommendations for governance.

Participants at the above events included:

Aisling McMahon, Maynooth University
Alfonso Martinez Arias, Universitat Pompeu Fabra (Barcelona)
Amy Wilkinson, Babraham Institute
Ana Pereira Daoud, Maastricht University
Austin Smith, Medical Research Council Professor at the University of Exeter
Azim Surani, University of Cambridge
Bobbie Farsides, Brighton and Sussex Medical School

Christina Rozeik, Cambridge Reproduction, University of Cambridge
Christopher Gyngell, University of Melbourne and Murdoch Children's Research Institute Christopher Rudge, The University of Sydney
Dave Archard, Emeritus Professor at Queen's University Belfast
David A Jones, Anscombe Bioethics Centre
David Lawrence, Durham Law School
Dianne Nicol, Emeritus Professor at the University of Tasmania
Douglas Gray, The Francis Crick Institute
Emily Jackson, London School of Economics and Political Science
Ge Guo, University of Exeter
Giulia Cavaliere, King's College London
Ilke Turkmendag, Newcastle Law School, Newcastle University
James Lawford Davies, LDMH Partners
John B Appleby, Lancaster University
Jonathan Pugh, University of Oxford
Marta Shahbazi, MRC Laboratory of Molecular Biology
Megan Munsie, University of Melbourne and Murdoch Children's Research Institute
Michael Morrison, Faculty of Law, University of Oxford
Naomi Moris, The Francis Crick Institute
Nicholas Rivron, Austrian Academy of Sciences
Peter Rugg-Gunn, Babraham Institute
Rachel Ankeny, Wageningen University and The University of Adelaide
Ramiro Albeiro, University of Nottingham
Robin Lovell-Badge, The Francis Crick Institute
Roger Sturmey, Hull York Medical School
Rosamund Scott, Centre of Medical Law and Ethics, King's College London
Sandy Starr, Progress Educational Trust
Sarah Carter-Walshaw, Leeds University
Sarah JL Edwards, University College London
Søren Holm, University of Manchester and University of Oslo
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* This list reflects everyone who was a member of the Council within the period of January – October 2024.