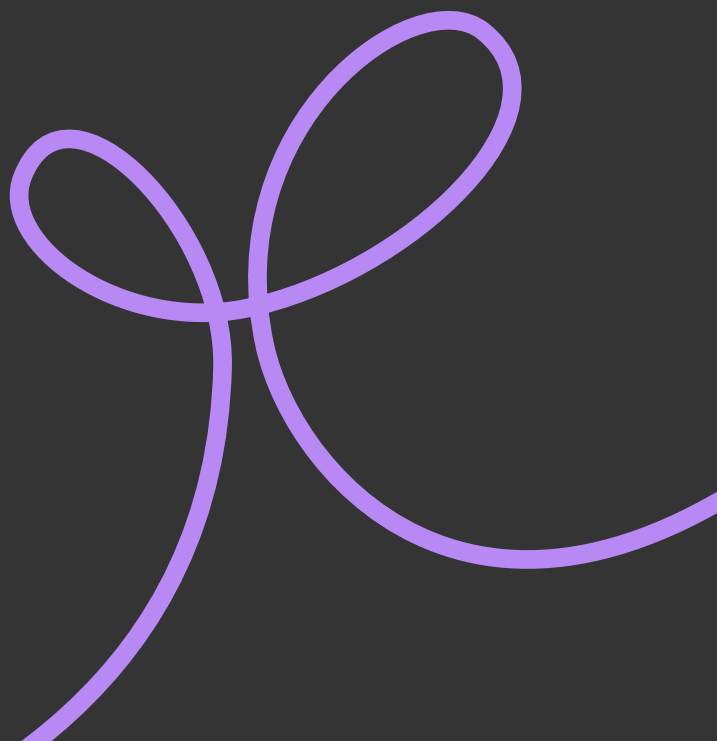
Nuffield Council on Bioethics

POLICY BRIEFING

Human stem cell-based embryo models:

A review of ethical and governance questions



Executive summary

The Nuffield Council on Bioethics (NCOB), through an **expert Working Group**, has completed a review of the ethical and governance questions arising from research involving human stem cell-based embryo models (SCBEMs).

We recommend a governance framework to facilitate scientific progress in this area of research, while ensuring ethical standards are upheld and public interests are reflected.

Our proposed framework has three stages:

1. Embed voluntary oversight via the **Code of Practice for the Generation and Use of Human SCBEMs** developed by Cambridge Reproduction & the Progress Educational Trust (hereafter, the UK SCBEM Code).
2. Enable regulatory control by amending the Human Fertilisation and Embryology Act 1990 to set up a regulatory sandbox and prevent direct use of SCBEMs in assisted reproduction to produce pregnancy.
3. Settle the regulatory scheme for relevant SCBEMs.

This staged approach facilitates learning and reflection to ensure that governance is targeted and proportionate. Ultimately, the framework should create an environment where the morally relevant considerations and legal status of SCBEMs are clear. It will encourage responsible investment and stability, whilst guarding against potential adverse outcomes. Finally, it will create governance mechanisms that can anticipate and respond flexibly to emerging scientific developments.

SCBEM is an umbrella term for a range of small, three-dimensional structures created from stem cells that model stages, processes, and/or features of embryonic development. These stem cells can be derived either from embryos (embryonic stem cells) or through the reprogramming of cells from other human tissue such as skin or blood cells (induced pluripotent stem cells).

SCBEMs vary in their level of complexity, the methods by which they are derived, and the extent to which they accurately mimic complete embryos or aspects of embryonic development. Some SCBEMs model particular tissues or cells, whilst others attempt to model the embryo more completely.

Overview

As a research tool, SCBEMs have the potential to bring public benefit. However, there is no specific legal or regulatory framework that governs SCBEM research in the UK, and there is debate about their status in relation to human embryos – this raises questions about how they should be used.

SCBEMs could provide us with ways to better understand human development and identify therapeutic interventions. For example, using them to study how drug or toxin exposure during pregnancy might affect embryonic development could deliver insights into clinical risk management for pregnant people. However, as an emerging technology, it is not possible to predict with accuracy which applications of SCBEMs will be realised and when they could be expected. Their wide variation, dynamic nature, and the early stage of the research also make them difficult to define and categorise.

In combination with the existing ethical debate about the moral status of the embryo at different stages of development, consensus on the ethics of SCBEM research is difficult to achieve. The report explores further what considerations could factor into ethical analysis now and in future, including human dignity, associations with the embryo and value of human life, donation and consent, and developmental and reproductive potential. However, we identified emerging points of consensus around 'red lines' for research and a balance of interests which are reflected in our recommendations below.

As such, the development and use of SCBEMs without adequate oversight mechanisms poses ethical risks. This includes the potential for unethical research, which could damage public trust, or conversely a disproportionate regulatory response, which would be contrary to the public interest. We propose a staged governance framework that would mitigate both risks.

Whilst our primary focus for this review has been on the UK research environment and governance context, we have taken into consideration international efforts to address the lack of clarity about the ethical and legal position of research involving SCBEMs.[1]

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

Given the global nature of the research, and the UK's leading reputation for successful regulation of sensitive and/or complex biotechnologies, it would be reasonable to assume that the UK's regulation of SCBEMs could have international influence.

Current UK regulatory context

To date, no specific legal or regulatory frameworks have been created to govern SCBEM research in the UK. The UK SCBEM Code takes steps to fill the gap and our recommendations build on that foundation.

The regulation of human stem cell cultures from which SCBEMs are created is covered by two Acts:

1. The **Human Fertilisation and Embryology Act 1990** (as amended) governs research on embryos, but not embryonic stem cells derived from embryos and maintained in culture (as 'stem cell lines') for research. Stem cell lines must be banked at the UK Stem Cell Bank (UKSCB) and then the UKSCB Steering Committee bases its decisions on whether to approve UK human embryonic stem cell research upon the principles set out in a 2010 Code of Practice. In the case of human embryonic stem cells lines, compliance with the 2010 Code is reinforced by virtue of being an HFEA licensing requirement.[2]

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, from which induced pluripotent stem cells can be derived. However, once induced pluripotent stem cells have been created and established into stem cell lines, the Acts and licensing regimes do not apply.

2 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.

Recommendations

To address the current lack of legal and regulatory oversight in SCBEM research, we propose that a new governance framework is developed and implemented.

This framework should facilitate scientific progress, uphold ethical standards and reflect public interests by creating an environment in which there can be clarity on the morally relevant considerations and legal status of SCBEMs.

Embedding the governance structures needed to anticipate developments and respond in an agile and appropriate way will encourage responsible investment and stability, and guard against potential adverse outcomes.

Our proposed framework for these governance structures consists of three stages:

1. **Embed voluntary oversight via the UK SCBEM Code.**
2. **Amend the Human Fertilisation and Embryology Act 1990 to enable regulatory control.**
3. **Settle the regulatory scheme for relevant SCBEMs.**

Stage 1 – Embed voluntary oversight via the UK SCBEM Code

We support the recently published **UK SCBEM Code**. We recommend the immediate establishment and funding of the proposed Oversight Committee and register. This will improve transparency and accountability, and develop expertise in the review of SCBEMs.

We consider it the role of the oversight committee to set case-by-case limits to ensure that models are cultured to the minimum stage required, as proposed in the UK SCBEM Code. As with human embryos, which have a current laboratory culture limit of 14 days, we recognise there is also merit in setting an overall upper culture limit for SCBEMs. This is because, as SCBEM research advances, some model types may increasingly share features with embryos. However, we acknowledge that at

present there is considerable uncertainty about how such a limit should be agreed. We also recognise that culture limits placed on SCBEMs that more closely resemble the embryo should not unnecessarily restrict important research on SCBEMs that do not resemble the complete embryo, such as models of a particular embryonic tissue.

Pending the necessary scientific learnings and public dialogue that would enable a more reliable assessment and setting of a limit, we propose that the UK SCBEM Code is amended to incorporate an interim threshold to ensure that, should it ever becomes feasible to do so, SCBEMs are never in future developed:

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

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 a meaningful understanding of public views, values and interests. As such, 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.

We note that as stem cell-based embryo modelling is a young technology, there is an opportunity to co-create broader scientific aims and objectives before it matures. We believe one objective during this period should be to learn 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.

Stage 2 – Enhance regulatory control

Whilst we are assured that compliance with the UK SCBEM Code will improve research and investor confidence in the short term, we believe risks may arise in the longer term.

As SCBEMs become more sophisticated, we believe there is an increased possibility of a development raising public or parliamentary concern which could trigger a disproportionate regulatory response. There are mechanisms by which SCBEMs could be incorporated within the legal definition of 'embryo' and be regulated as such. If one of these mechanisms are triggered prematurely, or encompass too wide a range of SCBEMs, they risk leading to disproportionate, disruptive, and costly regulation.

We recommend that *for regulatory purposes*, SCBEMs and embryos must be considered distinct from one another. The Human Fertilisation and Embryology Authority has recently proposed a number of necessary reforms to the 1990 Act, which governs embryo research in the UK.[3] We recommend that the Act is revised to make provision for the *separate* regulation of SCBEMs.

We recommend that the Act is amended to enable the introduction of a 'regulatory sandbox' for SCBEMs. This agile form of regulation is supported by the HFEA as a new way "to support innovation in treatment and research".[4] It will mean that future governance options set out in our report can be proactively tested. We propose that the development of SCBEMs be overseen by the HFEA, in a collaborative venture with other relevant regulators.

The 1990 Act should be revised to set out delegated powers that can be activated through secondary legislation/regulation. The powers to make regulations should take three forms, powers to:

1. regulate SCBEMs under a regulatory sandbox;
2. develop from the sandbox a bespoke and targeted regulatory scheme; and
3. put the SCBEM Oversight Committee on an independent statutory footing, as one of the possible sandbox exit strategies.

We recommend that the SCBEM regulatory sandbox has 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 (see below). 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 both what is learned and to scientific developments.

The 1990 Act should also be amended to prohibit direct use of SCBEMs in assisted reproduction to produce pregnancy, so as to provide additional public reassurance about the purpose and governance of SCBEM research.

Stage 3 – Settled regulation of relevant SCBEMs

A tailored and proportionate regulatory scheme for SCBEMs will become feasible as it becomes clearer how they will be used and categorised.

3 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/

4 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/

Considering that these regulatory controls could be graded according to the risks and benefits SCBEMs pose, we suggest:

- Low-risk categories of SCBEM become subject to streamlined (e.g. based on previous cases) review of the Oversight Committee.
- Medium- to high-risk categories of SCBEM are subjected to a higher level of regulatory oversight, which the sandbox should be used to test and develop. We set out a range of options including inspections, certification, registration and licensing that might be considered.

Appropriate governance can enhance the trust of researchers, funders, and investors in an academic environment, and bolster public confidence that a proportionate response will be taken to minimise risks and ethical implications.[5]

There are distinct advantages in starting to address this now while SCBEM science is in its infancy, but there is also an imperative to advance the implementation of regulation in the sector cautiously and incrementally to limit the risk of disproportionate regulation.

Our report sets out a staged and proportionate roadmap for how this might be achieved.

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