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CODE OF PRACTICE FOR THE GENERATION AND USE OF HUMAN STEM CELL-BASED EMBRYO MODELS

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1. Purpose and remit

The *Code of Practice for the Generation and Use of Human Stem Cell-Based Embryo Models* (hereafter the *Code*) is intended to support the development of best practice for the generation and use of human stem cell-based embryo models (SCBEMs) for research in the United Kingdom (UK).

When cultured under appropriate supporting conditions *in vitro*, pluripotent or totipotent stem cells may assemble into organised, three-dimensional structures that exhibit certain features present in human embryos at an early stage of development. These structures are widely defined as stem cell-based embryo models (SCBEMs). This is an umbrella term intended to capture a range of multicellular, organised structures that recapitulate features of early human development. Some of these structures model extraembryonic tissues, whereas others do not.

The *Code* focuses on SCBEMs, which recapitulate features of an early human embryo. Organoids – which are self-organised, three-dimensional models of specific tissues or organs (such as placenta, brain, gut or liver) – are beyond the scope of this document.

1.1 Why the *Code* is needed

Research using *in vitro* models of early development can improve knowledge of human development, including early pregnancy loss and pregnancy disorders, congenital defects, and precursor events that affect adult human health and disease. The insights gained will advance understanding in developmental biology and clinical embryology, which may in turn translate into diagnostic and therapeutic interventions for a range of conditions, including infertility. SCBEMs and SCBEM-derived cellular products – such as somatic cells, germ cell-like cells or stem cells – may have many uses, including (but not limited to) basic research, development of clinical practice, drug discovery and toxicological studies. SCBEMs representing preimplantation stages of human development may be useful for training personnel in research and clinical practice, for example, in embryo manipulation, embryo biopsy, cryopreservation, and mitochondrial donation. SCBEMs may also be useful for the refinement and development of technologies, methods and products related to *in vitro* fertilisation (IVF), new stem cell and SCBEM culture media and devices, and single-cell resolution analytics technologies.

Whilst SCBEM research has the potential to advance scientific and medical knowledge, the following factors indicate the need for the *Code*:

- Lack of a clear governance framework: current UK regulation, such as the Human Tissue Act 2004 (hereafter the HT Act) and the Human Fertilisation and Embryology (HFE) Act 1990 (as amended) (hereafter the HFE Act), does not address SCBEM research directly (see Appendix 1). Given the particular scientific and ethical considerations raised by research involving SCBEMs, existing research ethics committees may not be compatible with or suitable for reviewing proposals on SCBEMs and our recommendation is that researchers seek specialist oversight (as outlined in Appendix 3).

- Ethical considerations: although SCBEMs are distinct from embryos, they do model aspects of early development and include cellular material found in the embryo. They can self-assemble into three-dimensional, organised structures that transition between stages of development. These characteristics, and the emerging nature of this field, raise a variety of ethical considerations (explored in Section 3).

- Public perspectives: we note that a recent public dialogue indicates public support for oversight of research involving SCBEMs, as well as appreciation of the potential of this emerging area.[1]

1. *Addressing the governance gap: a public dialogue on the governance of research involving stem cell-based embryo models* (April 2024). Available at https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf (accessed 20/06/24).

The International Society for Stem Cell Research (ISSCR) 2021 *Guidelines for Stem Cell Research and Clinical Translation* (hereafter the *ISSCR Guidelines*) recommend that SCBEMs 'shall be subject to review, approval, and ongoing monitoring, as appropriate, through a specialized oversight process capable of evaluating the unique aspects of the science and the associated ethical issues'.[2] It has been suggested that any governance framework for SCBEMs should be less stringent than the regulations governing human embryo research but more exacting than the governance of research involving human stem cell cultures.[3]

The *Code* has been produced to fill the gap in UK governance by addressing the ethical, legal and regulatory questions specific to SCBEMs and to provide guidance on the responsible use of SCBEMs in research. This is important given the pace of developments and the wide-reaching potential of SCBEMs.

1.2 About the *Code*

The defining characteristics of the *Code* are as follows:

- **Goals:** to support robust and transparent processes of decision-making and implementation regarding the generation and use of SCBEMs, and to encourage public trust in related research and researchers.

- **Stakeholders and users:** the *Code* is addressed to all who have an interest in this area, including researchers, research institutions, companies, ethics committees, policymakers, funders, publishers and the lay public.

- **International relevance:** the *Code* has been designed specifically for use within the UK's regulatory system but researchers working on SCBEMs in other countries are invited to use the *Code* in addition to adhering to local regulations as required.

- **Scope:** except where explicitly stated otherwise, the *Code* relates to all SCBEMs that contain human cells, regardless of their starting material, including entities that combine material of human and non-human animal origin.

- **Exclusions:** the following research falls outside the scope of the *Code*:

  - Research involving human embryos, including the generation of human embryonic stem cell lines, which in the UK context is regulated by the Human Fertilisation and Embryology Authority (HFEA) under the HFE Act.

  - Research involving established human embryonic stem cell lines, which is overseen by the Steering Committee for the UK Stem Cell Bank and for the use of stem cell lines.

  - Research involving (fully) non-human SCBEMs, which is regulated in some cases by the Home Office under the Animals (Scientific Procedures) Act 1986.

- **Use:** the *Code* is not legislative. We hope that widespread adoption will lead to greater confidence in research, and increased transparency and accountability, and will deter publication and funding of research that fails to meet these standards.

We propose that UK researchers, funders, research organisations, professional societies and publishers adopt the *Code*. This will maintain and build confidence that research in this area adheres to robust principles of research integrity and ethics. We also hope that the *Code* will inform deliberations on SCBEMs and related research currently underway in other countries. Given the pace of research, the *Code* will be subject to regular review.

2. International Society for Stem Cell Research (ISSCR), *Guidelines for stem cell research and clinical translation*, version 1.0 (May 2021), Recommendation 2.1.1 (p. 6). Available at https://www.isscr.org/guidelines (accessed 20/06/24).
3. Bruno, C. *et al*. *Opinion of the Conseil d'orientation: stem cell-based embryo models* [English translation] (September 2023). Available at: https://www.agence-biomedecine.fr/IMG/pdf/22-06_avis_du_co_embryoi_des_eng-2.pdf (accessed 21/06/24).

2. Scientific background

In recent years, researchers have devised techniques that guide pluripotent stem cells to form organised, three-dimensional structures called SCBEMs that show features of early-stage human embryos.[4] Depending on how they are formed SCBEMs capture different stages and processes of embryo organisation and development. SCBEMs open new research avenues that can complement the limited studies possible with actual human embryos, such as research into post-implantation processes.[5]

SCBEMs may be generated from a variety of sources, including human totipotent stem cells, human embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), or during the reprogramming of somatic cells or by mixing embryonic and extraembryonic stem cells.

'SCBEM' is the preferred umbrella term to describe such models, following the *ISSCR Guidelines*.[6] However, other terms abound, including embryoid, stembryo and synthetic embryo, as well as terms for specific types of model, such as blastoid, gastruloid, embryoid, and iDiscoid.

At the time of drafting the *Code*, the ISSCR classifies SCBEMs as either 'integrated' or 'non-integrated', with differing levels of recommended oversight.[7] While this classification can be scientifically useful, it does not necessarily assist us in making helpful moral distinctions. For example, SCBEMs that may typically be considered non-integrated (such as those without placental progenitor-like cells) can go on to develop to advanced stages and form complex structures. Consequently, there is no distinction made in the *Code* between integrated and non-integrated SCBEMs.

The *Code* applies to all types of human SCBEMs irrespective of the starting material and degree of integration. That said, the degree of oversight is intended to be proportionate to the complexity of the SCBEM and proportionate for each individual project.

2.1 SCBEMs are a useful tool in addition to embryo research

SCBEMs can offer new opportunities for studying paradigms in developmental biology that cannot easily be investigated using human embryos donated to, or created for, research. Unlike human embryos used in research or training, SCBEMs are available in large numbers because they are generated *de novo* from stem cell lines in laboratories.

SCBEMs may be generated from a single cell line, thereby making them isogenic. This can be useful for certain types of experiments where it is beneficial to minimise genetic variation, such as small molecule drug screening. SCBEMs are also amenable to genetic modification, which is a powerful means of investigating molecular mechanisms underpinning embryonic development. These and other properties mean that SCBEMs have significant utility in studying the biology of human development, in toxicological studies, and in optimising assisted reproductive technologies (ART).

4. E.g.: Sozen, B. *et al.* Self-assembly of embryonic and two extra-embryonic stem cell types into gastrulating embryo-like structures. *Nat Cell Biol* **20**, 979–989 (2018). doi: 10.1038/s41556-018-0147-7;
Moris, N. *et al.* An in vitro model of early anteroposterior organization during human development. *Nature* **582**, 410–415 (2020). doi: 10.1038/s41586-020-2383-9;
Yu, L. *et al.* Blastocyst-like structures generated from human pluripotent stem cells. *Nature* **591**, 620–626 (2021). doi: 10.1038/s41586-021-03356-y;
Yanagida, A. *et al.* Naive stem cell blastocyst model captures human embryo lineage segregation. *Cell Stem Cell* **28**, 1016-1022.e4 (2021). doi: 10.1016/j.stem.2021.04.031;
Kagawa, H. *et al.* Human blastoids model blastocyst development and implantation. *Nature* **601**, 600–605 (2022). doi: 10.1038/s41586-021-04267-8;
Yu, L. *et al.* Large-scale production of human blastoids amenable to modeling blastocyst development and maternal-fetal cross talk. *Cell Stem Cell* **30**, 1246-1261.e9 (2023). doi: 10.1016/j.stem.2023.08.002;
Ávila-González, D. *et al.* Pluripotent stem cells as a model for human embryogenesis. *Cells* **12**, (2023). doi: 10.3390/cells12081192.
5. E.g.: Lau, K. Y. C. *et al.* Mouse embryo model derived exclusively from embryonic stem cells undergoes neurulation and heart development. *Cell Stem Cell* **29**, 1445-1458.e8 (2022). doi: 10.1016/j.stem.2022.08.013;
Weatherbee, B. A. T. *et al.* Pluripotent stem cell-derived model of the post-implantation human embryo. *Nature* **622**, 584–593 (2023). doi: 10.1038/s41586-023-06368-y;
Oldak, B. *et al.* Complete human day 14 post-implantation embryo models from naive ES cells. *Nature* **622**, 562–573 (2023). doi: 10.1038/s41586-023-06604-5;
Ai, Z. *et al.* Dissecting peri-implantation development using cultured human embryos and embryo-like assembloids. *Cell Res* **33**, 661–678 (2023). doi: 10.1038/s41422-023-00846-8;
Pedroza, M. *et al.* Self-patterning of human stem cells into post-implantation lineages. *Nature* **622**, 574–583 (2023). doi: 10.1038/s41586-023-06354-4;
Karvas, R. M. *et al.* 3D-cultured blastoids model human embryogenesis from pre-implantation to early gastrulation stages. *Cell Stem Cell* **30**, 1148-1165.e7 (2023). doi: 10.1016/j.stem.2023.08.005.
6. *ISSCR Guidelines*, Glossary (p. 64).
7. *ISSCR Guidelines*, Glossary (p. 64).

The HFE Act stipulates that human embryos *in vitro* may only be studied up to 14 days of development or the appearance of the primitive streak, whichever comes first,[8] and may only be used in research for specified purposes. Because SCBEMs are different from embryos, research involving SCBEMs may provide insights beyond what is permissible with human embryos. For example, SCBEMs could offer insights into development beyond 14 days. This may be of great value for studying dynamic processes, including implantation and gastrulation, and for furthering our understanding of early pregnancy loss.

It is our view that SCBEM research and embryo research, while distinct, complement and benefit one another. Neither of these areas of research can or should replace the other in the foreseeable future.

2.2 SCBEMs are currently considered to be biologically distinct from human embryos

SCBEMs differ from human embryos in several ways, most evidently:

- Current SCBEMs are not the products of a process of direct bi-parental fertilisation involving eggs and sperm.
- At present, SCBEMs are relatively basic and do not recreate the full complexity of embryo development. There are differences in rate and order of development as well as differences in molecular processes.
- It is not known to what extent SCBEMs have the potential to undergo normal embryological development.
- Few SCBEMs are generated with the aim of modelling a complete human embryo.

Furthermore, differences from human embryos in cellular composition, in processes that shape the formation of the embryo, and in gene activity and epigenetic features associated with development have all been reported in SCBEMs.

Current SCBEMs do not proceed through developmental stages equivalent to those observed in the first five days of development in embryos that have arisen from fertilisation. Rather, SCBEMs are engineered to initiate development at specific timepoints/stages of development after these earliest events.

The degree to which SCBEMs align with conventional developmental timings is often not clear-cut. It is neither practical nor accurate to apply conventional developmental timings, such as 'days post-fertilisation', to SCBEMs. For all of these reasons, SCBEMs are currently considered to be biologically distinct from human embryos.

8. HFE Act section 3(3) and 3(4): "A licence cannot authorise—(a) keeping or using an embryo after the appearance of the primitive streak [...] For the purposes of subsection 3(a) above, the primitive streak is to be taken to have appeared in an embryo not later than the end of the period of 14 days beginning with the day on which the process of creating the embryo began, not counting any time during which the embryo is stored." Available at https://www.legislation.gov.uk/ukpga/1990/37/contents (accessed 30/06/24).

3. Ethics

As detailed in Section 1.1, research involving SCBEMs advances scientific and medical knowledge – which is a significant ethical consideration in its own right – but it is important that this research is ethically robust as well as scientifically valuable.[9] To ensure public trust and support, researchers must demonstrate an awareness of the ethical issues raised by their work and a willingness to work with others to ensure that high standards are set and maintained.

As discussed elsewhere in the *Code*, research involving SCBEMs is not currently subject to explicit legislative regulation in the UK. However, this research – particularly when it involves development of more complex SCBEMs – is considered to merit some form of governance. There are several reasons for this.

In Section 2.2, we explain that SCBEMs are distinct from embryos. That said, SCBEMs do recapitulate features of early human embryos, and embryos are the subject of ethical, legal and public attention and concern in various contexts. The Warnock Report, which shaped the original HFE Act, found that the human embryo 'ought to have a special status' and that it 'should be afforded some protection in law'.[10] The human embryo is thus subject to specific legal and ethical protections in the UK: as noted in Section 2.1, research on the human embryo is prohibited beyond 14 days or the appearance of the primitive streak, whichever comes first.

In formulating an ethical approach to SCBEMs, it is important to consider which of their features, if any, could be morally (and legally) relevant. In this process, it is not sufficient simply to invoke the regulatory framework for human embryos, precisely because these entities are different in ways that carry moral weight. However, it could be constructive to consider what it would mean to treat SCBEMs in a manner compatible with the values directing the ethical governance of research involving human embryos.

A key difficulty, given the current state of SCBEM research, is that much is still unknown, in particular about whether at least *some* SCBEMs could ever have developmental potential equivalent to that of a human embryo.

There are also significant ethical challenges involved in answering these developmental questions. So, for example, it would not be permissible to seek to establish the facts of the matter by transferring a SCBEM to the reproductive tract of a human or non-human animal host (see Section 5.4 and Appendix 1). We are therefore required to consider possible futures and our ethical responses to them. For example, 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. Should this be achieved, then the entity would be subject to prevailing legal protections afforded to *in vitro* human embryos under the HFE Act (see also Appendix 1).

This current lack of knowledge itself has ethical implications. Arguably, it implies the need for a cautious approach pending further knowledge: one which recognises the benefits the research may bring, but which balances this with the need to monitor the progress of that research carefully in light of ethical, legal and public attention to and concern about the entity that SCBEMs model, namely the human embryo. The public dialogue that informs the *Code* shows that most participants were mindful of the importance of this balance;[11] in turn, the *Code* can be seen, in part, as a response to this. Perhaps the most significant point of ethical concern, for all parties, is the possibility (the likelihood of which is currently unknown) that a particular SCBEM may at some point be judged (based on best scientific understanding rather than by seeking to test such knowledge by transfer to a human or non-human animal host) in fact to *be* a human embryo. This raises in turn the question of time limits on the development of SCBEMs.

9. At the time of drafting the *Code* (June 2024), the Nuffield Council on Bioethics is undertaking a Rapid Review of the ethical issues arising from research involving SCBEMs; see https://www.nuffieldbioethics.org/publications/stem-cell-based-embryo-models (accessed 20/06/24).
10. Warnock Committee, Department of Health and Social Security, *Report of the Committee of Inquiry into Human Fertilisation and Embryology* Cmnd 9314 (July 1984) (Warnock Report), para 11.17. Available at https://iiif.wellcomecollection.org/pdf/b32220789 (accessed 22/06/24). Note that on one view, which is not widely shared, the embryo is considered to have the moral status of a person from the moment of conception. The Warnock Report, and the approach taken in the UK legislation, is not in accordance with this view.
11. *Addressing the governance gap*, Section 5: Governance of embryo model research (pp. 41–42).

Extensive thought has been given to the question of whether the *Code* should itself set a *single* fixed limit on the development of SCBEMs. The significance of this question is evident from the above points. There was also considerable interest in, and support for, a limit (albeit not necessarily a single timepoint) among the public dialogue participants.[12] The possible development of a SCBEM to a state at which it might experience pain was a concern to some participants in that dialogue.[13] Such concern is justified as, ethically, the acquisition of the capacity for sensation is judged to be of considerable significance.

Thus, one reason for placing a time limit on the development of SCBEMs would be to ensure that they were not developed to a point where they might experience pain. A 2022 report by the Royal College of Obstetricians and Gynaecologists concluded that 'evidence indicates that the possibility of pain perception before 28 weeks of gestation is unlikely'.[14] Given the current state of SCBEM research, it can be stated confidently that no SCBEMs approach this point. The *Code* therefore advises a different approach which is expanded upon below.

The Warnock Report also found that 'no one should undertake research on human embryos the purposes of which could be achieved… *in some other way*'.[15] Arguably, unnecessarily restricting SCBEM research could thwart this stipulation. At the same time, there are compelling scientific arguments against the idea that we should seek to replace human embryos with SCBEMs in all cases.[16]

Choosing not to set a *single* fixed limit might be viewed as a 'holding position', pending advances in this area, and the acquisition of further knowledge. That position may evolve in future iterations of the *Code*, particularly as SCBEMs become more sophisticated and as technology advances. It is also of note that, while the legislature has clear authority to set legal prohibitions, a *Code* aiming to guide best practice, such as this, is necessarily differently situated. So, in the absence of a compelling case in favour of a *single* fixed limit, the *Code* does not currently set one.

In place of a fixed time limit for all SCBEMs the *Code* suggests case-by-case consideration. As set out in Section 5.1 below, all SCBEMs shall be subject to review by a SCBEM Oversight Committee and shall only be experimented on for the minimum time needed to achieve the scientific objective proposed. As regards that objective, it is an important principle of the *Code* that research should have a well-justified purpose (see Section 5.3). This aligns with the legal approach taken to research involving embryos or embryonic stem cell lines, and also with the *ISSCR Guidelines*.[17] Given the need, as noted above, for a cautious approach, the degree of review and oversight by the Oversight Committee will be commensurate with the complexity of the SCBEM in question and its use.

We are aware of concerns raised during the public dialogue relating to SCBEMs displaying such recognisable features as a spinal cord or heartbeat.[18] While such features are part of the development of a human embryo and fetus, they are not necessarily *ethically* (or legally) significant in either,[19] though they are likely to elicit an emotional response to the embryo and fetus if observed in an established pregnancy. We recognise that, likewise, there may be a range of emotional responses to the (apparent) emergence of such features in a SCBEM and also – importantly – that for some people these features may have ethical significance. Researchers should be aware of and sensitive to these concerns, irrespective of whether they are thought to be ethically or legally relevant. Whilst the formal status of SCBEMs may not be dependent upon the presence or absence of such features, attitudes to the treatment and use of SCBEMs may be shaped by how both researchers and the public regard entities that display recognisable bodily structures.

12. *Addressing the governance gap*, Section 5: Governance of embryo model research (pp. 43–45).
13. *Addressing the governance gap*, Section 5: Governance of embryo model research (pp. 46–47).
14. Royal College of Obstetricians and Gynaecologists, *Fetal Awareness Evidence Review* (December 2022, Section 6: Conclusions and implications for clinical practice (p. 9)). Available at https://www.rcog.org.uk/media/gdtnncdk/rcog-fetal-awareness-evidence-review-dec-2022.pdf (accessed 20/06/24).
15. Warnock Report, para 11.17, emphasis added.
16. Rossant, J. Why study human embryo development? *Dev Biol* **509**, 43–50 (2024). doi: 10.1016/j.ydbio.2024.02.001; Rugg-Gunn, P. J. *et al*. Technical challenges of studying early human development. *Development* **150**, dev.201797 (2023). doi: 10.1242/dev.201797.
17. *ISSCR Guidelines*, Recommendation 2.1.2 (p. 7).
18. *Addressing the governance gap*, Section 5: Governance of embryo model research (pp. 43, 46–47).
19. Apart from the argument that the embryo has the status of a moral person from the moment of conception, noted above, some ethical arguments regarding the fetus have focused, for example, on sentience (the capacity to feel pain, distress or pleasure), viability, or gradualism (that is, the idea that the fetus has a growing moral claim as a pregnancy progresses), and sometimes a combination of some of these.

Beyond the issues noted above, the *Code* sets out additional prohibitions in Section 5.4, and notes the ethical and legal issues relating to consent (see Section 5.3(b) and Box 1). The *Code* also emphasises trust, transparency and accountability as important elements in securing public confidence in the way SCBEM research is conducted (see Section 4). Seeking a regulatory framework that earns and retains public trust may be considered an ethical goal. For this reason, policy principles such as those just noted – as well as scrutiny, expertise, consultation and proportionality – underpin the *Code*.

Other ethical issues relevant to the *Code* include respecting the privacy and autonomy of human donors, who donate tissue, gametes and stem cells that serve as the source material for creating SCBEMs, and ensuring that such donations are put to good use and not wasted.

As noted in Section 1.2, as SCBEM research advances, regular review of the *Code* will be needed. Careful consideration of the need for revision would align with views expressed in the public dialogue.[20]

20. *Addressing the governance gap*, Section 6: Responses to the draft Code of Practice graphic summary (pp. 61–62).

4. Trust, transparency and accountability

The *Code* has been informed, but not bound, by the *ISSCR Guidelines*.

The *Code* has been developed through consultation and debate, engaging a wide range of relevant stakeholders including members of the general public. A list of named stakeholders may be found in the Acknowledgements section and a fuller account of this engagement – including public dialogue and engagement activities – is given in Appendix 4. The *Code* aims to promote trust that this area of scientific research will be carefully monitored from an ethical perspective, given the current lack of legislative regulation in this area.

The *Code* notes the value of open engagement between researchers and the wider public about research involving SCBEMs as a way of promoting transparency and building public trust. Researchers should share their research findings widely and accessibly, and should participate in the exchange of knowledge. To ensure that research using SCBEMs is conducted with support and trust from the wider public, researchers should consider the need for clear and measured communications in public settings (for example, at public events and in traditional and social media).

The *Code* proposes a SCBEM Register that will record applications for approval of SCBEM research projects, and that will also record the outcome of those applications (see Appendix 3).

The *Code* encourages the use of terminology that is clear, unambiguous and consistent. As noted in Section 2, the *Code* adopts the term 'stem cell-based embryo model' as an appropriate umbrella term, following the *ISSCR Guidelines*.

As noted elsewhere, it is anticipated that the *Code* will be periodically updated, as needed and appropriate.

5. Core principles

5.1 Oversight of research

All SCBEMs shall be subject to an oversight process, as proposed in Appendix 3 (SCBEM Oversight Committee).

SCBEMs have the ability to organise into complex structures that approximate aspects of human development – for example, the formation of integrated primordia of organs such as a beating heart, complex neural structures capable of signalling, sensory perception, or limb-like structures – and may model aspects of fetal stages of human development. Some of these features may evoke sensitivities and ethical concerns. In the absence of evidence as to whether SCBEMs do, or do not, have the potential to develop into a viable entity, research involving SCBEMs requires specialised oversight.

5.2 Limits for culture

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.

Temporal limits are not straightforwardly applicable to SCBEM development because:

- there is no equivalent to fertilisation for a SCBEM and therefore no clear point to be taken as developmental 'day 0' (as distinct from the start of culture);
- SCBEMs may be established at stages that approximate different, non-equivalent developmental stages in a human embryo;
- SCBEMs may develop at differing rates, so their 'developmental time' may not equate to the chronological time elapsed;
- SCBEMs do not necessarily develop with a canonical trajectory, and may bypass certain stages of development or undertake a different sequence of steps.

It is therefore proposed that, instead of a single, fixed limit for culture, all SCBEMs shall be subject to review by the SCBEM Oversight Committee and the models shall only be cultured *in vitro* for the minimum time needed to achieve the scientific objective proposed. The more complex the structure, the more rigorous the review and the greater the degree of oversight that will be required by the SCBEM Oversight Committee.

5.3 Fundamental research principles

Research that involves generating or using a human SCBEM should not proceed unless it meets the following conditions.

Research proposals must:

a. have a well-justified scientific objective;

b. consider what donor consent is in place (if any), in what form consent has been obtained, and whether the research is in accordance with consent and with prevailing legal and policy frameworks (see Box 1);

c. explain the potential benefits of the research, and how relevant ethical considerations have been taken into account (see further Sections 3 and 4);

d. justify the choice, including the complexity and degree of integration of the model, and (if applicable) explain why a simpler model is not suitable;

e. propose and adhere to an approved period of culture *in vitro* no more than the minimum duration necessary to achieve the relevant scientific objective (see Section 5.2). Researchers must not go beyond this limit without further review of a modification of the project proposal by the SCBEM Oversight Committee;

f. include details of a defined 'terminal' step that ends the experiment (see Box 2);

g. not breach the prohibitions set out in Section 5.4;

h. be reviewed and approved by the SCBEM Oversight Committee (see Appendix 3);

i. agree to have their project listed in the SCBEM Register (see Appendix 3).

5.4 Prohibited uses

Transfer to a human or non-human host

No person shall transfer a SCBEM (whether human or non-human) to the *in vivo* reproductive tract of a human host.

No person shall transfer a human SCBEM to the *in vivo* reproductive tract of a non-human animal host.

Ectogenesis

Full ectogenesis is development to viability of an organism entirely outside a host organism.

Full ectogenesis using a human SCBEM, for research or reproductive purposes, would be incompatible with the approach set out in the *Code*.

BOX 1: CONSENT

When considering prevailing requirements for consent, researchers should consult guidance and legislation relevant to the countries involved in their research. For example, in the UK in 2024, legislation (such as the HT Act and HFE Act) requires consent for the use of human samples in research. Researchers could consult the Human Tissue Authority's *Codes of Practice* (of which the most relevant are *Code A: Guiding principles and the fundamental principle of consent* and *Code E: Research*), the UK Stem Cell Bank's *Code of Practice for the use of Human Stem Cell Lines* and the HFEA's *Code of Practice*. The *ISSCR Guidelines* also include relevant recommendations.

BOX 2: TERMINATION OF EXPERIMENTS

SCBEMs are considered to be terminated in their development when their cellular integrity, or physical or biological properties, are irreversibly altered through any of the following (or equivalent) operations:

- incubation to 56°C or higher (water bath) for up to 10 minutes;
- mechanical force that homogenises or macerates all of the SCBEMs;
- disruption of the cell membrane by chemicals;
- lysis by protein, RNA or DNA denaturing compounds;
- withdrawal of culture medium;
- flash-freezing without cryoprotectants, leading to ice crystal formation;
- chemical fixation by aldehydes or alcohols that terminates any ongoing biochemical reactions.

6. Expected standards for research and materials

This section of the *Code* seeks to promote standardised best practices that ensure rigorous and reproducible research, uphold ethical principles, and maximise the translational potential of findings in regenerative medicine and disease modelling. We advise that researchers follow the ISSCR 2023 *Standards for Human Stem Cell Use in Research* for best practice recommendations.[21]

6.1 Source of starting material

SCBEMs may be generated from a variety of sources, including human totipotent stem cells, ESCs, iPSCs, during the reprogramming of somatic cells, or by mixing embryonic and extraembryonic stem cells. Therefore, the *Code* applies regardless of the source of starting material (for example, iPSC-derived SCBEMs are treated in the same way as ESC-derived SCBEMs).

6.2 Record keeping in generating the model system

To ensure reproducibility of the methodology and the quality of the model system, all key components, equipment and reagents used must be documented in experimental plans. Each step in the generation of the SCBEM should be recorded with sufficient detail to enable the results to be reproduced and validated.

To ensure that *in vitro* development is not extended beyond a predefined endpoint, all experimental plans must define the terminal step (see Box 2). This endpoint should be approved by the SCBEM Oversight Committee. Extension beyond this predefined culture duration may only be undertaken subject to SCBEM Oversight Committee approval.

6.3 Validating SCBEMs

It is important to contextualise the findings and conclusions of research involving SCBEMs in terms of similarities to, and differences from, human embryos. It is necessary to define how and to what extent SCBEMs resemble conceptuses at a specific developmental stage through *multiple* criteria. When validating SCBEMs in relation to human embryos and non-human primate embryos at equivalent developmental stages, quantified morphological *and* molecular criteria are recommended. Validation may be through pre-existing datasets or through *de novo* validation. (Any research involving *in vitro* human embryos is subject to the HFE Act.)

6.4 Applications in basic biology and clinical translation

When using SCBEMs to model disease or developmental disorders, the karyotype of the starting cell line should be validated, both prior to the experiment and at the experimental endpoint, especially if the research involves genetic modification of SCBEMs.

Variability between the starting stem cell lines needs to be considered and reported, especially for iPSC-derived SCBEMs (given the inherent clonal variability among iPSC lines). The genetic background of the starting cell line should be considered, especially in the context of introducing or correcting mutations. The sex of all cell lines used should be documented.

6.5 Nomenclature

Researchers should use terminology that is clear, unambiguous and consistent. As far as possible, researchers should use terms that are already in common scientific usage.

21. International Society for Stem Cell Research (ISSCR), *Standards for Human Stem Cell Use in Research* (June 2023). Available at https://www.isscr.org/standards-document (accessed 20/06/24).

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SCBEM Code of Practice Working Group

Professor Roger Sturmey (Hull York Medical School and University of Manchester, UK) (*Chair*)
Professor Kathy Niakan (University of Cambridge, UK) (*Principal Investigator*)
Heather Briggs (Regulatory Support Centre, Medical Research Council – UKRI, UK)
Professor Andrew Copp (University College London, UK)
Professor Bobbie Farsides (Brighton and Sussex Medical School, UK)
Professor Deborah Henderson (Newcastle University, UK)
Julian Hitchcock (Biolawgy, UK)
Professor Kathleen Liddell (University of Cambridge, UK)
Dr Naomi Moris (Francis Crick Institute, UK)
Professor Jennifer Nichols (University of Edinburgh, UK)
Dr Peter Rugg-Gunn (Babraham Institute, UK)
Professor Rosamund Scott (Centre of Medical Law and Ethics, King's College London, UK)
Professor Austin Smith (University of Exeter, UK)

SCBEM Code of Practice Project Team

SCBEM Code of Practice Project Manager: Christina Rozeik (Cambridge Reproduction)
SCBEM Code of Practice Consultant: Sandy Starr (Progress Educational Trust)
SCBEM Code of Practice Oversight Group: Professor Sarah Franklin (University of Cambridge); Professor Nick Hopwood (University of Cambridge); Sarah Norcross (Progress Educational Trust)

Reviewers and commenters

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Dr Chris Burns (Medicines & Healthcare products Regulatory Agency, UK)
Dr Lee Carpenter (UK Stem Cell Bank, UK)
Professor Susana Chuva de Sousa Lopes (Leiden University Medical Center, Leiden University, Netherlands)
Dr Laurent David (Nantes Université, France)
Dr Nienke de Graeff (Leiden University Medical Center, Leiden University, Netherlands)
Professor Henry T Greely (Stanford University, USA)
Dr Andy Greenfield (University of Oxford, UK)
Dr Uta Grieshammer (California Institute for Regenerative Medicine, USA)
Professor Jacob Hanna (Weizmann Institute, Israel)

Dr Lyn Healy (Francis Crick Institute, UK)
Dr Idse Heemskerk (University of Michigan, USA)
Dr Insoo Hyun (Museum of Science, Boston, USA)
Professor Ana Iltis (Wake Forest University, USA)
Professor Emily Jackson (London School of Economics and Political Science, UK)
Dr Erica C Jonlin (University of Washington, USA)
Dr Rosario Isasi (University of Miami, USA)
Dr Geraldine M Jowett (University of Cambridge, UK)
Professor Kazuto Kato (Osaka University, Japan)
Dr Sigal Klipstein (American Society for Reproductive Medicine, USA)
Tyler Lamb (International Society for Stem Cell Research, USA)
Katherine Littler (Global Health Ethics and Governance Unit, World Health Organization, Switzerland)
Professor Robin Lovell-Badge (Francis Crick Institute, UK)
Professor Alfonso Martinez Arias (Universitat Pompeu Fabra, Spain)
Dr Raj Mathur (Manchester Academic Health Science Centre, UK)
Dr Kirstin Matthews (Rice University, USA)
Kevin McEleny (Newcastle Hospitals NHS Trust, UK)
Dr Pete Mills (PHG Foundation, UK)
Dr Melanie Moore (Medicines & Healthcare products Regulatory Agency, UK)
Dr Jack Mosher (International Society for Stem Cell Research, USA)
Professor Megan Munsie (Murdoch Children's Research Institute and University of Melbourne, Australia)
Professor Alison Murdoch (Newcastle University, UK)
Dr Vincent Pasque (KU Leuven, Belgium)
Professor Martin Pera (Jackson Laboratory, USA)
Dr Ana M Pereira Daoud (Maastricht University, Netherlands)
Dr Teresa Rayon (Babraham Institute, UK)
Dr Nicolas Rivron (Institute of Molecular Biotechnology of the Austrian Academy of Sciences and Vienna BioCenter, Austria)
Professor Tristan Rodriguez (Imperial College London, UK)
Professor Janet Rossant (University of Toronto and SickKids, Canada)
Dr Marta Shahbazi (MRC Laboratory of Molecular Biology, UK)
Dr Berna Sozen (Yale University, USA)
Dr Desislava Staneva (University of Cambridge, UK)
Professor Patrick Tam (Children's Medical Research Institute and University of Sydney, Australia)
Dr Güneş Taylor (University of Edinburgh, UK)
Dr Thorold Theunissen (Washington University in St Louis, USA)
Peter Thompson (Human Fertilisation and Embryology Authority, UK)
Professor Maria-Elena Torres-Padilla (Helmholz Munich, Germany)
Dr Adrián Villalba Felipe (Université Paris Cité, France and Universidad de Granada, Spain)
Dr Bailey Weatherbee (Cincinnati Children's Hospital Medical Center, USA)
Dr Jun Wu (University of Texas Southwestern Medical Center, USA)
Professor Magdalena Zernicka-Goetz (University of Cambridge, UK and Caltech, USA)

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We are grateful to the participants at the policy workshop 'Governance of Stem Cell-Based Embryo Models in the UK' (see Appendix 4), held in Cambridge on 12 October 2023. Their discussions helped shape the current form of the *Code*:

Dr Rob Doubleday (Centre for Science and Policy, University of Cambridge, UK) (*Chair*)
Dr Catherine Blewett (Health Research Authority, UK)
Heather Briggs (Regulatory Support Centre, Medical Research Council – UKRI, UK)
Dr Chris Burns (Medicine & Healthcare products Regulatory Agency, UK)
Professor Andrew Copp (University College London, UK)
Professor Sarah Franklin (University of Cambridge, UK)
Julian Hitchcock (Biolawgy, UK)
Professor Emily Jackson (London School of Economics and Political Science, UK)
Professor Kathleen Liddell (University of Cambridge, UK)
Katherine Littler (Global Health Ethics and Governance Unit, World Health Organization, Switzerland)
Professor Robin Lovell-Badge (Francis Crick Institute, UK)
Professor Anna Middleton (Kavli Centre for Ethics, Science and the Public, University of Cambridge, UK)
Dr Pete Mills (PHG Foundation, UK)
Professor Kathy Niakan (University of Cambridge, UK)
Christina Rozeik (Cambridge Reproduction, University of Cambridge, UK)
Dr Peter Rugg-Gunn (Babraham Institute, UK)
Professor Rosamund Scott (Centre of Medical Law and Ethics, King's College London, UK)
Sandy Starr (Progress Educational Trust, UK)
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Appendix 1: Legal framework

UK legislation does not refer expressly to the generation or use of stem cell-based embryo models. However, legislation does affect various aspects of scientific work relating to SCBEMs.

The summary below is not exhaustive but illustrates the regulatory landscape in the UK. Note that it differs from the regulatory frameworks in other countries, which may be relevant for imported SCBEMs or stem cell lines.

The Human Tissue Act 2004 (outside Scotland)

Some SCBEMs, such as iPSC-derived SCBEMs, are generated from material classified as 'relevant material' under the Human Tissue Act 2004 ('HT Act'), such as skin fibroblasts, that 'has come from a human body' (e.g. by biopsy). Thus, following the HT Act provisions, donor consent is required to establish a stem cell line.One exception covers imported tissue, in which case the legal and ethical frameworks of the exporting country apply.[22]

When consent is the basis for using tissue to create a stem cell line, the conditions of the consent must be respected. For instance, if the donor specified restrictions on the use of their tissue, those restrictions apply to the resulting stem cell line. Particular attention is drawn to HTA Code A ('Guiding Principles and the fundamental principle of consent'), and to the four Guiding Principles of the HTA Act (consent; donor dignity; quality and honesty; and openness) discussed in Section 1 of Code A.

Once a cell line is established, the use and storage of cells from the cell line are not subject to the licensing or consent requirements under the HT Act. The HT Act governs the use and storage of primary cell cultures but not cell *lines*, cells that have divided in *culture*, or embryonic *stem cells*. These are generated or divide outside the human body, and are not considered to have 'come from a human body'. Scientists using iPSC-derived SCBEMs should nevertheless recognise that their work is part of a chain; the donor's consent or research ethics approval that established the stem cell line could affect their work. They should ensure that the terms are broad enough to encompass their work.

The Human Fertilisation and Embryology Act 1990 (as amended)

hESC-derived SCBEMs are derived from embryonic stem cells. It is primarily for this reason that the Human Fertilisation and Embryology Act 1990 ('the HFE Act') is relevant.

hESC-derived SCBEMs

Research involving human embryos is regulated by the HFE Act, requiring donor consent and a licence from the HFEA. The HFE Act also restricts research purposes, limits *in vitro* culture to 14 days or the appearance of the primitive streak (whichever comes first), and mandates record-keeping for embryos used in research.

Stem cell lines derived from human embryos must be banked at the UK Stem Cell Bank. Researchers can seek approval from the Steering Committee for the UK Stem Cell Bank and for the use of stem cell lines to use stem cells from these lines, for example in order to generate SCBEMs.

Researchers should thus ensure that their work aligns with the Steering Committee's authorisation and with the original donor's consent that established the stem cell line.

22. Health Research Authority, *Use of human tissue in research* (February 2024). Available at https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/use-tissue-research/ (accessed 24/06/24).

Embryo models and 'embryos' in UK law[23]

The definition of 'embryo' is pivotal in the HFE Act, although it lacks detail. Section 1(1) currently defines 'embryo' as 'a live human embryo…'.

In *R (on the application of Quintavalle) v. Secretary of State for Health* [2003] UKHL 13 ('*Quintavalle*'), the UK's highest court interpreted an earlier version of the legislation in the context of cell nuclear transfer. The judges gave different reasons for their conclusion, meaning there is no clear, concrete basis for concluding whether SCBEMs fall within the definition of 'embryo'. Lord Millett highlighted the developmental capacity of human embryos to 'become a foetus and eventually a human being' (i.e. child). If this reasoning is adopted in future, the developmental potential of SCBEMs would be highly relevant. Other judges in the *Quintavalle* case (Lord Bingham, Lord Steyn, Lord Hoffmann, and Lord Scott) emphasised Parliament's purpose in passing the HFE Act, noting the intent to regulate the field of embryology comprehensively and strictly. The following passage was considered authoritative:

> [W]hen a new state of affairs, or a fresh set of facts bearing on policy, comes into existence [eg entities that were not known about when the legislation was passed], the courts have to consider whether they fall within the parliamentary intention. They may be held to do so, if they fall within the same genus of facts as those to which the expressed policy has been formulated. They may also be held to do so if there can be detected a clear purpose in the legislation which can only be fulfilled if the extension is made. How liberally these principles may be applied must depend upon the nature of the enactment, and the strictness or otherwise of the words in which it has been expressed. The courts should be less willing to extend expressed meanings … where the subject matter is different in kind or dimension from that for which the legislation was passed.[24]

If a court applies this reasoning, it might compare SCBEMs with entities like fertilised embryos, admixed embryos, research-grade fertilised embryos and cell-nuclear-transfer embryos. This comparison would assess whether SCBEMs 'fall within the same genus of facts as those to which the [legislation] has been formulated'. The comparison need not be limited to a consideration of the SCBEMs' developmental potential.

Alternatively, a future court might decide that the definition should be determined by regulations of the Secretary of State and Parliament under section 1(6); the regulation-making power was added to the HFE Act after the *Quintavalle* case.

Current scientific evidence from non-human animal SCBEM studies indicates that we are far from a situation where human SCBEMs have the capacity to develop into children. While not conclusive (see the points above) this strongly suggests that UK courts would likely conclude that SCBEMs are not embryos as defined in the HFE Act. Therefore, research with SCBEMs does not require a licence from the HFEA and is not subject to the 14-day rule under the HFE Act.

As science progresses, our understanding of SCBEMs' developmental potential and other characteristics could change, affecting comparisons with fertilised and admixed embryos. New evidence from non-human animal studies and *in vitro* human SCBEM research could also emerge. It is therefore sensible, periodically, to reassess whether SCBEMs fall within the definition of 'embryo' under the HFE Act.

23. See also Hitchcock, J. Why an embryo model is not an 'embryo' under UK law. Biolawgy.com (December 2023). Available at https://www.biolawgy.com/scbems/ (accessed 20/06/24).
24. *R (on the application of Quintavalle) v. Secretary of State for Health* [2003] UKHL 13 [10]. Available at https://www.bailii.org/uk/cases/UKHL/2003/13.html (accessed 24/06/24).

Section 3(2) of the HFE Act prohibits placing an 'embryo' in a woman unless it is a 'permitted embryo'. It is a criminal offence to breach this provision. 'Permitted embryos' are strictly defined under section 3ZA to safeguard the woman's health and uphold ethical standards. For example, 'permitted embryos' must originate from *in vivo*-derived eggs and sperm, and their nuclear DNA must not have been altered. If SCBEMs are not 'embryos' (see the discussion above), section 3(2) strictly speaking does not prohibit placing SCBEMs in a woman. However, such actions, particularly if they pose harm to a woman, could breach other laws, such as the law of negligence, or the criminal law of causing actual bodily harm or battery. Conducting scientific experiments to assess the *in vivo* developmental capacity of SCBEMs does not justify exposing a woman to serious harm.

Other laws

Additional laws regulate the use of human tissues and cells in the development of advanced therapy medicinal products. These include the Medicines for Human Use (Clinical Trials) Regulations 2004, ATMP-specific manufacturing standards and requirements, and legislation implementing or adapting EU Directive 2004/23 on the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells for clinical application ('EUTCD') such as the Human Fertilisation and Embryology (Quality and Safety) Regulations 2007, and the Human Tissue (Quality and Safety for Human Application) Regulations 2007.

The net effect of these regulations is that SCBEMs would need to meet exacting quality, safety and manufacturing standards before they could be used in a clinical trial or clinical treatment.

Research with SCBEMs must also comply with general laws such as the UK GDPR and Data Protection Act 2018.

Appendix 2: Overview of non-statutory guidance relevant to SCBEMs

ISSCR *Guidelines for Stem Cell Research and Clinical Translation* (2021)

The *Guidelines for Stem Cell Research and Clinical Translation* published by the International Society for Stem Cell Research (ISSCR) aim to promote, at an international level, 'an ethical, practical, appropriate, and sustainable enterprise for stem cell research and the development of cell therapies that will improve human health and should be available for patients in need'. The *ISSCR Guidelines* build on a set of widely shared ethical principles in science, research with human subjects, and medicines. They include guidance on the 'generation of stem cell-based models of human development', with recommendations for the types of scientific projects that should be subject to review, placing them in three review categories, each requiring different levels of oversight, and suggesting limitations.

Although the *ISSCR Guidelines* have no legal force and do not supersede local laws and regulations, they can provide guidance to researchers in the absence of applicable rules. In this sense, the *ISSCR Guidelines* complement existing legal frameworks and can inform the interpretation and development of national rules, statutory or otherwise, for the conduct of stem cell research. The UK *Code of Practice for the Generation and Use of Human Stem Cell-Based Embryo Models* was drafted with consideration for the *ISSCR Guidelines* and now takes precedence over the *ISSCR Guidelines* in the UK for research involving SCBEMs. Future versions of the *Code* will continue to pay due regard to the *ISSCR Guidelines*.

ISSCR *Standards for Human Stem Cell Use in Research* (2023)

The ISSCR *Standards for Human Stem Cell Use in Research*, which seek to establish technical standards applicable to human stem cell research, include a section (Section 4) on stem cell-based model systems.

Grant conditions

Whoever provides funding for research – for example, UK Research and Innovation, the Wellcome Trust or another charitable body, or Horizon Europe – sets conditions for that funding.

Institutional rules

Different research institutions may set different conditions.

Appendix 3: SCBEM Oversight Committee

Central to the *Code of Practice for the Generation and Use of Human Stem Cell-Based Embryo Models* is the establishment of a SCBEM Oversight Committee that will provide advice and review to researchers working with SCBEMs. In accordance with the International Society for Stem Cell Research *Guidelines for Stem Cell Research and Clinical Translation*, we believe that the scientific, ethical and legal issues raised by research involving SCBEMs are such that they are best addressed through a specialised process that is capable of considering all of these issues. This Appendix outlines a proposal for the establishment and operation of such a process.

This body would be established specifically to receive applications from researchers who are planning to generate or use SCBEMs in research. The SCBEM Oversight Committee would provide additional, dedicated oversight of this research, including:

- development of reporting mechanisms, including guidance and online tools to support the application and reporting processes;

- advice on ethical considerations that arise from the proposed work;

- review of, and advice about, compliance of the proposed work with the *Code*, in particular:
  - approval of the proposed work following the above reviews;
  - determining the limit for culture *in vitro* of the SCBEMs used in the proposed work (this limit to vary on a case-by-case basis);
  - recording applications in the SCBEM Register;
  - reporting annually on applications received and approved.

Review will be constructive and proportionate to the issues raised by each proposal. The more complex the SCBEM, the more rigorous the review and the greater the degree of oversight that will be required by the SCBEM Oversight Committee.

The SCBEM Oversight Committee is not intended to provide an in-depth peer review of the science (but see section 5.3 for the more general scientific justification expected of research proposals).

Establishment of the SCBEM Oversight Committee

Given the complex, evolving and potentially sensitive nature of research involving SCBEMs, it is essential that the SCBEM Oversight Committee is competent to evaluate the unique scientific and ethical issues raised. 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. Consideration of conflicts of interest (real or perceived) should be taken. Moreover, Committee members (particularly if their own research or other interests relate closely to SCBEMs) should treat all applications with appropriate confidentiality.

The SCBEM Oversight Committee's Terms of Reference will include information about membership, responsibilities, scope, decision-making, operations and review.

One of the first responsibilities of the SCBEM Oversight Committee will be to develop tools to support its decision-making and to promote efficient, transparent and impartial review of applications. These tools could include (for example) an online system to streamline the submission and review process, a scoring system to highlight projects most likely to require the greatest degree of oversight or scrutiny, and a decision tree to aid in review of projects.

We believe that the work of this Committee can and should promote both public and researcher confidence in research in this area.

The SCBEM Oversight Committee will not have retrospective powers, and there will be no requirement to submit proposals to this body for research that has already begun. Researchers will nonetheless be encouraged to add these projects to the SCBEM Register in the interests of transparency. The Committee will be established with sufficient notice to allow researchers to plan applications before beginning their experiments.

Operation of the SCBEM Oversight Committee

All UK-based research that involves the generation or use of SCBEMs should be reported in confidence to the SCBEM Oversight Committee. Researchers who plan to create or use SCBEMs should seek advice and review from the SCBEM Oversight Committee *prior* to commencing experiments.

By submitting their research to the SCBEM Oversight Committee, researchers are committing to follow the best practice described in the *Code*.

The SCBEM Oversight Committee will review applications as above, and will advise on whether the research proposed complies with the *Code*, in particular with Section 5.3 (Fundamental research principles). The Committee will aim to complete reviews as rapidly as possible.

Research should not proceed until it has received favourable review from the SCBEM Oversight Committee, including confirmation of a limit for *in vitro* culture of the SCBEMs used in the proposed work (to be determined during the course of the application process). Researchers must adhere to this limit and may not go beyond this point without further review by the SCBEM Oversight Committee.

Where research proposals are not approved by the SCBEM Oversight Committee, researchers are advised to revise and resubmit their proposals in line with feedback received.

All applications to the SCBEM Oversight Committee will be recorded in the SCBEM Register. Basic information about approved projects will also be made publicly available (see below).

It is anticipated that many proposals (for example, those involving only the least complex SCBEMs) will require only 'light-touch' oversight. Where appropriate, 'prior precedence' will be applied to ensure expeditious review. Proposals that are scientifically or ethically complex will require a greater degree of oversight.

The SCBEM Oversight Committee will publish an annual report about its activity, including a summary of applications received and numbers approved.

The Committee's Terms of Reference will be reviewed on an ongoing basis.

SCBEM Register

The SCBEM Oversight Committee will establish and maintain a SCBEM Register to record pre-existing studies, applications for approval of projects, and the outcomes of such applications. Outline information about successful applications – including project title, type of SCBEM, project lead and institution – will be made publicly available. Researchers will be required to include a lay summary of their research, to advance public understanding of work in this area. The SCBEM Oversight Committee will determine how to balance *a)* the need to protect researcher confidentiality, proprietary details or IP disclosure, especially in a rapidly-moving field of research, with *b)* the need to provide transparent, timely, publicly-available information in the SCBEM Register.

Appendix 4: Development of the *SCBEM Code of Practice*

The *Code of Practice for the Generation and Use of Human Stem Cell-Based Embryo Models* has been developed through a process of deliberation and consultation, and is founded on principles of trust, transparency and accountability (as outlined in Section 4). We have listened to a range of views from stakeholders during the development of the *Code*, and have sought to be transparent and open-minded when considering such feedback. We are very grateful to everyone who has contributed to the development of the *Code*, including those named in the Acknowledgements section, and others who have asked to remain anonymous.

The key mechanisms for stakeholder engagement during development of the *Code* are described below.

Governance of Stem Cell-Based Embryo Models (G-SCBEM) project

The Governance of Stem Cell-Based Embryo Models (G-SCBEM) project is led by Cambridge Reproduction, an interdisciplinary research centre at the University of Cambridge, in partnership with the Progress Educational Trust (PET), a charity that improves choices for people affected by infertility and genetic conditions. The G-SCBEM project launched in March 2023, inspired by discussions during the two-day conference *Realising the translational potential of reproductive organoids* (Cambridge, 18–19 July 2022) and the policy workshop *The regulation of reproductive organoids in the UK* (Cambridge, 29 September 2022). Work was coordinated and overseen by the *SCBEM Code of Practice* Project Team. Project Team membership and project funding are detailed in the Acknowledgements section.

The project aims to develop the first dedicated governance for research involving SCBEMs in the UK (see Section 1 for a fuller explanation). An important part of achieving that aim has been the development of the *Code*, but the wider project has involved additional outreach and engagement activities, as outlined in this Appendix. These activities have informed the development of the *Code*, by providing a richer understanding of views, including those of the general public.

SCBEM Code of Practice Working Group

The *SCBEM Code of Practice* Working Group was convened in March 2023 and was tasked with responsibility for drafting the *Code*. Members were drawn from institutions around the UK and represented a range of expertise relating to SCBEMs, including science, law, ethics and regulation. Working Group membership is detailed in the Acknowledgements section.

The Working Group met in full on 27 occasions between March 2023 and June 2024. Sub-groups, responsible for drafting particular sections, held a further six meetings in July and September 2023.

Policy workshop (12 October 2023)

An early draft of the *Code* was presented at the policy workshop 'Governance of Stem Cell-Based Embryo Models in the UK' (Cambridge, 12 October 2023), which was facilitated by the Centre for Science and Policy (CSaP) at the University of Cambridge. This workshop aimed to bring together representatives of the principal regulators and funders of research involving SCBEMs. Participants gave feedback on the draft proposal, including discussion of how the *Code* might fit into the UK's existing regulatory space, and how the *Code* could be administered within a broader governance framework. A full list of workshop participants can be found in the Acknowledgements section.

Public dialogue (January 2024)

We believe that it is crucial to listen to public views when developing governance for a new and potentially sensitive area of science. Cambridge Reproduction commissioned a public dialogue, held in January 2024 and designed and facilitated by the social research agency Hopkins Van Mil, to ensure that public voices – as well as those of researchers, funders, policymakers and regulators – were taken into account while the *Code* was being drafted.[25] This public dialogue was the first in-depth exploration of public attitudes towards research involving SCBEMs in the UK.

Public dialogue is a deliberative process that brings together members of the public with subject experts, stakeholders and policy makers to consider issues relevant to future policy decisions. During the SCBEM public dialogue, a diverse group of 38 people – selected to achieve a range of ages, genders, ethnicities, UK locations and views on embryo research – were engaged in nine hours of focused activities, including a series of online workshops with researchers and practitioners in science, ethics and law. Participants explored a number of issues relating to SCBEMs, including how SCBEMs are similar to or different from human embryos, the use of SCBEMs in research, and the different ways that such research could be governed, including voluntary and legislative approaches.

The findings of the public dialogue were published in April 2024 and have informed development of the *Code* by clarifying public hopes, concerns and sensitivities relating to research involving SCBEMs.[26]

Stakeholder feedback on the draft *Code* (February 2024)

In July 2023, the *SCBEM Code of Practice* Project Team sent out a survey to stakeholders, to canvass opinions about the regulation of research involving SCBEMs, and to seek expressions of interest from potential reviewers of the draft *Code*. A rough draft of the *Code* was sent out to approximately 100 stakeholders in February 2024. These stakeholders included researchers and practitioners in diverse areas of science, ethics, law and regulation, as well as regulatory bodies, funding bodies and policy teams. Stakeholders comprised participants at the policy workshop, key researchers (identified from an informal survey of the academic literature) and other interested parties (who could self-nominate as reviewers).

We received feedback from 55 individuals and organisations, much of it in the form of detailed comments on the draft *Code*. The Working Group considered this – and other – feedback in detail, when revising the *Code* for publication.

25. UKRI Sciencewise. Governance of Stem Cell-Based Embryo Models public dialogue: project summary. Available at https://sciencewise.org.uk/projects/governance-stem-cell-based-embryo-models/ (accessed 20/06/24);
Rozeik C. Public views – the missing piece of the policy puzzle: commissioner reflections (May 2024). Available at https://sciencewise.org.uk/2024/05/public-views-the-missing-piece-of-the-policy-puzzle-commissioner-reflections/ (accessed 20/06/24).
26. *Addressing the governance gap: a public dialogue on the governance of research involving stem cell-based embryo models* (April 2024). Available at https://sciencewise.org.uk/wp-content/uploads/2024/04/StemCellBasedEmbryoModels_Report_Appendices.pdf (accessed 20/06/24).

Other outreach and engagement

The *SCBEM Code of Practice* Project Team and Working Group acknowledge the need for two-way public engagement, to gather informal feedback on the proposed *Code* and to contribute to public and professional understanding of research involving SCBEMs. To help achieve this, the Project Team and Working Group co-produced and spoke at two public events in March 2024, which reached a combined audience of around 200 people.

The first of these public events – *Stembryos: the future of reproduction?* – was held at the Science Museum in London, UK on 7 March 2024. Chair: Dr Philip Ball. Panellists: Dr Naomi Moris (Francis Crick Institute), Julian Hitchcock (Biolawgy), Professor Emily Jackson (LSE) and Sandy Starr (PET).

The second of these public events – *Reproductive futures: stem cell-based embryo models* – was held as part of the Cambridge Festival on 17 March 2024. A panel discussion was followed by a reception and an opportunity to view a special exhibition about SCBEMs, embryo research, the SCBEM public dialogue and the *Code*, as well as to talk to members of the *SCBEM Code of Practice* Project Team and Working Group. Chair: Professor Kathy Niakan (University of Cambridge). Panellists: Dr Peter Rugg-Gunn (Babraham Institute), Professor Kathleen Liddell (University of Cambridge), Professor Sarah Franklin (University of Cambridge).

The *SCBEM Code of Practice* Project Team has also commissioned two videos relating to the SCBEM research and governance: a brief account of the governance issues raised by SCBEMs and of the G-SCBEM project to address these; and an animated explainer about SCBEMs (currently in production).

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