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Human embryo models: the importance of national policy and governance review

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Integrated and non-integrated stem cell-based embryo models are becoming widely adopted tools in biomedical research with distinct advantages over animal models for studying human development. Although SCB-EMs have tremendous benefits for research, they raise a number of social, ethical and legal questions that affect future research and widespread adoption in industry and clinical settings. The 2021 International Society for Stem Cell Research Guidelines for Stem Cell Research and Clinical Translation provide helpful guidance on many of these issues but do not have force in domestic law. Careful appraisal and development of national legal and ethical frameworks is crucial. Paving the way to better regulation provides an ethical and social foundation to continue using human embryo models and to fully realise their potential benefits for reproductive medicine.

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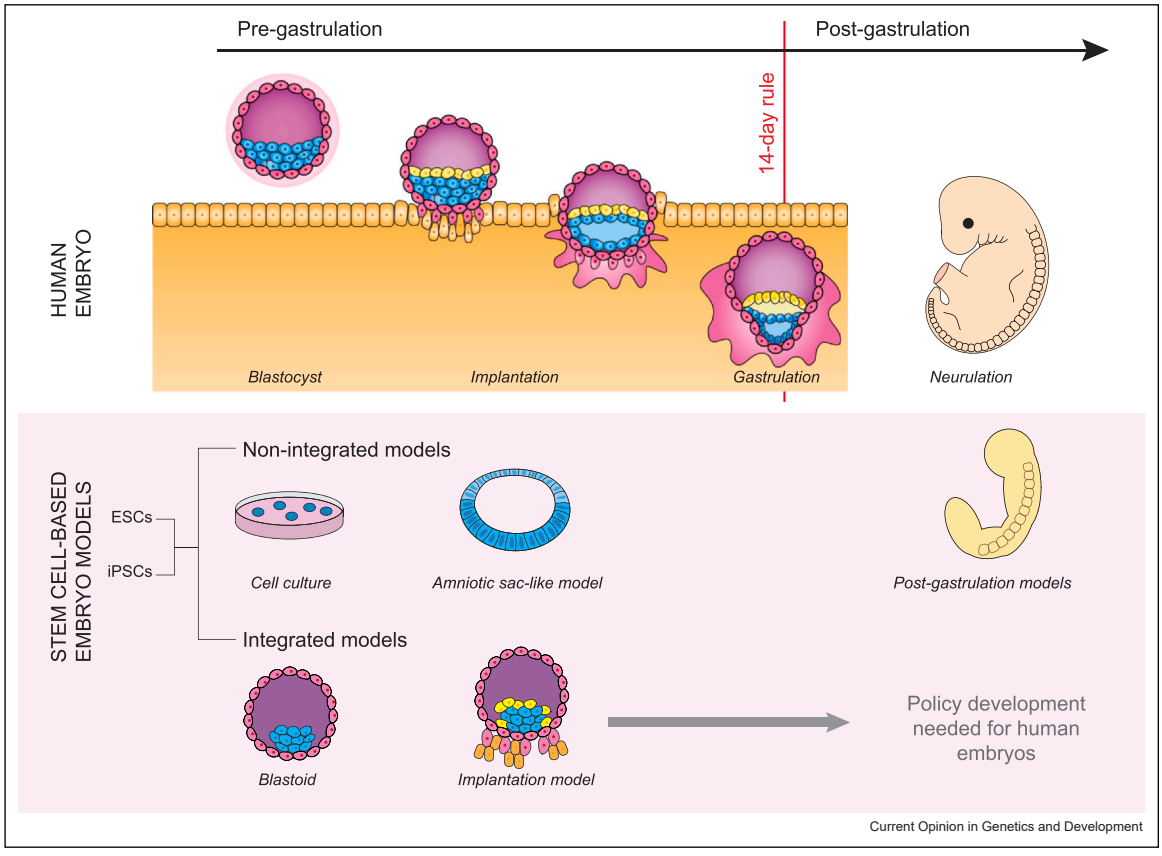
Introduction

Under specific conditions, human embryonic stem cells (ESCs) and induced pluripotent stem cells can model embryos and aspects of organogenesis. These 'stem cell-based embryo models' (SCB-EMs) (also referred to as gastruloids, blastoids, synthetic embryos and stembryoids) broadly fall into two categories: i) Integrated SCB-EMs, consisting of embryonic *and* extra-embryonic cell types found in the whole conceptus, mimic the entire early human embryo post fertilisation. Some integrated SCB-EMs are designed to mimic early human development as closely as possible throughout development, including in early embryogenesis and implantation (Figure 1) [1]. However, the benefits provided by these models also raise questions about the adequacy of current research governance. ii) Non-integrated SCB-EMs mimic limited aspects of human embryonic development and tissues (such as neurulation and somitogenesis) [2] and are thought to raise fewer ethical concerns. However, if future non-integrated SCB-EMs begin to resemble a sophisticated embryo with a beating heart, limbs or a spinal cord, they too could raise issues within embryo-based research ethics. The benefits of SCB-EMs for studying early human development are covered extensively elsewhere in this special issue.

Figure 1



Human stem cell-based embryo models can recapitulate pre- and post-gastrulation stages of development. Where and how these models fall within current legal frameworks and whether they are legally permissible, governed and ethically regulated, is currently unclear in national laws around the globe. Non-integrated SCB-EMs represent specific tissues, organs and cell structures; this includes the epiblast cavity in implantation and post-gastrulation models of specific tissues and developmental stages (e.g. neurulation). Non-integrated SCB-EMs have no potential to form a viable embryo but may be deemed to require legal and technical oversight the closer they resemble the fertilised embryo, particularly for ethically sensitive tissue types (e.g. combined brain and heart SCB-EMs). Integrated SCB-EMs mimic blastocyst and implantation stages, but it is not yet technically feasible for these models to develop past 14 days post fertilisation, the legal limit for culturing embryos *in vitro*. It is currently unclear whether such models are or should be legally permissible and if they require specialist oversight and governance.

Ethical issues with advanced SCB-EMs

The recent *in vitro* culture of integrated and non-integrated stem cell-based *mouse* embryo models post gastrulation [3,4] demonstrated that researchers are able to grow embryo models to sophisticated levels, albeit currently with limited efficiency. These self-organising models have defining features such as a gut tube, beating heart-like region, forebrain, hindbrain, neural tube and somites. The technical feasibility of coaxing *human* SCB-EM models to similar levels of development is increasing and more recently several groups have established stem cell-based models of human post-implantation development [5-10]. In the future, these models could be used to studyhuman embryo development *in vitro* well beyond the equivalent of 14 days when embryo research currently routinely ends. This could bring important benefits for infertility treatment and regenerative medicine, for example, by revealing mechanisms underlying germ-cell development [11], developmental disorders (e.g. with heart and spine) and recurrent miscarriages [12].

However, more advanced human embryo models also amplify ethical issues by replicating milestones such as the emergence of primitive neural folds, early brain, blood islands, arm buds and early heart-like regions, which may have the potential to further develop into beating heart tissue, circulating blood and neurons. With yet further advances, it will become increasingly difficult to be certain that the models could not reach the point of pain perception, consciousness or viability in supportive conditions. Thus, the public will soon ask, quite rightly, whether SCB-EMs are appropriately regulated? Are scientists using them in ethically responsible, socially acceptable and suitably accountable ways?

Table 1

The ISSCR Guidelines 2021: principles specific to SCB-E/Ms (REFS).

CATEGORY 1A **Permissible and exempt from specialised oversight (ordinary laboratory/institutional research ethics oversight only)**	CATEGORY 1B **Permissible but reportable to specialised oversight body (ordinary laboratory/institutional research ethics oversight)**	CATEGORY 2 **Permissible but subject to comprehensive review by specialised oversight body (ordinary laboratory/institutional research ethics oversight)**
• Most in vitro human pluripotent stem cell (hPSC) research, including stem cell culture systems modelling *specific* stages of development or *specific* anatomic structures not covered in Categories 1B and 2. • Reprogramming human somatic cells to pluripotency	• Research on non-integrated SCB-EMs not intended to represent the entire embryo	• Research on integrated SCB-EMs representing the entire embryo • Most research on fertilised human embryos and totipotent cells • Generating human totipotent cells

International regulatory approaches to SCB-EMs

SCB-EMs sit at the interface between stem cell and embryo research regulation. To a large extent, stem cell and embryo research is governed by national or state/province laws, which vary, but there is nevertheless some considerable policy influence from legal frameworks in other countries and international scientific guidance. The International Society for Stem Cell Research Guidelines (ISSCR), updated in 2021, are particularly relevant [13] (Table 1). Whilst national laws take priority over the guidelines, the latter are more readily accessible, more permissive in some respects and less ambiguous in their reference to SCB-EMs. This has prompted calls for national policy reviews by governments and researchers [14].

A publication reviewing 11 countries identified multiple ways in which national laws vary from each other and the ISSCR Guidelines [14]. Variations include (1) the definition of an embryo and the principles upon which this definition is based; (2) the limits on research embryo culture (e.g. the 14-day rule); (3) systems for overseeing embryo research; (4) prohibitions on creating embryos purposefully for research; (5) systems for overseeing human stem cell research; (6) whether hESC regulations govern derivation, use or both; (7) different penalties for non-compliance; (8) types of regulatory instrument (e.g. legislation, professional guideline, ministry guideline and research-funding rules); (9) scope of regulatory coverage (e.g. in the US, the research-funding rules apply to federal public sector research funds only); (10) frequency of regulatory review.

As it stands, the ISSCR Guidelines are far from a global consensus statement on the principles that currently govern, should govern or will govern SCB-EMs [14]. Such a consensus may be challenging as the degree of difference in national policies on embryo and stem cell research is likely to endure and reflect different social, cultural and political histories. However, by setting out a policy system, the guidelines are well-placed to catalyse national dialogues between scientists, regulators, experts and the public.

A key issue is the role of the widely adopted 14-day rule for human embryo cultures (Box 1), which has been the cornerstone for more than 30 years of relatively stable governance of embryo research. The ISSCR Guidelines notably suggest that, *if* broad support develops in a country following in-depth public engagement, and if local policies and regulations permit, the 14-day rule could be relaxed if there is a strong scientific justification. Scientifically, this could enable better validation of the extent to which SCB-EMs precisely model a natural embryo beyond morphological and molecular signatures [13,15].

However, an ill-considered move away from the 14-day rule could result in increased opposition to scientists' research. Historical and political lessons need to be heeded to avoid fracturing the public's current acceptance of embryo research. Dame Mary Warnock's work provides several salutary lessons [18]. First, some regulations guiding embryo research are preferable to none. Avoiding 'none' was Warnock's main, and in some ways one could even say 'sole', objective [19,20]. Another lesson is that it is morally responsible to make difficult decisions about difficult topics rather than shirking them. Third, it is preferable that decisions are reached in a transparent and collaborative way with broad dialogue involving scientists, clinicians, patients, bioethicists, sociologists, legal experts and other stakeholders. Fourth, there will never be an all-encompassing agreement on the moral status of the human embryo, or its definition. Nevertheless, a definition of what is regulated (whether this is called an embryo, a 'regulated embryo' or something else) is possible. Fifth, rules must be practical, if they are to be implemented and enforced. Sixth, a degree of arbitrariness is inevitable, that is the nature of line-drawing [19,20]. However, the arbitrariness can be buttressed by supporting arguments, for example, that the limits are practical to implement and the result of a deliberative public process.

The ISSCR Guidelines are careful not to presume that their recommendations are compatible with existing national frameworks or that they can be implemented immediately. But they serve at least three purposes. (i) Comparison: The issues they identify are a starting point against which nations can compare their current frameworks and consider future regulatory reform. (ii) Policy content: The suggested framework could be adopted to replace or supplement national regulatory systems following public dialogue with experts, regulators, the public and other stakeholders. (iii) Consensus-building: They also represent an important avenue for consensus-building within and beyond the scientific community.

Improving national governance for SCB-EMs: the United Kingdom and Australia as examples

The United Kingdom and Australia offer good examples of the challenges posed for regulation of SCB-EMs. They have some of the oldest and most comprehensive regulatory regimes for embryo research in the world.

In Australia, the legislation governing embryo research passed in 2002 has a broad definition of embryo (see Research Involving Human Embryos Act 2002 s.7). Many SCB-EMs fall within the definition because they are a 'discrete entity' with 'organised development' and 'a human nuclear genome' that 'has the potential to develop [at least] up to the stage at which the primitive streak appears'. As a result,

Box 1 The 14-day rule

The development of *in vitro* fertilisation in the 1970s challenged traditional conservative norms in the United Kingdom and internationally, with changes in fertility research becoming of increasing public and political concern. Responses in the United States ('Report on Embryo Research' for the Ethics Advisory Board to the Department of Health, Education and Welfare [16]) and United Kingdom ('Warnock Committee of Inquiry into Human Fertilisation and Embryology' [17]) initiated debates that led to the 14-day rule on embryo research, a rare case of an internationally adopted scientific standard that has remained in place for nearly three decades [18].

The 14-day rule was established after extensive public and parliamentary consultation following a debate that lasted, in effect, from 1978 to 1990. During the six years preceding the original recommendation by the Warnock Committee to make the 14-day rule the centrepiece of proposed legislation governing embryo research, members of the medical and scientific community played a key role facilitating public dialogue that eventually led to widespread agreement on the regulatory framework that became the 'Human Fertilisation and Embryology Act' [19,20]. The United Kingdom is a global leader in combining 'overlapping public consensus' with such a comprehensive regulatory structure governing both research and treatment in the field of 'human fertilisation and embryology'. The 'Warnock Consensus', as it has been termed [18], became the default global standard in no small part due to the absence of similar schemes outside of Britain [21]. Altering this consensus has rightly been viewed, including by Mary Warnock herself, as an option that should only be pursued with considerable caution, including the risk that it might prove very difficult to deliver a similarly comprehensive and robust alternative [19,20].

Since its adoption, the 14-day rule was not revisited until 2016, when it became possible to culture embryos *in vitro* past nine days post fertilisation [22]. In 2017, one of the first reviews of international embryo law delivered by the Nuffield Council of Bioethics, reassessed the rules' impact on emerging technologies [23]. In 2018, the ISCCR suggested that an increase from 14 to 28 days should be considered in light of research advances in embryo development [24]. In the 2021 revised guidelines, no upper limit is suggested [12]. However, public dialogue on the scientific utility as well as the societal, moral, ethical and policy issues are recommended before embryo research is permitted for any duration longer than 14 days [12,25]. Without this public dialogue, there is concern that 'what could be done' scientifically is not 'what should be done'.

SCB-EM research in Australia is challenging because it is largely as limited as research with fertilised embryos.

In contrast, the United Kingdom has a different definition of embryo, and the challenge is that it remains unclear whether SCB-EMs fall under the embryo research governance framework. To take this forward, a national policy review, catalysed by the ISSCR Guidelines, could be useful particularly considering the UK's historic role in establishing national embryo governance. The United Kingdom could consider whether it has, or should establish, the specialised oversight processes the ISSCR recommends for integrated SCB-EMs (para 2.2.2), and the reporting frameworks for non-integrated SCB-EMs (para 2.2.1) [12]. It could also take up the suggestion (para 2.2.2.1) for a national public conversation on whether to relax the 14-day rule [12].

The definition of 'embryo' in the Human Fertilisation and Embryology Act 1990 (Box 2) is imprecise; some say even circular: regulated embryos include 'live human embryos' (section 1). Presently, there are clear scientific differences between SCB-EMs and embryos produced by fertilisation. However, the differences are decreasing. Furthermore, a SCB-EM need not be *identical* to a *viable fertilised* embryo to fall within the regulated definition. Regulated embryos are not limited to the 'permitted embryos' used in fertility treatment (created through fertilisation of permitted gametes) but include embryo-like entities created through cell nuclear transfer, low-grade unviable human embryos and admixed embryos that include a mixture of animal and human genetic material.

If SCB-EMs fall within the UK's legal definition of 'embryo', or advance to this point, it is highly relevant that its legislative framework requires research involving regulated embryos to be licensed by the Human Fertilisation and Embryology Authority (HFEA), and researchers must retain records as directed by the HFEA

Box 2 Is a SCB-EM a human embryo?

Intriguingly, despite its importance to the continuation of our species, there is no agreed definition of a human embryo nor any agreement about the moral status or rights owed to one. Views differ within academic disciplines, across religious and ethical philosophies and even between authors with similar backgrounds. Nevertheless, legal systems can stipulate what is regulated (whether this is called an embryo, a 'regulated embryo' or something else).

Fabbri et al. summarise the legal definitions of human embryo in 11 countries based on comparative legal research [14]. They draw attention to three factors that permeate the legal definitions: the potential of 'human embryos', the method of creation and the developmental stage [14]. A fourth factor in some jurisdictions is the intention of Parliament (or the body drafting the definition): reading the definition in context, what did the legal decision-maker intend to regulate with the word 'embryo' and why (e.g. what traits and issues were at stake)?

UK legislation defines an 'embryo' as a 'live human embryo' (s.1 of the Human Fertilisation and Embryology Act 1990). It is odd for a definition to contain the word it is intended to define, so an authoritative decision of the House of Lords in 2003 (then the highest court in the UK) held that the word 'embryo' should be given its ordinary language meaning, and that the words 'live' and 'human' specify which *types* of embryo are covered by legislation (i.e. animal and dead embryos are not subject to regulation).

In *R (Quintavalle) v Secretary of State for Health* [26], the House of Lords held — in line with standard principles of statutory interpretation — that regard could also be had to *Parliament's intention*. In deciding that embryos created by cell nuclear replacement were subject to regulation, the House of Lords was clear that 'Parliament intended the protective regulatory system in connection with human embryos to be comprehensive', and there 'was to be no free for all'. Would the same reasoning apply to SCB-EMs? Skin cells can be manipulated to create an embryo using cell nuclear replacement, but skin cells are plainly not 'embryos'. One approach would be to ask whether the *traits* that SCB-EMs *share* with *regulated embryos* put them in the category that Parliament intended to subject to strict and comprehensive control? Relatedly one can ask whether their *differences* from regulated embryos are such that Parliament intended they should fall outside the statutory regime? A similar approach has been recommended for research ethics committees [27].

Some commentators argue that SCB-EMs differ substantially from fertilised embryos because if implanted in a woman, only the latter can create healthy foetuses and babies. However, when assessing similarities and differences, it is relevant to recall that the comparison group (regulated embryos) includes embryo-like entities other than robust fertilised embryos. SCB-EMs might differ from *fertilised* embryos *but* be very similar to other regulated embryos. Regulated embryos also include embryo-like entities created by cell nuclear replacement, embryo-like entities created by any other technological process, embryo-like entities incorporating animal genetic material and other embryo-like entities with low durability that are destined to be destroyed or to die in a few days. Simply because an embryo-like entity has poor integration and might not last more than a few days in culture does not mean the definition of embryo disapplies (many embryos created by *in vitro* fertilisation fall in this category).

If asked whether SCB-EMs are 'embryos', the UK courts might conclude, following the House of Lords' precedent, that *at least some* integrated and non-integrated SCB-EMs fall within the ordinary language meaning of 'embryo'. They are entities with a human genome, organised progressive development, to which the public might attribute 'special respect' and human dignity. On the other hand, the courts could conceivably reach the opposite conclusion, concluding that SCB-EMs do not fall within the ordinary language meaning of embryos, and are merely laboratory tools for simulation. The addition of the regulation-making power in section 1(6) in 2008 might lend further weight to this conclusion. It allows the Secretary of State to extend the definition of embryo in the light of developments in science or medicine.

Given this complexity, we recommend the formation of a specialist committee consisting of diverse stakeholders to evaluate not only potential, molecular and morphological criteria, but also public opinion, and the risks and benefits of deeming SCB-EMs as regulated embryos, or not. Because hundreds of SCB-EMs may be formed at any one time, it will be important to consider methods for tracking and reporting given that currently the regulations require reporting on the use of each individual embryo.

for audit and scrutiny, be inspected by the HFEA, cease using or storing any embryo past 14 days or the appearance of the primitive streak, prove that research involving embryos is necessary, and that it is necessary or desirable for at least one of the research objectives set out in the Act and abide by the conditions of written consent given by the donors of primary tissue or gametes. The framework also prohibits scientists placing a human embryo used in research in a woman or animal. Failure to comply with these rules could potentially give rise to criminal proceedings and research licence suspension, revocation or refusal, with major impacts for a scientist's career.

Notably, however, the research rules within the HFEA Act were not designed with knowledge of SCB-EMs and do not fit neatly. There are distinct challenges when applying the 14-day rule to SCB-EMs, which develop at a different rate than fertilised embryo systems, particularly where a legal endpoint is based on a period of time (e.g. the HFEA Act states 14 days after 'the process of the creating the embryo began' rather than morphological features). Current HFEA licensing practices also require thorough reporting on every embryo used in research, including their 'ethical destruction', this is highly impractical for SCB-EMs that can be produced in batches of well over 100 individual entities.

Conversely, if SCB-EMs are *not* covered by the UK's statutory definition of embryo, very little legal regulation would govern their current use in research. The UK's Human Tissue Act 2004 does not apply: it governs primary cell cultures but not the storage or use of cell lines, cells that have divided in culture or ESCs [28,29]. Apart from being required to observe the limits of donors' consent [29] during the cell line production, none of the embryo research rules mentioned in the previous paragraph would be legally required of embryologists, nor would research with SCB-EMs need to undergo ethical review under the Human Tissue Act 2004 or NHS research governance systems [29,30]. Currently, for SCB-EMs that fall outside the HFEA's definition of an 'embryo', there are no legal instruments in place requiring the scientist to undergo ethical review (subject to the rules of their employer), that prevent the development of SCB-EMs for as long as technically possible (i.e. beyond the 14-day rule), that regulate the introduction of any degree of genetic manipulation or that inhibit the implantation of SCB-EMs into an animal or human host. It is doubtful that such a laissez-faire approach matches the public's expectations for increasingly sophisticated embryo models. This is problematic for scientists as well as the public; most stem cell scientists prefer to know and abide by boundaries that identify socially acceptable and unacceptable research [31].

Passing legislation to clarify and update the UK's framework is likely to be a sensible long-term goal but it is challenging and time-consuming. For the foreseeable future, the legal situation in the United Kingdom will remain unclear. In the interim, there are good reasons for the research community and relevant stakeholders to foster and adopt voluntary guidelines. 'Soft law' in the form of quasi-legal self-regulation lacks full binding force but would nevertheless influence behaviour and build trust with the public. Such a code of conduct could conceivably be implemented by a respected scientific institute, learned society or research funder with the establishment and support of a relevant overseeing committee and unilateral agreement from relevant stakeholders. The principles and processes within the ISSCR Guidelines serve as a helpful starting point for a code of conduct.

The United Kingdom has experience with processes of pragmatic public deliberation leading initially to interim self-regulation and eventually to legislation and more formal regulation. The work led by the Warnock committee is a classic example (Box 1). It recognised that for embryo research to be acceptable, it must occur within defined limits that are clearly comprehensible to the lay person [19]. Underestimating the strength of public sensitivity about human embryos is perilous, as shown by legal shifts in US abortion law [32] and knock-on effects for *in vitro* fertilisation and embryo research. One issue to consider carefully is whether interim self-regulation should propose a 14- or 28-day limit on the storage and use SCB-EMs, or something roughly equivalent based on readily visible morphological features (e.g. upper limb and somite development [15]).

It is impossible to inform and involve all members of the public (or even representatives of all constituent groups) and with such diverse ethical views, full consensus is a far-fetched objective. A more achievable goal is a process that identifies viewpoints and ideas across society, resulting in a framework that is justified not for being ethically 'right' but for being a reasonable response in the face of enduring ethical disagreement [33,34]. The goal could be described as an 'overlapping consensus' [34] or 'accountability for reasonableness' [35]. A 'social contract' is another way to understand the dynamic: the public permits cutting-edge ethically controversial research in return for careful and transparent articulation of risks and benefits, and a regulatory response that includes checks, balances and transparency.

Conclusion

SCB-EMs provide promising avenues of research and treatment for developmental biology, regenerative medicine, drug discovery, and reproductive health. However, nations need to review their legal frameworks and consider whether greater clarity and policy development is required. If science outstrips regulation, it could trigger considerable public concern with serious implications for continued research.

In the United Kingdom, national reflection and comparison with the ISSCR Guidelines would be highly valuable because currently the applicable legal framework is unclear and unsuitable. A process of reflection and deliberation could lead to an interim code of conduct, addressing practical and ethical concerns. It would avoid a situation where SCB-EMs are, in essence, unregulated. In time, the Code could be the basis for more formal regulation. Meanwhile, it would be a positive for the public to see scientists voluntarily and pro-actively taking this step in collaboration with members of the public, clinicians, patients, bioethicists, sociologists, legal experts and other stakeholders. It is likely to increase trust in research from stakeholders, including the public, government and funders, and set the best future basis for realising the benefits of stem cell-based embryo models.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare no conflict of interest.

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