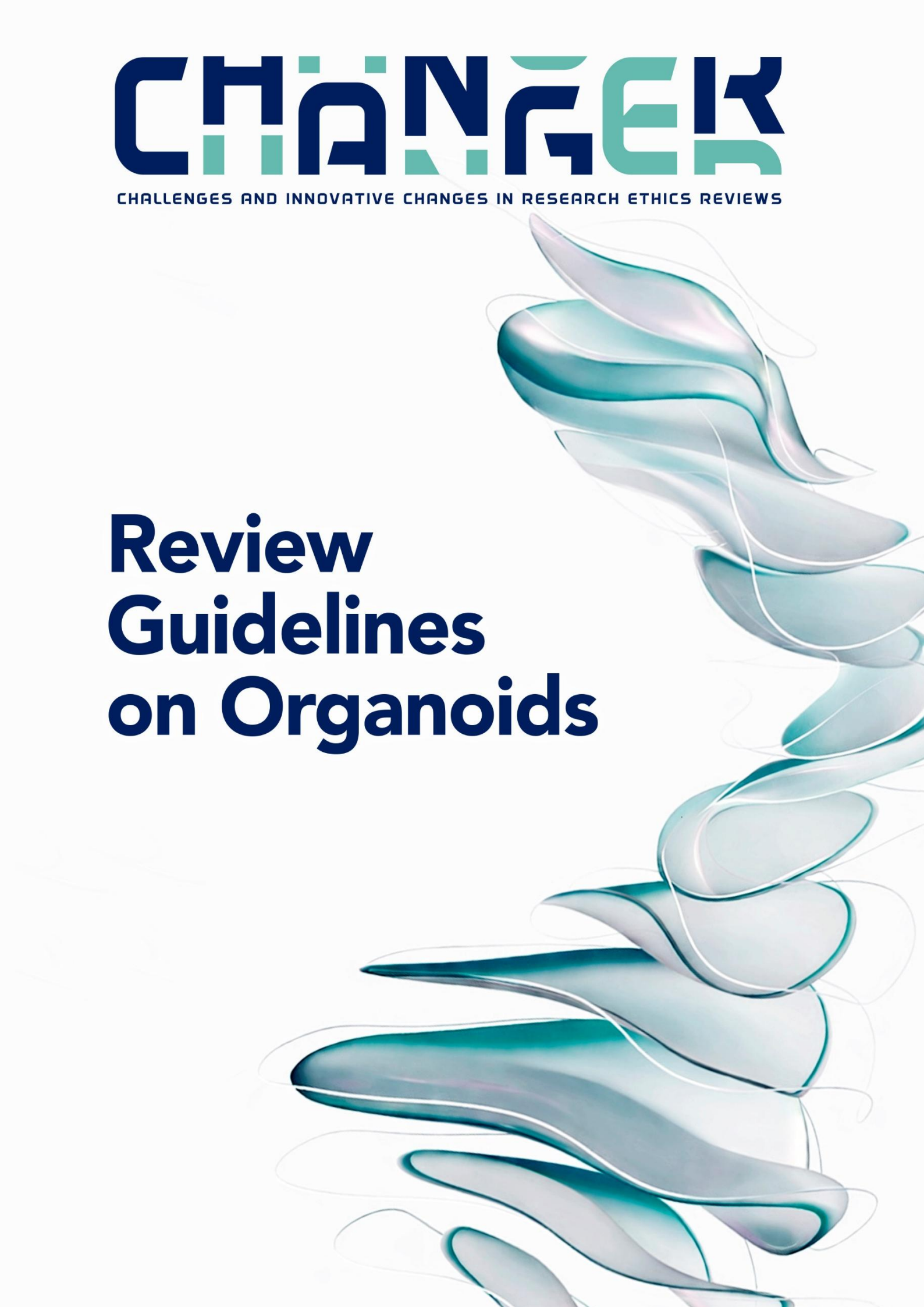
CHANGER

CHALLENGES AND INNOVATIVE CHANGES IN RESEARCH ETHICS REVIEWS

Review Guidelines on Organoids



Document Revision History *(including peer reviewing & quality control)*

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1. Introduction

Research Ethics Committees (RECs), ethics experts, and policy stakeholders play a crucial role in guiding the responsible development and application of organoids. Since these committees are tasked with evaluating research proposals, they have a unique responsibility to ensure studies meet all ethical standards, protect donors' rights, and effectively minimize potential harm. As use of organoids in research increases, the oversight of RECs becomes even more essential, especially in ensuring that the creation of brain organoids and embryo models does not outpace the ethical frameworks needed to guide it.

2. Organoids

Before discussing the ethical issues and guidelines associated with the various types and uses of organoids, it is important to establish the fundamental and contextual details of the different types and sources of organoids. The following sections will provide a scientific background to organoid research, as well as a detailed explanation of organoid technology.

2.1 Scientific background of organoids

Stem cells are early-stage, undifferentiated cells, meaning they have not yet become specialized for a specific tissue or organ. They have two key abilities: self-renewal, which means they can make copies of themselves, and multidirectional differentiation. In normal human development, cells progress from an undifferentiated pluripotent state, meaning they can give rise to almost any cell type in the body, to differentiated and specialized states, such as skin cells, blood cells, neurons, or liver cells. For many years, this process was considered irreversible. However, differentiated adult cells were shown to be reprogrammable back into an undifferentiated pluripotent state through the introduction of four specific genes, now commonly referred to as the Yamanaka factors. These reprogrammed cells, known as induced pluripotent stem cells (iPSCs), behave similarly to embryonic stem cells: they can self-renew indefinitely and differentiate into almost any cell type in the body, which is a major breakthrough in biology. Importantly, iPSCs enabled the generation of pluripotent stem cells without requiring the destruction of human embryos, using adult cells instead (1).

Researchers subsequently began using pluripotent stem cells to generate three-dimensional (3D) self-organizing cellular structures, now known as organoids, by guiding their differentiation *in vitro* (2–4). Organoids are 3D stem cell-derived structures that closely replicate key structural and functional features of real tissues on a miniature scale (5). Their generation relies on advanced cell engineering and tissue culture techniques involving *in vitro* cell cultivation, proliferation, differentiation, self-organization, and maturation. In the laboratory, scientists grow organoids by providing stem cells with supportive scaffolds and signaling cues that enable them to self-assemble into tissue constructs containing many of the same cell types and interactions found in vivo (6). Unlike traditional two-dimensional cell cultures, organoids maintain more complex tissue architecture and specialized cellular functions (7). Organoids have since been developed to model a wide range of tissues and organs, including the intestine, retina, brain, liver, kidney, stomach, and pancreas (6–8),

transforming the study of human development, disease mechanisms, drug testing, and potential therapeutic approaches (5,8,9).

2.2 Types of stem cells

Organoids can be generated from three main stem cell sources: embryonic stem cells (ESCs), iPSCs, and adult stem cells (ASCs). ESCs originate from the part of an early-stage embryo that would eventually develop into the fetus (7). Adult stem cells are found in fast-renewing tissues such as the intestine, can self-renew and produce specialized cells of their tissue. However, organoids made from adult stem cells contain only epithelial cells, so they capture only a limited number of interactions that occur in the intestinal system. In contrast, pluripotent stem cells, including ESCs and iPSCs, can give rise to all cell types from the three main embryonic layers. Therefore, organoids derived from pluripotent stem cells can include multiple tissue types, allowing more complex intercellular interactions (6).

The formation of organoids *in vitro* mirrors how organs acquire structure during development, heavily relying on self-organization. Successful organoid cultivation requires a 3D culture environment, such as an extracellular matrix or an air-liquid interface, appropriate induction of regional identity through regulation of developmental signaling pathways, and culture media tailored to the nutrient needs of each organoid type. Organoids can also be generated from tumor cells using dissociated patient samples combined with specific signaling factors. This specific type of organoid is called a tumoroid (7).

2.3 Clinical utility of organoids

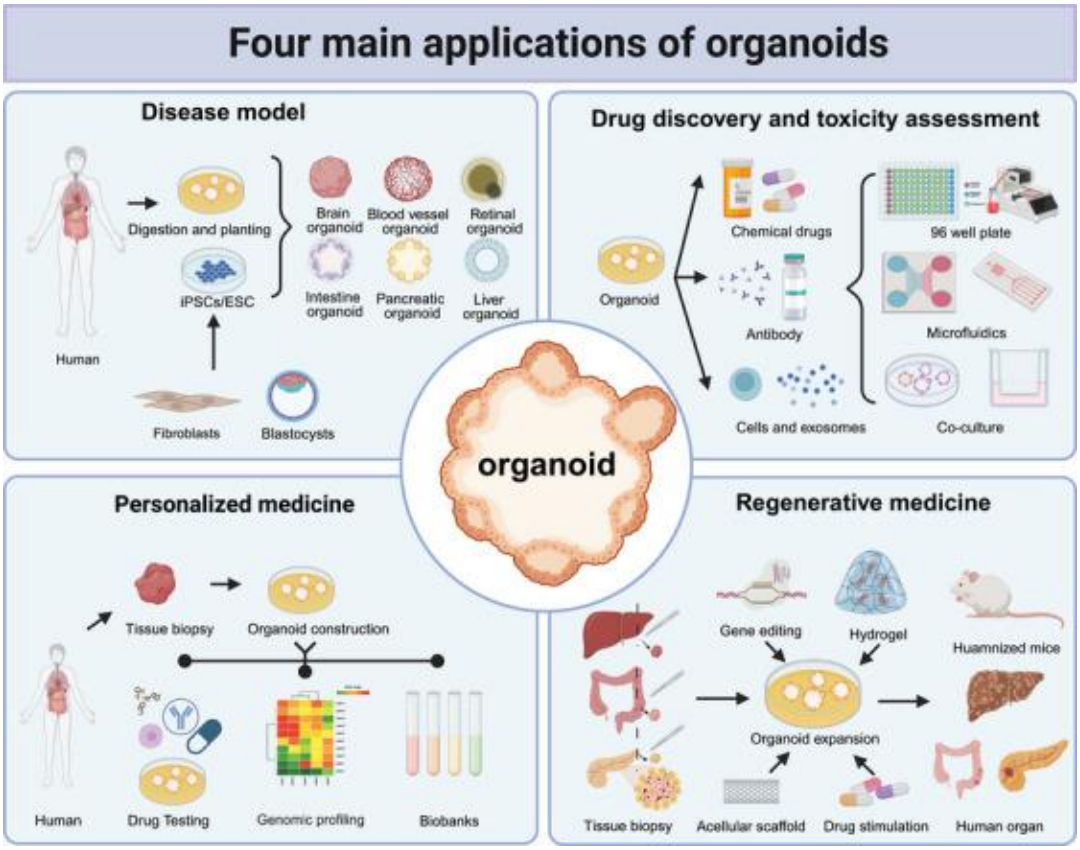


Figure 1. Organoids applications. Reproduced from Yao et al. (10) *under the terms of the Creative Commons Attribution License (CC BY).*

Currently, organoids are used in various contexts (**Figure 1**). Organoids may provide an alternative to many animal models, which are limited by interspecies differences, ethical concerns, and high costs, as well as to conventional cell lines, which may have altered genetics and pose a risk of contamination. Unlike flat, two-dimensional cell cultures, organoids grow in three dimensions, allowing cell-cell and cell-matrix interactions that more closely mimic real tissue. Organoids are also valuable for drug discovery and assessing drug efficacy, as they exhibit more organ-specific functions and genetic characteristics than conventional cell lines and can sometimes be more time-efficient than animal models. In personalized medicine, organoids can be derived directly from a patient's own cells and therefore retain the patient's unique genetic makeup. This allows clinicians to test different drugs on a patient's organoid before administering a treatment, helping to predict which therapy may be most effective for that individual. In regenerative medicine, organoids may also offer new therapeutic possibilities. For diseases causing irreversible organ failure, organ transplantation remains the most effective treatment, but donor shortages and side effects linked to immunosuppressive therapies lead to thousands of deaths each year. Because organoids can integrate, mature, and vascularize, they may one day contribute to the generation of functional tissues or organs for transplantation (10). Different organoids can also be combined to create assembloids, which are used to model more complex biological structures and interactions between

tissues or organ systems. For example, combining retinal, thalamic, and cortical organoids enables researchers to study aspects of the visual pathway (11).

Despite their many advantages, organoids also have important limitations. They often do not contain all cell types of real organs, such as blood vessels, immune cells, or nerve cells. Hence, it can be difficult for organoids to fully mimic adult tissue function or to accurately model diseases, especially when the organoids are made from diseased tissues (6). Additionally, organoids derived from pluripotent stem cells, such as ESCs and iPSCs, often display characteristics more similar to fetal than mature adult tissue. This occurs because they do not mature enough or receive enough nutrients and oxygen while growing. Generating patient-specific organoids for personalized medicine remains costly and resource-intensive. Moreover, organoid culture is technically difficult and currently limited to specialized laboratories. Results can vary a lot between laboratories because they use different experimental conditions, such as growth factors, culture media, and cell sources (7).

To overcome these challenges, researchers are combining stem cell research with biomaterials and bioengineering to better recreate the diversity and structure of human tissue. One strategy is adding specific signals that encourage the development of certain cell types. Scientists are also creating new scaffolds that mimic the epithelial microenvironment of real tissues. Microfluidic devices (often called “organ-on-a-chip” systems) can provide controlled fluid flow, similar to what happens inside the body, which helps organoids mature and stay alive longer. In addition, assembloids (fused organoids) help address some of these limitations by enabling more complex cellular interactions. Gene editing is also being used to improve organoid models and advance regenerative medicine and personalized treatments (6).

2.4 Ethical implications of organoids

The ethical landscape of organoid research is shaped by the rapid expansion of technology across both research and clinical settings. Rather than a single overriding concern, it presents a cluster of interconnected challenges – spanning misapplied nomenclature, informed consent, commercialization, access, and the emerging ethics of clinical application - none of which can be addressed in isolation.

2.4.1 The nomenclature issue

A first overarching issue is the one of nomenclature. What is the correct terminology for organoids? This is relevant since how we name things can influence how they are perceived and accepted. The term “organoid” itself can be misleading, as many organoids do not recapitulate whole organs but rather specific tissues, regions, or aspects of organ function. Hence, this terminology can create unrealistic expectations among the general public, patients, policymakers, and other stakeholders regarding their level of complexity and their clinical potential. Even more problematic is the use of the term “mini-organ” to describe organoids. Organoids lack the full complexity, vascularization, innervation, and systemic integration of real organs (12). The term “mini-organ” is therefore scientifically inaccurate. It creates unrealistic expectations among patients, funders, and the public, implying that fully functional replacement organs are imminent when in fact organoid technology remains largely at the research stage. Similarly, terms such as “mini-brains” or “artificial embryos”

might mislead people into attributing higher moral status to organoids than warranted as organoids might be assimilated to actual “brain” and “embryos”. Accurate nomenclature – for example, ”cortical organoid,” “intestinal organoid,” or “tumor organoid” – is therefore an ethical obligation, not merely a stylistic preference. It is also an epistemic obligation, as accurate terminology promotes scientific transparency and helps stakeholders make informed judgments about the capabilities and limitations of organoid research. Misleading terminology may undermine informed decision-making by donors, patients, research participants, funders, and members of the public. RECs should flag and require correction of any misleading terminology in proposals, consent materials, and dissemination outputs (12).

2.4.2 Informed consent

Informed consent in organoid research is structurally more complex than in conventional biomedical research. Because organoids can be expanded indefinitely, shared between laboratories, and repurposed for uses that did not exist at the time of donation, it is hard for researchers to anticipate - or for donors to consent to - all the uses a biological sample may eventually serve. This creates a specific issue for biobanks and collections that obtained consent years before organoid technology existed (14). Moreover, questions arise regarding how to handle the use of (historical) collections of residual samples in this regard.

Several consent models have been proposed to navigate this tension. Traditional signed informed consent offers transparency and strong donor protection, but it makes sample reuse difficult and creates obstacles for longitudinal research. Dynamic informed consent, which uses digital platforms to maintain an ongoing relationship between donors and researchers has often been proposed as an approach that allows donors to update their preferences as research evolves, but it requires significant logistical infrastructure and depends on donors remaining contactable and engaged over time. The two-step consent model, explored within the CHANGER project, offers a structured alternative: an initial consent from the donor covers the collection and creation of induced pluripotent stem cells, while a second step delegates further decisions to a competent ethics committee, guided by the donor's pre-stated values and constraints (15). Each model involves trade-offs between donor autonomy, research flexibility, and practical feasibility, and no single approach is universally appropriate. The choice of consent model should be proportionate to the sensitivity of the organoid type involved and clearly justified in any proposal submitted for ethical review. Factors that may increase sensitivity include the potential to reveal information about a donor's identity, health status, cognitive traits, or genetic predispositions, as well as the complexity and intended use of the organoid.

Transparency regarding future uses of donated tissue, potential findings, and possible commercial applications of organoids derived from donor cells is an important consideration. Donors are entitled to this information. Yet the involvement of multiple stakeholders – including researchers, clinicians, companies, and institutions – makes it structurally difficult to design consent procedures that simultaneously ensure transparency, protect donor interests, and preserve the flexibility required for unforeseen future research uses, incidental findings, and potential commercial applications involving organoids derived from donor cells (14).

Full anonymization (irreversibly removing all identifiers) is legally permitted in some jurisdictions, but it does not resolve any of the ethical challenges outlined here. Modern genomic methods make reidentification increasingly feasible, particularly in rare diseases where organoids carry unique mutations. Stripping identifiers also prevents researchers from returning clinically relevant findings to donors and eliminates meaningful donor control over future use. Moreover, under the EU General Data Protection Regulation (GDPR), pseudonymization (replacing direct identifiers with a code, while keeping the key separately and securely) is the preferred standard for scientific research. Pseudonymization allows donors to be re-contacted, consent to be withdrawn, and clinically significant results to be returned. Many donors feel a personal connection to their organoids as they carry their DNA - and this attachment is especially pronounced for brain organoids, where donors may have concerns about what the organoid could reveal about their cognition, identity, or predispositions (14). This reflects broader developments in research ethics that increasingly recognize participants as contributors to, and in some contexts co-creators of, the research process rather than merely as research subjects.

Several consent models have been proposed in response: broad consent, tiered consent, dynamic consent, and governance-based consent. These differ in how much ongoing control donors retain and how frequently they must be re-contacted. The HYBRIDA consortium - a European Union-funded project with the main goal to develop a comprehensive ethical and regulatory framework for organoid research to help ensure that science progresses responsibly - identified informed consent and responsible governance as the two issues most consistently raised by the public, researchers, and clinicians. HYBRIDA proposes a specific solution: the TRUSTED framework (Donor's Tissue Research Under Secure Transparent Ethical Donation), which requires donors to complete a structured questionnaire at the time of donation, explicitly authorizing or prohibiting specific future uses of their tissue and data. This is implemented as part of a three-part consent document: a written information letter, the TRUSTED questionnaire, and a signed consent form. Where re-contacting donors is not feasible, HYBRIDA recommends a governance-based model in which an independent third party represents donor interests and ensures that TRUSTED conditions are honored. HYBRIDA recommends that RECs should verify that the TRUSTED questionnaire has been completed and that any donor-imposed restrictions are technically feasible to comply with (14).

As organoids become scientifically and commercially valuable, questions of profit, ownership, and fairness become unavoidable. Companies may patent organoid-based methods, develop commercial products, or use donor tissue to generate revenue - often without any direct benefit returning to donors. While commercial involvement can accelerate innovation and broaden access to new therapies, it creates a tension between economic interests and donor rights that existing consent frameworks do not adequately resolve (14). We endorse the HYBRIDA's conclusions that benefits to donors, where they exist, are generally recommended to be non-monetary - such as access to research results, early access to therapies developed from the research, or reinvestment of revenues into publicly beneficial science. RECs should ensure that any commercial dimension of a proposal is clearly disclosed in consent documentation and that donors have been informed of potential commercial use (16).

2.4.3 Ethical concerns in clinical settings

In clinical settings, two ethical concerns are particularly prominent. The first concerns personalized medicine: organoid production in the context of personalized medicine is time-consuming and expensive, requiring an individualized, labor-intensive process that is difficult to scale. Each patient sample requires its own culture protocol, specialized, costly reagents (such as growth factors and extracellular matrix components), and weeks of careful monitoring by skilled personnel. Moreover, not all biopsies yield organoids, resulting in wasted time and resources. The lack of standardized protocols across laboratories further contributes to variability, and each organoid line must undergo rigorous quality control to confirm that it accurately represents the patient's disease, raising concerns about equitable access (5). There are also legitimate questions about predictive accuracy - organoids cannot fully replicate the complexity of the human body, and clinicians must exercise careful judgment about how much weight to place on organoid-based evidence. This highlights the importance of communicating both the capabilities and limitations of organoid models accurately and transparently, out of respect for the autonomy and dignity of patients and other stakeholders. Standardization - including reproducibility across laboratories and good manufacturing practice compliance will be essential before organoid-based personalized medicine can be offered equitably and responsibly at scale (14).

The second concern involves transplantation. Organoids derived from a patient's own cells - potentially combined with gene editing to correct genetic mutations - may one day offer a less invasive alternative to donor organ transplantation. However, the ethical challenges are significant: the risks of tumorigenicity or uncontrolled growth from stem cell-derived material, the invasiveness of transplantation procedures, and the broader societal implications - including changes in how patients experience illness and recovery - require careful and ongoing ethical scrutiny (17). Researchers and clinicians must resist hype, communicate clinical timelines realistically, and document all outcomes, including negative results, in line with FAIR principles, meaning that data should be Findable, Accessible, Interoperable, and Reusable, as clinical applications of organoids are still in the early stages of research (14).

Across both research and clinical contexts, equity is a cross-cutting concern. Organoid technology must not add to existing healthcare inequalities. Where donor contributions are essential to science, the benefits of research, whether in the form of knowledge, therapies, or commercial gains, should not flow exclusively to well-resourced institutions or high-income populations (14). RECs play an important role in surfacing these concerns during proposal review.

2.5 The regulatory framework around organoids

The legal landscape must be prefaced by a clear distinction between hard law and soft law, and their relevance in the context of organoids' ethics. Hard law refers to legal obligations that are binding and enforceable in court. In contrast, soft law refers to non-binding instruments such as guidelines, position statements, and recommendations, often developed by ethics committees and professional societies; these provide flexible guidance rather than enforceable rules. Organoids research risks falling into regulatory gaps where practical, moral, or legal issues are not satisfactorily addressed by existing legislation or legally binding definitions. At the same time, technology is also vulnerable to

over-regulation, particularly where uncertainty about which laws apply leads to conflicting legal requirements or disproportionate restrictions that impede legitimate research, and therefore, soft laws play a significant role in aiding research.

Several existing hard law instruments are relevant to organoid research, such as the EU Tissues and Cells Directive (2004/23/EC), which aims to minimize the risk of infection and prevent the transmission of disease during the transplantation of human tissues and cells. It covers the entire chain of activities from donation to procurement, testing, processing, preservation, storage, and distribution. It requires that all tissues and cells used in the EU be traceable from donor to recipient and vice versa, with data kept for a minimum of 30 years after clinical use. For non-clinical organoid research, the directive does not directly apply, but its principles, traceability, donor screening, and quality management are considered good practice. For therapeutic organoids, the directive is fully applicable until it is repealed and replaced by the new SoHO Regulation (EU) 2024/1938 coming into force in 2027. The new regulation aims to establish a more harmonized and future-proof framework across EU Member States, strengthening standards for quality, safety, traceability, and oversight of substances of human origin while accommodating emerging biomedical technologies (17,18).

GDPR (Regulation (EU) 2016/679) governs the processing of personal data, including health and genetic data, which are categorized as “special categories” of personal data that require additional protection as they provide unique information about that person's physiology or health. For organoid research, this means that usually donor consent must be explicit and informed; transparency obligations apply throughout the data lifecycle, and data minimization principles must be observed. However, the processing of genetic and health data may be permitted without consent with legitimate interests as legal ground or with reasons of public interest, subject to suitable and specific safeguards (19).

EU Animal Research Directive (2010/63/EU) regulates the protection of animals used for scientific purposes. The directive sets out legal requirements to implement the 3Rs principles of replacement, reduction, and refinement: replacing animals with non-animal methods where possible, reducing the number of animals used to a minimum while still obtaining scientifically valid results, and refining practices to reduce any possible pain, suffering, distress, or lasting harm to the animals. For organoid research, this means that when organoids are transplanted into live animals, the animal experiment requires a project authorization and must comply with the 3Rs. Conversely, organoids themselves are recognized as a replacement strategy, and the directive encourages their development as alternatives to animal experimentation (20). But at least for now, organoids are considered more complementary to animal research than a full replacement for it.

The Oviedo Convention (Council of Europe, 1997) on Human Rights and Biomedicine is a key international agreement of the Council of Europe that establishes legal rules governing biomedicine. It is designed to protect the dignity and identity of all human beings and to guarantee, without discrimination, everyone's respect for their integrity and other fundamental freedoms in the application of biology and medicine. Specific provisions address informed consent, protection of private life, the human genome, scientific research, and the prohibition of using the human body or

parts thereof for financial gain. For organoid research, this means that organoids derived from human cells cannot be treated as commodities, donors must give free and informed consent, and while organoids are not human embryos, advanced models that recapitulate embryonic development require careful interpretation under the Convention (21).

The International Society for Stem Cell Research (ISSCR) is the world's leading professional organization in stem cell research and regenerative medicine. Its guidelines are highly influential because they are widely used by researchers, institutions, funders, publishers, and ethics committees internationally, especially in areas where legislation remains limited or unclear. In organoid research, the ISSCR Guidelines provide recommendations on ethical oversight, permissible and prohibited research activities, informed consent, and specialised review processes for scientifically and ethically sensitive models. They recommend a proportional oversight approach in which the level of ethical review depends on the scientific complexity, developmental potential, and ethical sensitivity of the model (22).

At the European level, the HYBRIDA project developed operational guidelines specifically intended to support researchers and RECs members in the ethical evaluation of organoid and related research. As presented in **Table 1**, the consortium proposes a practical classification framework to help determine the appropriate level of ethical oversight required for different types of organoid and related research.

Category	Ethical review requirement	Type of organoid
Cat. 1a	General ethical review	"Simple" organoids (kidney, liver, etc.)
Cat. 1b	Specific ethical consideration recommended	"Complex" organoids (neural, sexual reproduction organoids, etc.)
Cat. 2	Specific approval by an ethics committee required	Stem cell-based embryo models, complex neural assembloids, etc.
Cat. 3	Prohibited	Gestating human stem cell-based embryo models, transfer of human-animal chimeric embryos to a human or non-human primate uterus, etc.

Table 1. Ethical categories proposed by the HYBRIDA Consortium. Table adapted from 'Executive summary of HYBRIDA's operational guidelines', page 4.

In addition, HYBRIDA developed several practical tools for ethical and scientific assessment. These include the MIAOU ("Minimum Information About Organoids and Their Use") framework for researchers, the EChOES ("Evaluation Checklist for Organoid Experimental Studies") checklist, and the RICOCheck tool designed for Research Ethics Committees and research integrity bodies to support the review of organoid research protocols. These tools aim to promote transparency, reproducibility, ethics-by-design, and harmonised ethical evaluation practices in organoid and embryo model research (16,23).

2.6 Recommendations to RECs for organoids

- RECs must require correction of any language that refers to organoids as “mini-organs” or similar misleading terms, as this is scientifically inaccurate and constitutes research misconduct. Accurate naming following consensus nomenclature (e.g. “cortical organoid”) is an ethical obligation. RECs should amend proposals or dissemination materials that use hype-inducing or inaccurate terminology.
- Require comprehensive, understandable consent forms from all tissue donors (including embryonic or fetal tissue), clearly disclosing the research purpose, risks, implications, future uses of samples, data sharing, commercialization, and privacy protections, particularly where genetic data may be shared. RECs should ensure that the proposed consent model is appropriate for the type and sensitivity of the organoid research.
- Ensure that proposals explicitly state whether the organoid is for research or clinical application, as the ethical and legal implications differ significantly.
- Confirm that organoid research complies with applicable national and international laws, regulations, and ethical guidelines, including requirements related to data protection, human tissue use, and animal research where applicable.
- Organoids are not a full substitute for animal research, as their findings still require validation against *in vivo* models. Claims of replacement should therefore be made with caution, avoiding hype or overstatement of this potential.
- Ensure that ethical oversight remains proportionate to the complexity, intended use, and societal sensitivity of the organoid type involved, while also considering issues of equity and fair access to future clinical applications.

3. Brain organoids

Brain organoids are 3D brain-like structures grown from ESCs or iPSCs, which self-organize into early neural tissues (4). They can form cortical layers, synaptic networks, and coordinate electrical activity, including simple versions of early brain structures and nerve cell communication. Unlike other organoids, such as intestinal or liver organoids, which model structural or metabolic functions, brain organoids uniquely reproduce aspects of human neurodevelopment, including region-specific organization and spontaneous neuronal firing. They can even develop small, recognizable brain region “zones,” such as early cortex or retina-like patches, all within the same tiny organoid. This makes them powerful tools for studying early brain development and the conditions that affect it. For example, organoids have been used to model microcephaly, Zika-virus-induced cortical defects, and autism-related changes (4,24,25).

3.1 Ethical implications of brain organoids

Some cerebral organoids have already shown Electroencephalogram-like oscillations resembling those of preterm infants (26). Their increasing complexity raises concerns that they might one day develop sentience, meaning they could potentially feel basic forms of discomfort or have simple

experiences (27). As their neural networks mature, they may even acquire capabilities "similar to human sentience," setting them apart from many other organoid systems and making them a major focus of current ethical debates (24).

3.1.1 Considerations on the moral status of brain organoids

The moral status of brain organoids is debated because they can exhibit developed neural features such as network activity, oscillations, and the emergence of organized brain regions, raising the possibility of primitive forms of consciousness or subjective experience. Moral status refers to the degree to which an entity deserves ethical consideration, protection, or rights based on its potential to be harmed or to have interests. Some scholars have argued that future advances in brain organoid research could eventually raise questions about the emergence of morally relevant mental capacities, such as sensory processing, emotional states, suffering, or minimal phenomenal consciousness. Although there is currently no evidence that existing brain organoids are conscious, some scholars contend that the possibility of future developments justifies anticipating ethical safeguards before morally relevant capacities emerge. A developmental threshold is a point at which new biological or psychological capacities emerge, potentially changing how an entity should be treated ethically. These thresholds include the potential for suffering, sensory deprivation, or the emergence of minimal phenomenal consciousness. According to a precautionary approach, if brain organoids were ever shown to approach such thresholds, they could no longer be regarded solely as biological material and might warrant protections similar to those used in animal research, including limits on harm, welfare monitoring, and strong scientific justification for any intervention (26,27).

Some authors propose special oversight mechanisms for advanced brain organoids because of the uncertainty surrounding their potential for consciousness or other morally relevant mental capacities (24). Proposed approaches include "guardian-like stewardship" models, meaning systems in which specific individuals or oversight bodies would act in the interests of advanced organoids if there were uncertainty about their potential consciousness, subjective experience or moral status (29). Other proposals include specialized ethics committees including neuroscientists, stem cell researchers, ethicists, and other relevant experts capable of evaluating neural activity and developmental complexity (27), as well as functional assessment frameworks and gradual, closely monitored research protocols designed to detect potentially significant forms of consciousness or awareness, such as the ability to process information or respond to stimuli in increasingly organized ways (24). Some authors also emphasize governance models promoting participant engagement, transparency, and additional oversight for sensitive applications, particularly where organoids may acquire a form of "hybrid" moral value between biological tissue and living organism or involve commercial interests (30).

Some scholars distinguish between different levels of morally relevant capacities, ranging from simple sensory-like activity to sentience, meaning the ability to consciously experience pain or pleasure, and more advanced cognitive capacities such as learning or memory (31). Related discussions have also emerged around "neurorights", meaning rights intended to protect mental functions and brain-related information, including mental privacy (protection of brain-related data),

cognitive liberty (freedom to control one's own thoughts and mental processes), and mental integrity (protection against unwanted alteration of mental states), particularly in the context of organoid intelligence and AI integration (32).

Brain organoids are generally derived from human cells, often iPSCs, meaning adult cells reprogrammed into stem cells. This raises questions regarding informed consent, donor rights, ownership, commercialization, and psychological sensitivities linked to the symbolic association between the brain, identity, and personhood, particularly because organoids may later be used for applications donors did not anticipate, including neurocomputing, AI integration, transplantation, or commercial development (31).

The transplantation of human brain organoids into animals, creating forms of human-animal neural chimeras, raises additional ethical and legal concerns. A chimera in organoid research refers to a model in which human cells or organoids are introduced into an animal, creating an organism composed of cells from two different species. These experiments may alter animal cognition or behavior and have led to debates about the possible "humanization" of animals, meaning the acquisition of more human-like neurological or behavioral traits. Some authors therefore argue that animals receiving neural transplants may require additional welfare protections or stricter oversight, while future human clinical applications would raise further concerns regarding participant protection and the possibility that transplanted organoids could eventually develop morally relevant capacities (31,33).

Scientists can also generate assembloids, a more complex type of organoid created by combining multiple organoids or different cell types to model interactions between distinct regions, tissues, or organ systems. For example, researchers may connect brain organoids with muscle organoids to study nerve-muscle communication or combine gut and stomach organoids to better reproduce interactions within the gastrointestinal tract. Unlike organoids that model a single tissue or organ, assembloids can provide insights into broader physiological and pathological processes involving interactions between multiple systems. Their increased complexity may raise additional ethical concerns regarding consciousness and appropriate oversight (11,23).

3.1.2 Implications for neurodiversity

Brain organoids reshape how neurodiversity is understood, studied, and governed. Neurodiversity refers to the natural variation in human brain functioning and cognition, including conditions such as autism, Attention-Deficit/Hyperactivity Disorder (ADHD), or dyslexia. Brain organoids allow researchers to model individual differences in early brain development, including how genes, environment, and natural variation lead to different cognitive and behavioral traits, such as those seen in autism, ADHD, or dyslexia. New approaches, such as "*in vitro* epidemiology," use large numbers of organoids from different donors to compare these differences in a controlled setting, helping researchers map neurodiversity (33). Organoids can also reproduce key features of early brain development, such as early cell behavior, the formation of cortical layers, and disease-related changes, such as altered early cell-development patterns seen in microcephaly (4).

At the same time, organoid research on conditions often uses a medical framework, focusing on cellular "deficits" or differences from a neurotypical baseline. This can conflict with neurodiversity perspectives, which see such traits as natural and valuable forms of human variation (25). For example, one microcephaly model highlights abnormal spindle orientation and early neuronal differentiation as pathological features, while another study reports unusual oscillatory patterns (brain rhythms) as signs of dysfunction (4,36). Although these findings are scientifically valid, such framings can reinforce the idea that difference equals deficit (25).

However, organoids also show that variation is inherent to brain development. Single-cell studies reveal diverse cell types, developmental trajectories, and gene regulatory patterns even within a single organoid (34). Researchers have reported substantial differences in how cortical regions, progenitor zones, and neuronal subtypes form (4). Organoids develop oscillatory patterns with variable timing, regularity, and complexity, mirroring the natural diversity seen in preterm infant EEGs (brain wave recordings) (36). Vascularization (blood vessel growth) protocols yield highly variable outcomes, reinforcing the idea that developmental randomness is not noise but a fundamental biological feature (37). Together, these findings support a continuum-based view of neurodiversity, where traits exist along a spectrum rather than in fixed categories. As organoids become more complex (37,38), different developmental trajectories, oscillatory patterns, or computational architectures raise the question: are such differences abnormalities or simply distinct forms of neural organization?
Finally, inclusive governance is essential to ensure that organoid research does not become a tool for narrowing acceptable forms of human variation. Instead, it should help build a richer understanding of the diversity inherent in human neurodevelopment.

3.2 Legal implications of brain organoids

Brain organoids do not fit neatly into existing legal categories. They are neither embryos, animals, nor human research subjects, yet they may display biologically relevant neural activity. As a result, they exist in a regulatory grey zone, meaning that current laws do not clearly specify how they should be classified or regulated (31,39). Some authors have therefore explored whether highly advanced brain organoids could eventually require some form of legal personhood, especially in the context of "synthetic biological intelligence," where neural organoids are connected to computational systems. Discussions have also emerged regarding organoids potentially capable of integrating into a body or supporting advanced cognitive functions, raising questions about possible distinctions between legal personhood and human personhood (40).

Currently, there is no binding European legal framework specifically dedicated to brain organoids. In Europe, governance mainly relies on existing biomedical research law, stem cell regulation, animal research law, data protection law, and non-binding ethical guidelines (39). Relevant frameworks include the Charter of Fundamental Rights of the European Union (41), the Oviedo Convention (21), the GDPR (19), or animal welfare legislation (20).

At the international level, governance of brain organoids is currently driven mainly by soft law and professional guidelines rather than binding legislation. The ISSCR Guidelines explicitly address neural

organoids and human-animal neural chimeras. They recommend specialized ethical oversight, proportional review depending on organoid complexity and intended use, additional scrutiny for transplantation experiments, rigorous scientific justification, and caution regarding claims about consciousness or human-like cognition. The guidelines also state that there is currently no scientific evidence that existing brain organoids possess consciousness or the capacity to feel pain, while acknowledging that future advances may require reassessment of current oversight approaches (22,42).

Similarly, the U.S. National Academies report *The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance* focuses specifically on neural organoids, transplantation into animals, and human-animal neural chimeras. The report recommends continuous ethical monitoring, interdisciplinary oversight, public engagement, animal welfare assessment, and adaptive governance capable of evolving alongside scientific advances. It also highlights concerns regarding possible changes in animal cognition following transplantation and the need to monitor future developments related to consciousness and morally relevant capacities (33,43).

In Europe, the EU-funded HYBRIDA project developed operational guidelines addressing organoids, neural organoids, and related bioengineering technologies. These guidelines focus on ethical oversight, governance gaps, donor consent, public communication, proportional governance depending on model complexity, and the need to avoid exaggerated claims regarding the capacities or future potential of organoid systems. HYBRIDA also emphasizes anticipatory governance approaches for emerging technologies whose future applications remain uncertain (16,23).

The Nuffield Council on Bioethics in the UK also launched a dedicated project specifically examining neural organoids. Its work highlights concerns related to possible consciousness, transplantation into animals, donor consent, public trust, and proportional oversight. The Council emphasizes that current governance frameworks may become insufficient as neural organoids become more sophisticated and argues for ongoing ethical reassessment as the science evolves (44).

Overall, these governance frameworks remain precautionary but flexible. They generally agree that present-day brain organoids are not considered conscious or persons, while recognizing that future increases in neural complexity could eventually require stricter oversight, new legal categories, or revised ethical protections (33,42).

3.3 Recommendations to RECs for brain organoids

- RECs should consider classifying brain organoid proposals using the HYBRIDA four-category framework, as explained further. Simple neural organoids without sensory connections fall under Category 1b (requiring specific ethical consideration and formal declaration), while complex assembloids or organoids transplanted into animal brains require full ethics committee approval (Category 2). Proposals that do not specify their complexity level should be rejected.

- For advanced brain organoids (Category 2), RECs should appoint or consult a specialist subcommittee with expertise in cognitive neuroscience and neuroethics. This group should evaluate neural activity data, assess developmental thresholds, and advise on moral risks. Where commercial interests are involved, additional safeguards must ensure that financial pressures do not compromise oversight.
- In countries where the legal framework permits it, proposals that transplant human neural organoids into animal brains require explicit ethical justification demonstrating that the scientific goal cannot be achieved by other means. Applicants must address whether transplantation confers human-like properties to the engrafted tissue.
- RECs should scrutinize proposals modeling neurodevelopmental conditions (autism, ADHD, microcephaly, dyslexia) to ensure they do not adopt an exclusively deficit-based framework. Applicants should acknowledge that variation is inherent to brain development and plan to communicate results in ways that do not equate neurological difference with dysfunction. This approach respects principles of non-discrimination, respect for persons, and equal moral worth.
- RECs must verify that the informed consent procedure includes the points addressed by the TRUSTED questionnaire, allowing donors to authorize or prohibit the generation of neural organoids explicitly and to place restrictions on future uses. When appropriate, RECs should also consider alternative and suitable methods for informed consent, such as the CHANGER two-step consent for biobanking (15). Donors should be informed of the remote possibility that organoids may develop neural activity. A pseudonymized "passport" (information letter, consent form, TRUSTED list) must accompany any distributed samples.

4. Stem cell-based embryo models

Stem cell-based embryo models (SCBEMs) are three-dimensional structures generated from pluripotent stem cells that are designed to resemble and recapitulate specific aspects of early embryonic development. Rather than being derived from fertilization, these models self-organize *in vitro* and can mimic key developmental processes such as cell differentiation, spatial organization, and early patterning events. Their primary goal is to provide insights into what is often referred to as the "black box" of early human development, particularly the period around and after implantation, which remains extremely difficult to study due to both technical and ethical constraints. These models open new possibilities for studying early human development, implantation, and pregnancy loss, while also raising distinct ethical and regulatory questions compared to other types of organoids (45).

Stem cell-based embryo models/embryoids differ from organoids in that they aim to replicate the integrated development of the whole embryo, or parts of it, rather than a single organ, and could potentially acquire features associated with a complete organism in the future. Because human SCBEMs share morphological and gene expression characteristics with natural embryos, they

currently represent the only available model for studying human embryonic development beyond the 14-day post-fertilization limit (46).

4.1 Ethical implications of stem cell-based embryo models

4.1.1. Ethical justification and conceptual framing

The literature demonstrates considerable terminological diversity, with 53 different terms used to refer to embryo models. These include general terms (such as “embryoids” or “synthetic embryos”), stage-specific terms (such as “blastoids” or “gastruloids”), and cell-based terms (such as “ETX embryos”, generated from embryonic, trophoblast, and extraembryonic endoderm stem cells). Overall, the terminology used plays an important role in shaping ethical interpretations and regulatory approaches. Terms such as “synthetic embryo” or “artificial embryo” may raise concerns about creation, destruction, or reproductive use, and should therefore be avoided (47).

Claims that SCBEMs reduce reliance on human embryos or animal research should be treated with caution. Although these models may reduce embryo use and support early-stage screening, they do not fully replace existing approaches and still require validation through comparison with human embryos and animal models before clinical application.

SCBEM research must be ethically justified by clear scientific and potential clinical benefits, including advancing knowledge of early development, implantation, and pregnancy loss. It should undergo appropriate ethical review and be conducted within clearly defined developmental timelines (22,47).

The ethical evaluation of stem cell-based embryo model research varies depending on the source of stem cells used. ESCs involve the destruction of human embryos, raising longstanding ethical concerns related to embryo research.

In contrast, iPSCs, derived from adult cells, avoid embryo destruction but raise other issues, as embryo models generated from iPSCs may be considered by some as cloned embryos due to their genetic identity with the donor. An important concern is the potential link between cloning and eugenics, as genetically modified iPSC-derived stem cell-based embryo models could be used to select desired traits, raising risks of social inequality and reduced human diversity (44,45).

A key ethical question is which features of stem cell-based embryo models are morally relevant and how they determine moral status, with criteria such as sentience, the capacity to experience pain, and organismic potential supporting a gradualist approach. The level of maturation is particularly important, as increasing development may bring stem cell-based embryo models closer to human embryos, potentially strengthening their moral status and justifying greater protection and stricter research limits, especially as rapid scientific advances enable models to exhibit increasingly complex features such as early organ formation or cardiac activity, thereby challenging previous assumptions and increasing uncertainty about their future capabilities. There is ongoing debate about whether embryo models should be afforded ethical and regulatory treatment similar to that of human embryos or whether they should be considered a distinct category requiring different forms of oversight and moral consideration. While some arguments emphasize similarities in structure or developmental processes, others highlight differences in origin and developmental potential,

creating a conceptual and normative grey zone that complicates ethical and regulatory frameworks (46,47).

4.1.2. Limits of research

Strict limits apply to SCBEM use, especially for reproduction: transfer into a human or animal uterus is internationally prohibited, as it raises major ethical concerns and may conflict with bans on human cloning. This reproductive ban also covers ectogenesis, meaning SCBEMs cannot be grown in artificial womb-like systems toward viability outside the body, to address concerns about possible reproduction (46). Several boundaries of embryo model research remain contested, including temporal limits, the emergence of morally relevant features such as developmental complexity, tissue or organismal integrity, neural activity, or the potential to form neural circuits, as well as the relevance of researchers' intentions. Questions also arise regarding the commercialization of human biological materials. The informed consent of tissue and cell donors also remains a significant ethical issue in SCBEM research, particularly because donated materials may later be used for applications, levels of developmental complexity, or future research purposes that donors did not initially anticipate (47).

4.1.3. Public engagement

Maintaining public trust in science is a key ethical priority, requiring meaningful public engagement and a careful balance between scientific progress and societal values, particularly in the context of embryo-related research. A distinction should be made between genuine engagement, involving two-way dialogue, and outreach, which is primarily informational (22,47,48). Although still limited, empirical studies have begun to explore public and stakeholder perspectives across countries including the Netherlands, the United Kingdom, and Japan, using methods such as interviews, focus groups, surveys, and workshops (49–54). There is also uncertainty about how the scientific community would respond to potential public demands for stricter regulation (47).

4.2 Legal implications of stem cell-based embryo models

Existing regulations on embryo research and cloning do not clearly apply to SCBEMs, since they do not fit established legal categories. As a result, SCBEM research frequently falls into a regulatory gap, with little explicit oversight, although in some jurisdictions it may be indirectly covered by embryo-related or stem cell research provisions. Their legal status therefore often remains uncertain, depending in part on how embryos are defined within national legal frameworks (46–48).

SCBEM research challenges the relevance of the 14-day rule, which has traditionally governed human embryo research. Because SCBEMs are derived from pluripotent stem cells and not from fertilization, defining "days post-fertilization" is not straightforward, making the rule difficult to apply. This raises questions about whether the 14-day limit should be maintained, adapted, or potentially exceeded for certain models. While some propose that existing markers such as the 14-day limit or the appearance of the primitive streak could still be used, others argue for revisiting these frameworks, and recent guidelines from the ISSCR have moved away from strict temporal limits toward more flexible oversight approaches (46,47).

In the absence of binding hard law specifically addressing SCBEMs, governance currently relies primarily on soft law instruments, notably the updated guidelines of the ISSCR (2025), which provide specific recommendations for SCBEM research (22). In Europe, several countries have also developed national soft law frameworks in recent years, including France (55,56), the United Kingdom (57), the Netherlands (54,58), Portugal (59), Sweden (60), and Belgium (61), reflecting a fragmented but evolving regulatory landscape. The regulatory landscape for SCBEMs therefore remains complex and varies across jurisdictions, with oversight mechanisms still evolving and interpretations differing between institutions, funders, and regulatory authorities (48). SCBEM research typically falls under Category 2 in the HYBRIDA categories table presented in the organoids section earlier, meaning it is permissible only after specialized scientific and ethical review, including evaluation of the scientific rationale, justification for using a specific model over less complex alternatives, and the establishment of defined culture timelines, with open-ended time limits explicitly considered inappropriate for a specific protocol.

The ISSCR 2021 guidelines introduced a distinction between “integrated” and “non-integrated” embryo models. Integrated models were designed to combine the main cell types found in early embryos, including embryonic lineages (cells that form the embryo itself) and extraembryonic lineages (cells that support development, such as those forming the placenta and surrounding tissues), and to reproduce their coordinated spatial organization and interactions. Because they included these supporting lineages, integrated models were considered to raise greater ethical concerns, particularly due to a theoretical potential for implantation in the uterus. Non-integrated models, in contrast, represented only specific parts or aspects of development and typically lacked this full combination and organization (22).

However, since 2021, SCBEMs have become more complex and diverse, with some models directly mimicking peri-implantation and post-implantation stages and showing features such as primitive streak formation, early organ structures, and organized tissue interactions. Importantly, such coordinated development can occur even without certain extraembryonic components, such as trophoblast (cells that normally contribute to the placenta), challenging earlier assumptions about what is required for higher-order organization. As a result, in its 2025 update, the ISSCR moved away from the integrated versus non-integrated distinction, as it no longer reliably captures the range of model complexity and developmental capabilities. Current approaches instead favor nuanced, function-based classifications and case-by-case oversight proportional to the level of model complexity and associated ethical concerns, recognizing that the absence of extraembryonic tissues alone is no longer sufficient to exclude a SCBEM from review and highlighting the need for governance frameworks that can adapt to rapidly evolving science. Important questions about SCBEM research remain unresolved, including which bodies should be responsible for its regulation (22,47).

The updated 2025 ISSCR Guidelines propose a review and oversight process based on three categories (**Table 2**) to help ensure that human embryo and related stem cell research is conducted responsibly, consistently across countries, and with appropriate ethical review depending on the type of project. These categories of review apply specifically to human SCBEMs and not to models derived from non-human cells, while other models such as organoids are governed separately (22).

CATEGORY 1	CATEGORY 2	CATEGORY 3
1A **Exempt from review by a specialized oversight process** • Most *in vitro* pluripotent stem cell research • Most *in vitro* organoid research • Trophoblast organoids, yolk sac organoids and other structures lacking pluripotent tissue derivatives • Differentiation of bioprinted 2D cultures of pluripotent stem cells • Transfer of human stem cells into postnatal animal hosts	**2** **Reviewed by a specialized oversight process** • Procurement of embryos, or gametes for the creation of embryos, for *in vitro* research • Derivation of cell lines from human embryos • Genetic alteration of embryos or gametes • *In vitro* culture of human embryos for research until the formation of the primitive streak or 14 days from fertilization, whichever occurs first • Human cells transplanted into nonhuman embryos that are gestated in a non-human uterus • 3D spatially organized stem cell- based embryo models (SCBEMs) • Transferring human embryos following MRT into a human uterus	**3A** **Not allowed; currently unsafe** • Heritable genome editing • Transferring mtDNA-modified (not including MRT) embryos into a uterus • Using gametes differentiated from human stem cells for reproduction
1B **Reportable, but not typically reviewed by a specialized oversight process** • *In vitro* culture of chimeric embryos (human cells into non- human embryos) • *In vitro* gametogenesis without fertilization or generation of embryos		**3B** **Not allowed: lacks compelling scientific rationale or is ethically concerning** • Transfer of human stem cell- based embryo models to the uterus of a living host (human or animal) or culture in an artificial *in vitro* system to viability (ectogenesis) • Human reproductive cloning • Breeding human-animal chimeras where there may be human germ cells. • Transferring human-animal chimeric embryo(s) to a human or ape uterus • Transferring human embryo(s), irrespective of origins, to an animal uterus

Table 2. Categories proposed by the ISSCR Guidelines 2025 for the ethical oversight of stem cell-based embryo model research (22).

Researchers are also expected to demonstrate awareness of applicable binding legislation (often laws on embryo, stem cell and biomedical researches) and regulatory policies in their jurisdiction and to explicitly state the relevant ISSCR guideline category in research proposals and publications, promoting transparency and accountability in SCBEM research (22).

2.7 Recommendations to RECs for stem cell-based embryo models

- Terms such as "synthetic embryo" should be avoided and it is recommended to use more neutral terms instead like SCBEMs.
- Researchers should also ensure responsible communication of results, avoiding hype or over-statement.
- Ensure that all SCBEM research is explicitly justified on the basis of its fundamental and clinical benefits. Researchers should justify the choice of model, explain why less complex or less ethically sensitive alternatives are not sufficient for the research question, and ensure that claims regarding the replacement of human embryo or animal research by SCBEMs are supported by strong evidence, including justification of how results will be validated against existing models, embryos, or animal systems.
- Ensure that the ethical implications of the stem cell source used are carefully assessed, distinguishing between ESC-derived and iPSC-derived models, including explicit consideration of cloning-related concerns, potential downstream uses, and commercialization pathways or conflicts of interest, particularly when human biological materials are involved. REC members should also ensure that the sex of the stem cell lines used is explicitly stated and justified where scientifically or ethically relevant. This aligns with the SAGER (Sex and Gender Equity in Research) guidelines, which recommend specifying the sex of any biological materials used, particularly when only one sex is included or when results apply to a specific sex.
- Ensure that researchers address risks related to genetic modification, reproductive potential, and potential eugenic applications, including how such risks are mitigated and misuse prevented in practice. Research involving the transfer of SCBEMs into a human or animal uterus, as well as the use of ectogenesis systems aimed at developing SCBEMs toward viability, should remain prohibited.
- Ensure that ethical oversight remains proportionate to the level of development, organization, and developmental capabilities of SCBEMs, including through case-by-case assessment taking into account the specific characteristics and intended use of the model. Researchers should define and justify clear stopping points for culture and experimentation, avoid open-ended timelines, and anticipate how future scientific developments could alter the ethical profile of their model, including increased complexity or functionality.
- Ensure transparency regarding compliance with applicable laws, regulations, and guidelines, including explicit reference to the relevant ISSCR category in protocols and publications. Governance approaches should remain flexible and adaptive, and researchers should explain how their project can respond to evolving scientific and regulatory standards.
- Ensure meaningful public engagement strategies appropriate to the sensitivity of the research, and ensure that public concerns are identified, considered, and, where appropriate, integrated into research design or governance processes.

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