CHALLENGES AND INNOVATIVE CHANGES IN RESEARCH ETHICS REVIEWS

D4.1 Review guidelines

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Executive Summary

In this deliverable, guidelines are presented for Research Ethics Committees (RECs), administrators, managers and research ethics officers on which organizations rely to review and oversee the ethical aspects of research, as well as to the researchers who design and carry out research studies. A core component of all contemporary research ethics guidelines is that research should be subject to prior ethical review by a competent REC to ensure that the ethical principles and practices put forward in guidelines and norms will be followed in the proposed research. Focused respectively on the relevant research ethics areas of gene editing, AI, electronic informed consent, and organoids, this task will provide guidance on the research ethics review process in these designated areas, will complement existing laws, regulations, and practices, and serve as a basis upon which RECs can develop their own specific practices, procedures and evaluations.

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List of Terms & Abbreviations

Abbreviation	Definition
REC	Research ethics committee
eIC	Electronic informed consent
AI	Artificial intelligence
GenAI	Generative artificial intelligence
GPAI	General-purpose AI
HLEG	High-Level Expert Group on AI
REC	Research ethics committee
RMF	Risk management framework
GE	Gene Editing
TALENs	Transcription Activator-Like Effector Nucleases
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
gRNA	guide RNA
GGE	Germline Gene Editing
WHO	World Health Organization
IRBs	Institutional Review Boards
DSMBs	Data Safety Monitoring Boards
iPSCs	Induced pluripotent stem cells
3D	Three-Dimensional
ESCs	Embryonic Stem Cells
GDPR	General Data Protection Regulation
TRUSTED	Donor's Tissue Research Under Secure Transparent Ethical Donation
FAIR	Findable, Accessible, Interoperable, and Reusable
ISSCR	International Society for Stem Cell Research
MIAOU	Minimum Information About Organoids and Their Use
EChOES	Evaluation Checklist for Organoid Experimental Studies

ADHD	Attention-Deficit/Hyperactivity Disorder
SCBEMs	Stem Cell-Based Embryo Models

1. Introduction

The ethics review of contemporary research is faced with the ongoing challenge of understanding and addressing the ethically relevant implications of ever-evolving research techniques and trends. Research ethics review is tasked with keeping up with the vexing and increasingly complicated research designs within the well-known constraints for deliberation, such as time and information scarcity. The CHANGER project was set up in an effort to coordinate both the procedural and content-related adaptations to research ethics review, the latter of which is addressed in this deliverable.

2. Purpose and Scope

This deliverable aims to provide guidelines and support for Research Ethics Committee (REC) members, administrators, managers and research ethics officers on whom organizations rely to review and oversee the ethical aspects of research, as well as to the researchers who design and carry out research studies. More specifically, it provides guidance on how to assess studies in which one or multiple of the following innovative research technologies and tools are used:

- Electronic informed consent
- Gene editing
- Artificial intelligence
- Organoids

3. Approach for Work Package and Relation to other Work Packages and Deliverables

This deliverable fits into Work Package 4 of the CHANGER project, which has the following objectives:

- To develop novel training material for all stakeholders, which are adapted to the changing research environment, and to provide training to ethics review experts.
- To develop guidelines for RECs and professionals involved in research ethics reviews that will complement existing laws, regulations and practices, and serve as a basis upon which RECs can develop their own specific practices, procedures and evaluations.
- To develop novel, digital training material, focused on specific new technologies and practices for ethics review experts, researchers and students.
- To provide training to stakeholders involved in the ethics review process of funders (European Commission), focused on specific new technologies and practices.

The current deliverable and Work Package 4 relate to the rest of the CHANGER project's work packages by consolidating up the insights developed through Work Package 2 (evidence base for challenges posed to contemporary research) and Work Package 3 (innovative approaches to ethics review). Thereby, the deliverable is one of the dissemination formats developed in Work Package 4, which also involves the development of four Massive Online Open Course and in-person training activities.

3.1. Methodology and Structure of the Deliverable

The current guidelines are developed based on the insights gathered throughout the CHANGER project. It aims to be sufficient for stand-alone use by those involved in the ethics review of contemporary research involving electronic informed consent, gene editing, artificial intelligence and organoids. Nonetheless, as not all particularities of future research studies can be anticipated, some additional guidance may at times be considered of use during research ethics review.

The guidelines are split into four stand-alone sections or sub-guidelines that each address one of the four innovative research tools and technologies mentioned earlier: electronic informed consent, gene editing, artificial intelligence and organoids.

4. Guideline 1: Organoids

4.1. 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.

4.2. 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.

4.2.1. 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).

4.2.2. 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).

5.2.3. Clinical utility of organoids

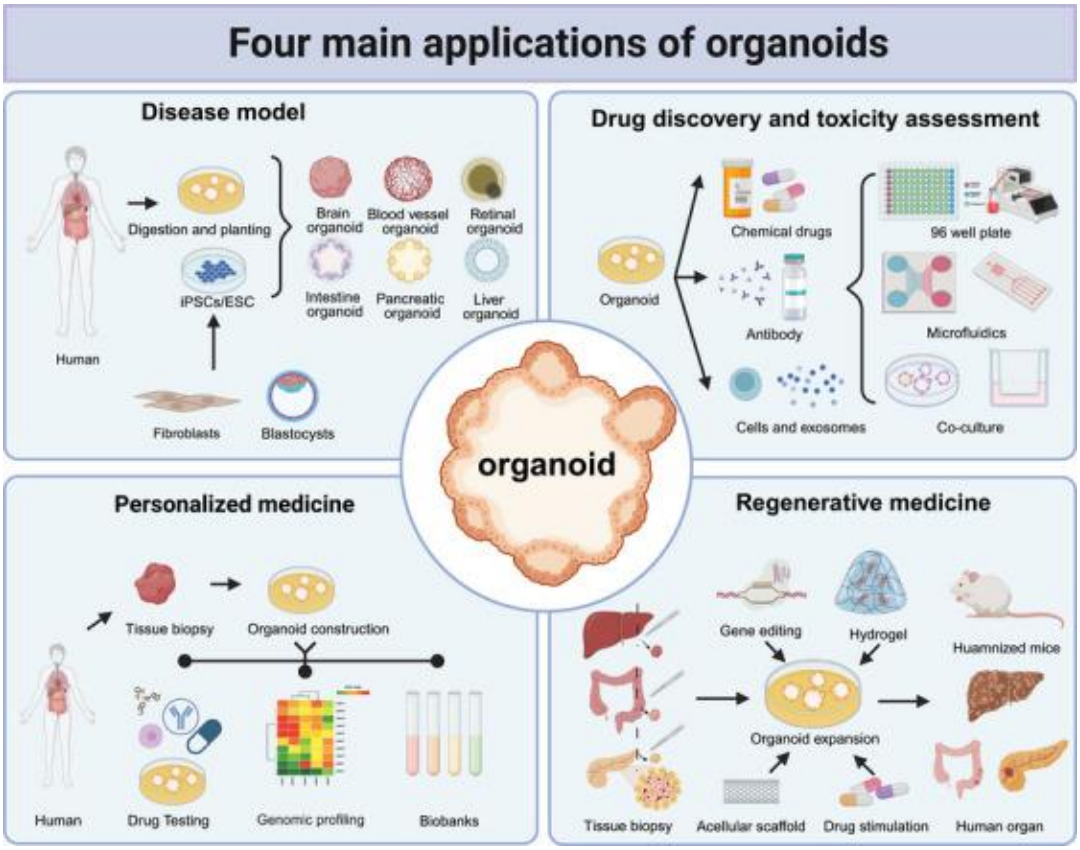

Figure 4.1. Organoids applications. Reproduced from Yao et al. (10) *under the terms of the Creative Commons Attribution License (CC BY).*

Currently, organoids are used in various contexts (**Figure 4.1**). 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).

4.2.4. 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.

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).

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).

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.

4.2.5. 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 4.1**, 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 4.1. 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).

4.2.6. 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.

4.3. 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).

4.3.1 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).

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).

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.

4.3.2 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).

4.3.3 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.

4.4. 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).

4.4.1 Ethical implications of stem cell-based embryo models

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).

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).

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).

4.4.2 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 4.2**) 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).

<table>
<tr><th>CATEGORY 1</th><th>CATEGORY 2</th><th>CATEGORY 3</th></tr>
<tr><td>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</td><td rowspan="2">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</td><td>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</td></tr>
<tr><td>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</td><td>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</td></tr>
</table>

Table 4.2. 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).

4.4.3. 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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5. Guideline 2: Electronic informed consent

This guidance document focuses on the use of electronic informed consent (eIC) specifically within the context of clinical research

5.1. Introduction

Informed consent is fundamental to the ethical conduct of clinical research (1). According to Good Clinical Practice (GCP) standards, informed consent is defined as "*a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate*" (2). Furthermore, informed consent could function as one of the legal grounds for the processing of participants' personal data, as outlined by the General Data Protection Regulation (GDPR) (3).

The digitalization in science has fostered the use of digital tools not only as research methods, but also as means to optimize the ethical conduct of research. One prominent example is the use of electronic informed consent (eIC). According to the European Medicines Agency (EMA), electronic informed consent refers to "the use of any digital media (e.g. text, graphics, audio, video, podcasts or websites) to firstly convey information related to the clinical trial to the trial participant and secondly document informed consent via an electronic device (e.g. mobile phones, tablets or computers)."(4).

The advent of electronic informed consent could offer several advantages over paper-based informed consent:

- Personalization: the information delivery could be tailored to research participants' needs (5).
- Long-term interaction: ongoing communication between participants and the research team could be facilitated during and in the follow-up of a clinical study. For instance, participants could receive new informed consent versions upon study amendments or study results could be returned (5,6).
- Documentation: documentation issues could be reduced by providing a time-stamped audit trail (7).

Other advantages include the use of audio-visual tools to enhance participant engagement with study materials, as well as short quizzes to assess comprehension and identify any questions that may require clarification prior to consenting (8).

Although an electronic interface for consent procedures provides various and tangible advantages, it is not without its challenges. Given the need the to consider both advantages and challenges, as well as the sheer variation of eIC procedures, the evaluation of study protocols using this digital tool may require additional care from RECs. Therefore, these guidelines offer a practical guide for those confronted with eIC, particularly in assessing its ethical justifiability. Readers interested in detailed guidance on the technical design aspects of eIC are invited to consult dedicated guidelines on this topic (4,9).

In clinical research, eIC is more than the result of embedding traditional informed consent for research in a digital context. It represents a shift in how consent is obtained and managed, enabling participation beyond the limitations of physical settings. Potential participants can for example be

invited to visit a website or navigate an application on a tablet handed to them by the researcher. What traditionally is an in-person conversation and/or written information on a piece of paper now becomes at least partially replaced by digital means of communication. In-person conversations may become video calls, email interactions or chat exchanges, and written text can be displayed on a monitor or made interactive through the use of buttons, links, visuals, sounds, tabs, clicks, tick-boxes, highlighting tools, personalization, scrollable and expandable sections, etc. Once information is taken up by the potential participant, they could be quizzed on their study understanding, asked to explain how the study will go, tick an "I consent" box or sign the informed consent form through a validated electronic signature application. Ongoing access to the eIC platform through their personal devices can allow participants to update their consent decisions, receive information about changes to an ongoing study, or be invited to future studies for which they could be eligible.

eIC would not be a subject matter of a guideline if it did not come with constraints and concerns too. Indeed, participants who navigate through an eIC application will have a different experience than those who consent in a traditional way. The digital realm may well be able to convey information to participants in ways that increase information uptake, it might not account well for all the non-verbal signals and information that normally makes up most of face-to-face communication. Moreover, it also opens up new non-verbal communication, such as through the use of intricate interface design to persuade participants to consent, and ethical challenges can relate to the transfer and storage of consenting information over the internet where this is less of an issue for informed consent forms stored in locked cabinets.

Sifting through these opportunities and limitations, values and concerns, the current guidelines aim to support those faced with eIC in making the most of this new digital tool. The following sections provide an insight into how traditional informed consent overlaps and differs from eIC in terms of ethics, law and regulations. It aims to facilitate the route of ethics deliberations through the common considerations relevant to eIC, whether ethical, regulatory or legal in kind. The recommendations at the end of each subsection can then assist in the assessment of whether a particular use of eIC is justified.

5.2. Traditional informed consent

Whether consent procedures occur through an electronic or paper-based interface, many of the same general ethical, legal and regulatory principles apply. This section briefly revisits the principles associated with traditional informed consent.

Legal and regulatory landscape of informed consent

Laws and regulations authoritatively determine the general possibilities for and limits of informed consent procedures in research. These laws and regulations can be differentiated into three relevant groups:

The first group of laws and regulations regulates how researchers should ask participants' **consent to participate** in a study. For example, the European Union's (EU) Clinical Trial Regulation and the Good Clinical Practice guidelines require that participants or their legally authorized representatives are well informed about the study, are able to freely and competently decide about their participation, and sign the informed consent form.

The second group of laws and regulations regulates how researchers should ask participants' **consent to the collection and processing of their (personal) data**. The EU's General Data Protection Regulation is a well-known example of a regulation that requires researchers to clarify the legal basis on which they would like to process non-anonymous data, the specific goals of the data processing, the data that is necessary and whether this involves sensitive data, and the measures in place to protect participants' data. Consent is not the only grounds for lawful processing personal data. Depending on the context and the circumstances, other legal bases can be relied on (10).

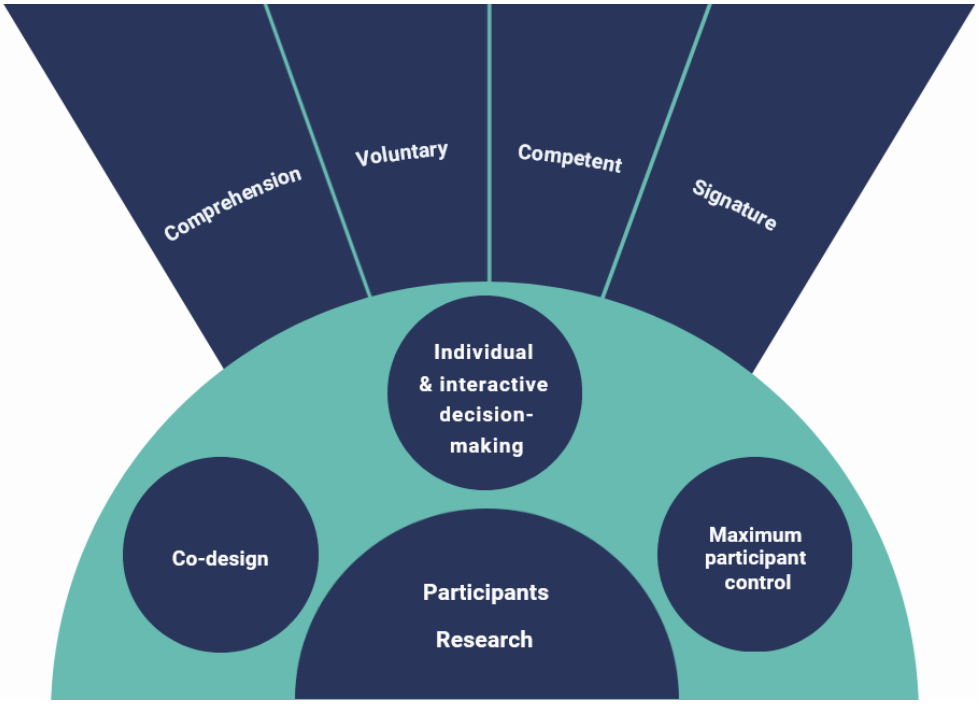
The third group of laws and regulations can have an **indirect effect** on what is required for consent to participation or data collection and protection. These indirect effects refer to legal and ethical obligations that arise when healthcare data or treatments are used in research contexts, even if consent was originally given for clinical care only. For instance, when an oncologist studies the effectiveness of standard of care treatment for their patients, they will also need to abide by the informed consent provisions for healthcare as stipulated in the applicable patient rights laws.

Although these laws have some common requirements, the conditions for obtaining a valid consent differ. For example, pursuant to the GDPR, consent must be free, specific, informed, an unambiguous indication of wishes and the individuals have the right to withdraw consent at any time and without detriment (11).

Research ethics of informed consent

Research ethics frameworks for informed consent can help RECs understand the different ethically relevant characteristics of consent that could be present, and how they relate to the justifiability of the consent procedure and the overall study. **Figure 5.1** represents a research ethics framework for informed consent, one which will be explained here:

Figure 5.1 – Research ethics framework for informed consent.



The elements on top relate to the level of autonomous control participants can realistically achieve during an informed consent procedure, as it is determined by whether the procedure facilitates comprehension, voluntary and competent decision-making, and authentic signatures. The three elements in the arch represent the intermediate purposes of informed consent, which are in turn prerequisites for achieving the general purposes.

First, the **general purpose** of the informed consent procedure should be determined. This general purpose can be determined by considering what the informed consent procedure should mean for the interests of participants' and the interests of society which are affected by the outcomes of the study. A REC might assess that a particular informed consent procedure upholds participants' autonomy and well-being to a certain extent, while ensuring that it does not undermine the recruitment and methodological rigor of the study.

The general purpose of an informed consent procedure is significantly affected by the applicable legal, regulatory, practical and scientific **possibilities and constraints**. The laws and regulations outlined in section 5.1 ensure that the interests of research cannot be prioritized to such an extent that the informed consent procedure completely neglects participants' autonomy. Practical constraints, such as the inability of a legally authorized representative to perfectly know what the participant they represent prefers, can again limit the degree of autonomy that can be ensured. Finally, scientific possibilities, such as the availability of both in-person and online methods to study the same research question, can expand the possibilities for the design of an accompanying informed consent procedure.

Besides possibilities and constraints, the **social context** can affect the preference for a general purpose of an informed consent procedure. When studying participants from societally disadvantaged or marginalized groups, including stigmatized groups, such as certain ethnic minorities, it becomes more important to ensure that their needs and preferences are adequately represented in the informed consent procedure (e.g., in the language used). Similarly, when a researcher simultaneously has another kind of relationship with the participant, such as a physician-

patient relationship, the importance of certain interests affected by the informed consent procedure can change (e.g., prioritizing the patient's well-being).

Second, RECs can evaluate whether the informed consent procedure is able to achieve its **intermediate purposes**, which are in turn prerequisites for achieving the general purposes. The framework described here differentiates three groups of intermediate purposes (**Fig.5.1**):

- *The maximal level of autonomous control participants' can achieve over their consent decision under ideal circumstances.*
- *The realistic level of autonomous control participants can achieve under non-ideal circumstances individually and/or in interaction with the researcher.*
- *Co-design of the informed consent procedure with participants to better represent their needs and preferences.*

The **maximal level of autonomous control** participants' can achieve over their consent decision, should they have perfect capabilities to make such a decision, is determined by the control participants get over different decision dimensions. That is, participants can give consent to a broader or more narrow scope of activities, whereby a consent to a broad range of study activities or studies offers less control than a study-specific consent. Furthermore, being able to make sub-decisions about one's participation or what happens to one's data, and the provision of repeated consenting moments throughout a study can also improve the degree of control. In addition, consenting oneself (when possible) or providing an opt-in consent upholds participants' autonomy more than asking a legally authorized representative to consent or allowing for an opt-out consent. Similarly, each of these dimensions can affect the methodological value of a study. For example, opt-out consent procedures may facilitate recruitment, while repeated consent moments require researchers to engage with participants at multiple points in time.

However, decision-making conditions are never perfect. Therefore, researchers can **optimize participants' realistic decision-making capacities** by ensuring that they sufficiently comprehend what their participation involves, are able to make voluntary and competent decisions, and can sign and authenticate their consent forms. A sufficient comprehension requires that all the information necessary for making a consent decision is disclosed to participants, and that it is disclosed in an intelligible way for the participants. Facilitating voluntary decision-making in turn requires the researchers to exert no unwarranted social influence on the participant so as to steer their consent decision in one way or the other. Competent decision-making should be properly assessed (e.g., through quiz-based assessments). Additionally, providing interactive support (e.g., offering opportunities to ask questions via the platform or scheduling consultations with responsible researchers) can be considered a way of supporting their decision-making competence. Finally, a participants' signature is meant to indicate that they made an agreement with the researcher about the study, which can be audited by authorized third parties to hold the researchers to account in case of irregularities.

Co-designing an informed consent procedure becomes more important when one is uncertain about the needs and preferences of the participants. This could, for instance, be a valuable activity when conducting (participatory) research with disadvantaged communities.

Shortcomings of traditional informed consent

Although paper-based informed consent is widely used in research practices, it has important shortcomings. For example, participants' do not always comprehend what they consent to, those with little physical access to the research site may not be able to consent and participate, the consent procedures are often static and generic instead of dynamic and personalized, and the storage of consent forms may make auditing onerous (9,12).

Recommendations*

- Ensure that for clinical trials under the scope of the **CTR**, that the consent procedure aligns with the CTR's consent requirements. Additionally, consider national requirements for consent to participate in research.
- Ensure that the requirements of the **GDPR** and its national implementations and guidelines of data protection authorities are complied with, regarding the legal basis for processing (sensitive) data, conditions for consent, and the information and transparency requirements.
- Ensure that the **indirectly** relevant requirements of other applicable laws and regulations are complied with.
- Ensure that the **general purpose** of the consent is ethically acceptable given the social context, and feasible within the legal, regulatory, technical and scientific constraints.
- Ensure that the **intermediate purposes** of the consent are able to lead to the general purpose through the implementation of their different dimensions.

* These recommendations are presented as those most relevant for the further application of electronic informed consent and are not intended to provide guidance on informed consent itself. For general principles and standards of informed consent, we refer to key references such as the Declaration of Helsinki, the Oviedo Convention, and other internationally recognized guidelines.

5.3. Electronic informed consent: Context

With the broader trend of the digitalization in healthcare, eIC is a relatively new and rapidly growing practice science research. For RECs to effectively assess whether its use is justified, it is important that the context in which eIC is being used is made clear. This context will in turn function as the boundaries within which the ethical evaluation takes place.

Use of electronic informed consent in research

In the context of research, eIC can take on in various shapes, depending on how its constituting criteria are operationalized:

> *"An informed consent process is considered to be an electronic informed consent process if one or multiple elements of the process are set up in a digital way. These elements may include (i) conveying information (e.g. information delivery via digital platforms to facilitate tailoring to the individual's needs), and (ii) obtaining and documenting informed consent (e.g. electronic documentation contributing to efficiency of trial sites)."(13)*

More specifically, eIC is used in research that is either partially or fully digital. In partially digital research, such as in biobanking or clinical trials, eIC can take on a wide range of forms, depending on which part of the informed consent process is digitalized (14,15). In one study, researchers may ask

participants to sign the consent form on REDCap after having a video call, and the rest of the study may take place in person (16). Another study may be conducted entirely in a laboratory, with participants signing the consent form on a tablet. Both are instances of eIC. In fully digital research, such as social media research or online surveys, all interactions occur digitally, including the entire informed consent process. Due to the lack of in-person contact, these studies may be particularly at risk of insufficiently autonomous consent decisions (see section 5.2).

Technical possibilities and constraints of electronic informed consent

The use of eIC procedures in research requires a **digital infrastructure** in which the informed consent procedure unfolds. These infrastructures or platforms need to manage participant-related and -unrelated information, log the different actions taken along the consent process, provide a user interface for the different user groups (e.g., participants, researchers, sponsors, RECs and auditors), and encode logical procedures for guiding participants through the consent procedure, facilitate authorization, etc. We refer the interested reader to dedicated guidelines for a more in-depth analysis of these technical requirements (4,9).

Various **resources** have been developed for researchers to deploy their eIC. These include platforms such as REDCap, and smartphone apps, among others (16,17).

Legal and regulatory landscape for electronic informed consent

While the same **laws and regulations** for informed consent apply to eIC (section 5.2), additional rules are relevant. Unlike the United States, the EU has no well-integrated regulatory framework for eIC. The CTR does not specifically address eIC, whereas the GDPR does mention that it allows the use of an electronic interface to request consent. Recent development such as the Data Governance Act (18) that regulates the provision of data intermediation services and a framework for entities which collect and process data for altruistic purposes can or the Regulation for a European Health Data Space, that specifies and complements the rights laid down in Regulation (EU) 2016/679 of natural persons in relation to the primary use and secondary use of their personal electronic health data (19), can have an impact on the requirements for eIC.

Another piece of European legislation that is relevant to eIC is the regulation on electronic identification and trust services for electronic transactions in the internal market (eIDAS Regulation). The eIDAS regulation provides rules for electronic signatures and identification, and some European countries differentiate the rigor of identification depending on the study risk (e.g., simple signature versus more rigorous identity check). Other European countries accept eIC without regulating it, or prohibit using eIC (20). Electronic signatures can be used to sign electronic informed consent forms, and thereby provide proof that the signer acknowledges the information in the consent form. eIC solutions can support one of these signature types provided in the eIDAS Regulation. But there is no general obligation to accept the use of electronic signatures for clinical trials in the EU, the legal acceptance of eIC significantly differs among the Member States.

The legal effect of the electronic signature and the advanced electronic signature is such that it may not be denied legal effect and admissibility as evidence in legal proceedings just because it is in an electronic form or because it does not meet the requirements for qualified electronic signatures. However, this does not automatically mean that a simple electronic signature is always valid. In case the signature is contested in court, it depends on the national legislation and the judicial discretion of the judge to decide whether it should be considered a valid signature. The advantage of a qualified

electronic signature is that its legal effect is equivalent to that of a handwritten signature. Furthermore, a qualified electronic signature based on a qualified certificate issued in one Member State shall be recognized as a qualified electronic signature in all other Member States.

Recommendations

- Ensure that the **technical infrastructure** used fulfils the necessary legal and regulatory requirements.
- Ensure that the **eIC is compliant** with the applicable laws and regulations, good clinical practices and the requirements of national regulatory authorities.
- Ensure that eIC platform only processes and stores valid consent signatures that are placed by the intended actors.
    - A valid signature should be unambiguously linked to, at least, the individual that placed the signature, the time of signing, and the exact version of the informed consent form that was signed.
    - In a longitudinal e-consent system, the long-term storage of valid signatures must be carefully considered, with particular attention to maintaining integrity in the presence of revocations and/or expirations of certificates and keys.

5.4. Electronic informed consent: Research ethics

While the legal, regulatory, technical and scientific context determine what design choices researchers can make for eIC, RECs and researchers still need to evaluate whether the eventual eIC is ethically justifiable. This is important, as for example the laws and regulations of this new scientific development may not be up to speed with all the relevant concerns that accompany eIC. To conduct a research ethics evaluation of eIC, RECs can start by considering the general and intermediate purposes that researchers aim for with their eIC. This will require knowledge of the practical realities of the eIC procedure, as the concrete design of the eIC will determine whether it will be able to achieve its purposes. This section will therefore provide guidance on where the realities of eIC converge and diverge from the framework for evaluating the justifiability of traditional informed consent (see section 5.2).

The general purposes of the electronic informed consent

In section 5.2, the **general purposes** of informed consent procedures were defined by the extent to which they address the interests of participants and of society, through rigorous research practices. These general purposes equally apply to eIC. However, one complicating factor for eIC is that due to the decreased in-person interaction between the researcher and the participant, it can make it more difficult for the researcher to know what the **participant interests at stake** exactly are. When having an in-person conversation, various verbal, non-verbal and situational cues can inform the researcher of the participant's needs. In electronic communication, these forms of communication are reduced significantly. Hence, it could become uncertain whether participants' needs are actually met when there is only limited interaction, which becomes especially relevant for populations that are disadvantaged or distrusting of research. In fully digital research, there may be even less interaction,

due to which some argue that certain kinds of research become unjustified (e.g., fully digital consent in clinical trials) (13). Increasing **interactivity and co-designing** the eIC with participants may (partly) overcome this shortcoming of eIC.

The intermediate purposes of the electronic informed consent

In section 5.2, the intermediate purposes of informed consent procedures were defined as the maximal and realistic levels of control participants can have over their consent decisions, along with the co-design of the informed consent procedure with participants. While these same components apply to eIC, specific challenges and advantages arise here as well.

- *Maximally achievable level of control: Questions regarding the effectiveness of data protection regulations for digital research may require assigning participants a higher maximum achievable level of control in privacy-risky research compared to those with lower privacy risks* (21)*. In general, one can argue that more risky/lower value studies require higher maximal levels of participant control in eIC* (22)*.*
- *Realistically achievable level of control: As the communication between the researcher and the participant is usually reduced in eIC, this can hinder participants' ability to make an informed, voluntary and competent consent decision.*
- *Co-design: The digital context can facilitate the co-design of eIC infrastructures and procedures with participants.*

Electronic informed consent and participants' realistic levels of control

The level of autonomous control participants can realistically achieve during an eIC procedure is determined by whether the procedure facilitates comprehension, voluntary and competent decision-making, and authentic signatures. These criteria are the same as those discussed for traditional informed consent in section 5.2. Nonetheless, for eIC, several different ethically relevant considerations come to the fore.

Participant comprehension

The use of eIC highlights a **challenge to participant comprehension** that is less likely to occur in in traditional informed consent evaluations, yet it is often overlooked. Besides informing the participant about the study, the verbal, non-verbal interactions, as well as the situated interaction between the participant and the researcher, provides the participant indicators of whether to trust the researcher with safeguarding their interests (e.g., as inferred from the researcher's demeanor or affiliation) (23). Both kinds of information are relevant to the consent decision (24). However, when the communication between researcher and participant is electronically mediated, researchers may not pick up on and act upon subtle signs of a participant's hesitancy or lack of comprehension (25). Additionally, participant may not have access to reliable indicators of the researcher's trustworthiness. In turn, this undermines participants' comprehension of the study.

Notwithstanding this challenge, eIC also provides several (**new**) **avenues for improving participants' comprehension**:

- *Initial information provision: the consent information should be concise, clear, easy and highlighted, convey non-misleading trustworthiness indicators (e.g. university logo), and information on eIC personalization and long-term use (e.g. contacting participants for future studies).*

- *Personalized information: the information for participants can be tailored to their specific needs (e.g. disclosing pregnancy risks to women of childbearing age), layered (e.g. hover-over text for more information), customizable (e.g, allow changing font sizes or highlighting) or comprising of multiple formats (e.g. audio, video).*
- *Interaction: the eIC can be guided by the researcher (e.g. parallel video-call) or it can encourage participants to ask questions (e.g., through chat).*
- *Comprehension check: intermediate or final measures could assess participants' comprehension (e.g. quiz, teach-back) and contingently provide support (e.g. schedule a video call) or deny participation under certain levels of understanding (e.g. less than 80% correctly answered quiz questions).*

Decision voluntariness

The most well-known instances of research conduct that **reduce the voluntariness of consent**, such as coercion or offering clearly excessive financial incentives, are arguably similar between traditional informed consent and eIC. Instead, some more subtle forms of influencing participants' consent decisions during eIC appear more bespoke to the digital context. For example, researchers could use persuasive designs to attract participants' attention to a study, device or software on which the eIC is provided (e.g. through push notifications, repeated emails). Moreover, they may contain misleading trustworthiness indicators which participants may be unable to scrutinize in an electronic context. Researchers may also employ attractive colors or pre-ticked "I consent" checkboxes to nudge participants to consent.

Several traditional and digitally enabled design choices can be made to **support participants' voluntary decision-making** during an eIC procedure:

- *Reduce persuasion, manipulation, nudging and related techniques: researchers can remove persuasive or otherwise influencing elements that are not strictly necessary, indicate to participants that these techniques will be used, and/or allow participants to switch them off (e.g., change colors, notification frequency).*
- *Future studies: Researchers can allow participants to set their preferences for being contacted through the eIC interface about future studies.*

Decision-making competence

eIC also poses particular **challenges to assessing and improving participants' decision-making competence** when it comes to consent decisions. Due to the potential difficulties associated with authenticating a participant's true identify, it can be difficult to assess whether that participant can be presumed to have decision-making competence (e.g., is a child impersonating an adult?). Furthermore, decision-making competence is a dynamic ability, which can be affected by emotional or other affective states (e.g. feeling apathetic or overwhelmed with fear) as well as social support (26). In eIC, the decreased interaction between the researcher and the participant makes it more challenging for researchers to identify whether participants require more support related to study comprehension, emotional reassurance, or acquiring the necessary skills and resources to use digital means necessary for eIC (e.g. a stable internet connection, access to a computer). This becomes even more pronounced when certain digitally less-educated populations would otherwise risk not being included in research (27).

To **support participants' decision-making competence** when going through the eIC process, the following approaches can be taken:

- *Assessment: researchers can have a more interactive and humane encounter with participants (e.g. a video call), during which they can pick up on more subtle cues that indicate the need for support.*
- *Support: researchers can provide participants with the necessary digital tools and infrastructure, educate them on using these tools, or allow them to fill out a paper-based informed consent form instead.*

Signing and authenticating

As for traditional informed consent, participants can sign eIC forms and thereby indicate their identity. Researchers are then tasked with protecting these digital traces of participants' identities from unauthorized access. However, eIC poses particular **challenges to signing and authentication**. In the absence of face-to-face interaction when a participant signs the eIC form, it becomes more difficult to assess whether it was actually the participant who signed the form. Additionally, it raises challenges in determining whether the signer is a human or an AI system. Additionally, when consent forms are stored on servers and transmitted over the internet, there is a risk of unauthorized parties accessing the consent forms digitally. This becomes even more damaging when the consent form links an individual participant to a study on a sensitive topic (e.g. on their experiences as illicit drug users).

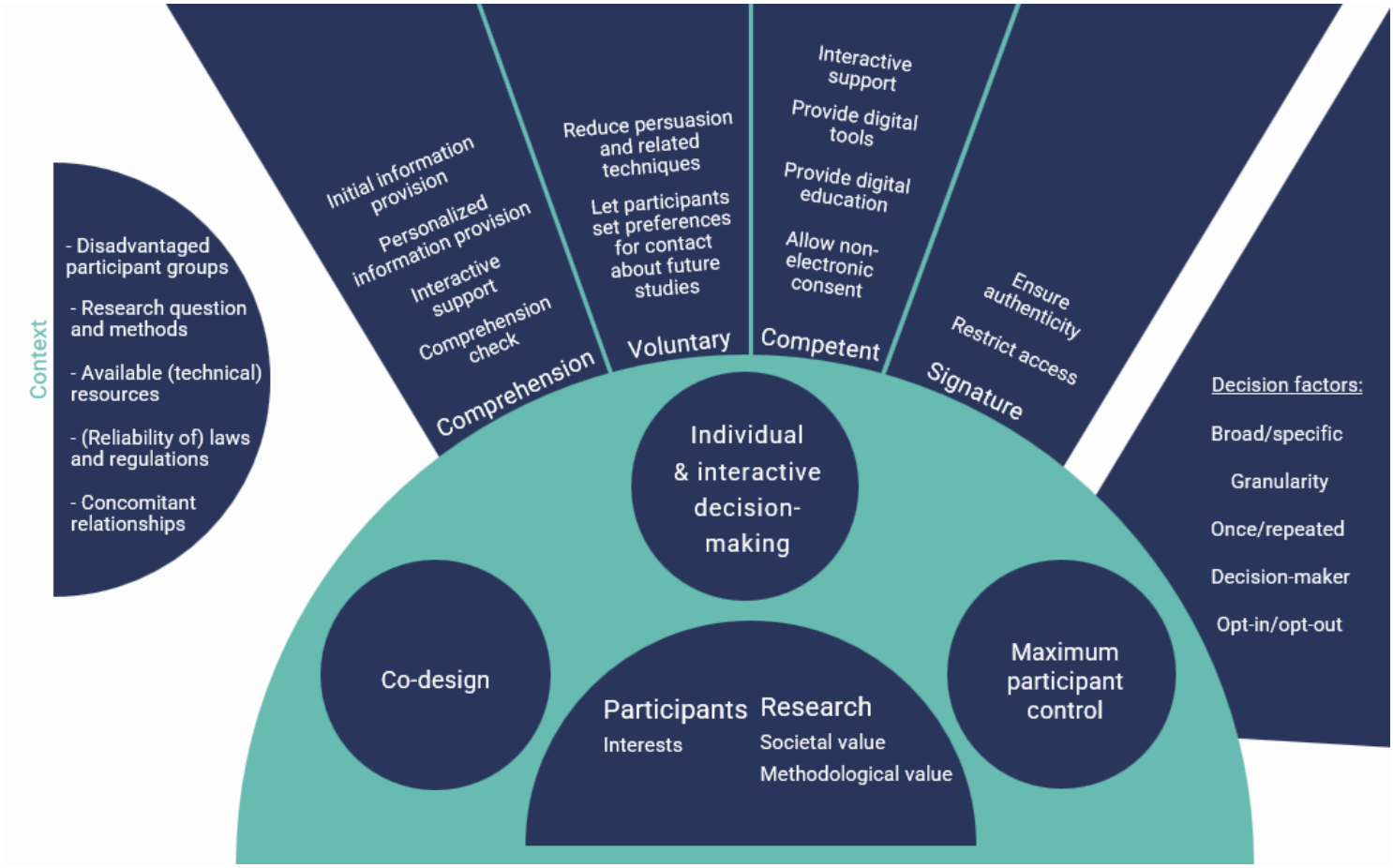
Researchers can take several approaches to **ensure that signing and authentication is both effective and safe**:

- *Ensure signature authenticity: researchers can ensure that the signature contains various identifiers (e.g. person, time, document version), and they can have an in-person interaction with the participant when the eIC is being signed (e.g, a video call).*
- *Protect signed documents from unauthorized access: researchers can provide unidentifiable data to certain parties (e.g. auditors, sponsors, RECs), assess whether unauthorized parties have access (e.g. eIC infrastructure providers), protect the data (e.g., limit and deidentify the collected consent data), the consent document (e.g. secure long-term storage, read-only documents) and the electronic infrastructure (e.g. the participants' device and their browser history, the eIC platform), and update protection measures.*

Integrating the research ethics assessment

RECs are tasked with evaluating the justifiability of eIC forms and the studies in which they occur. Based on the above recommendations and considerations, RECs can determine whether the general purpose of the eIC is justified, whether the intermediate purposes align with this general purpose, and if these intermediate purposes are realistically achievable given the eIC design or require further optimization. Figure 5.2 integrates these different considerations:

Figure 5.2 – Research ethics framework for electronic informed consent.



Recommendations

- Ensure that the **general purpose** of the eIC procedure is made clear, and that an electronic interface is appropriate given the usually reduced degree of researcher-participant interaction.
- Ensure that the **intermediate purposes** of the eIC procedure are clear and able to fulfill the general purpose, and that the protocol accounts for the impact of digital interactions on participants' realistic levels of control and the co-design of consent, as well as the impact of the novelty of eIC on the reliability of applicable laws and regulations.
- Ensure that **participants' study comprehension** is optimized with regards to the initial information provided, the personalized information, the interactive support and the comprehension check.
- Ensure that **participants' decision voluntariness** is optimized by reducing social influence techniques to a minimum and allowing participants to set their preferences for being recontacted about future studies.
- Ensure that **participants' decision-making competence** is assessed as adequately as feasible and necessary, while also providing support for their digital and comprehension-related decision-making needs.
- Ensure that **participants' signatures are authentic and protected** by verifying their identity and implementing adequate cybersecurity measures.

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6. Guideline 3: Gene editing

6.1. Introduction

Gene editing tools, especially technologies like clustered regularly interspaced short palindromic repeats CRISPR-associated protein 9 (CRISPR-Cas9) and its newer iterations, have transformed modern science and healthcare. By allowing scientists to precisely alter DNA sequences within living organisms, gene editing can be used to create novel therapeutics for previously incurable conditions (e.g. sickle cell anemia, Huntington's disease), prevent genetic conditions before birth, and offer a new method for tackling serious diseases (e.g. breast cancer, prostate cancer). Though gene editing has been used extensively in plants and animals, the use of gene editing in humans remains untested, complicated, and ambiguous. As a result, the novel prospect of editing the human genome brings a host of ethical dilemmas related to informed consent, safety, human enhancement, and more. Consequently, it becomes vital to balance the potential of gene editing with its ethical risks by championing ethical research practices and responsible governance.

6.1.1. Role of RECs for ethical development of Gene Editing

Research ethics committees (RECs) play a crucial role in guiding the responsible development and application of human gene editing technologies. While the Clinical Trials Regulation 536/2014 distinguishes ethical review from scientific evaluation, RECs are nonetheless responsible for considering aspects of scientific validity that directly affect participant protection. They do not duplicate the full scientific assessment conducted by competent authorities, but they assess whether the study design is sufficiently robust to justify exposing participants to risk. For example, RECs may scrutinize first-in-human gene editing studies for inadequate preclinical evidence, poorly defined endpoints, disproportionate risk–benefit ratios, or insufficiently justified patient selection. In this way, RECs ensure that ethical standards are upheld, participants' rights are protected, and potential harms are minimized. As gene editing moves closer to clinical application, this oversight becomes even more essential, ensuring that the pursuit of genetic advancement does not outpace the ethical frameworks needed to guide it.

6.2. Background and Context: Gene Editing

Before discussing the ethical issues and guidelines involved with the various types and uses of gene editing, it is important to establish the fundamental and contextual details associated with how gene editing works as well as to differentiate the types of editing that are possible with recent gene editing systems. The following sections will highlight the context behind various recent and historical gene editing tools as well as explain the scientific function of these tools for various human applications.

6.2.1. Scientific and Historical Background of GE

Gene editing refers to the method that allows scientists to make precise changes to the DNA of living organisms, such as plants, bacteria, animals, and humans, to change physical attributes, genetic variants increasing disease risk, and genetic sources of severe conditions (1). This concept has been a part of scientific discovery and can be traced back to the 1970s with the first efforts toward recombinant DNA technology, but the field advanced dramatically after certain key discoveries (2). First, the field boomed exponentially after the development of zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) in the early 2000s (3)(4). Both of these tools allowed researchers to make double-stranded breaks at specific locations in DNA, which could then

be repaired in a way that altered the genomic sequence. Both these methods, however, are complex, burdensome approaches that are also often expensive to design, which does not make them the ideal gene editing system for widespread use (5).

The field expanded again in 2012 with the discovery of CRISPR-Cas9, a powerful yet simple gene editing system adapted from a bacterial natural defense mechanism (6). CRISPR uses a guide RNA (gRNA), synthetic molecule that matches to a desired location in the genome, to direct the Cas enzyme to a specific part of the DNA sequence and make a precise cut in the DNA (7). The cell then attempts to repair the break, allowing scientists to disable a gene, fix a mutation, or insert new genetic material (7). CRISPR is set apart from some of the older gene editing tools because it bypasses those models' labor-intensive protein engineering required to reach a DNA target location, whereas CRISPR just needs the generation of a new gRNA (8). As a result, it is significantly more accessible, efficient, precise, and cost-effective.

In fact, newer iterations of CRISPR are constantly being patented. For instance, highly precise base editing allows scientists to change a single DNA base without even cutting the DNA strand, significantly lowering the risk of errors that may occur during DNA repair (9). Similarly, prime editing enables even more accurate edits, including gene insertions and deletions for large swaths of DNA similarly without making double-stranded DNA breaks (10). These advances have made gene editing safer and more precise, especially for human applications, which has sparked a recent explosion in therapeutics research and human health studies. However, it is also important to note that the rise of CRISPR technology has also sparked intense legal battles over intellectual property rights over these tools as it affects researchers' access to innovation and works counter to open science practices (11).

6.2.2. Types of GE and Therapeutic Uses for GE Tools

The key distinction when considering gene editing is between somatic gene editing and germline (or heritable) gene editing, which present vastly different consequences and ethical dilemmas. Somatic gene editing is a type of gene editing where the DNA changes are made only to somatic cells, or the body's tissues (12). The changes are not passed on to future generations and only affect the individual being treated (12). This type of editing is typically used as medical treatment for various diseases, such as cancers and genetic disorders since the goal is only to alter the DNA within affected tissues or organs (12). As a result, a lot of the ethical discussion focuses on the safety and efficacy of such an intervention.

Germline gene editing involves making changes to the DNA in reproductive cells and tissue, such as ovaries (eggs), sperms, embryos, and zygotes (13). Changes to these cells are intended to be passed on to future generations, which holds potential for eliminating genetic diseases before birth as well as permanently within a genetic line (13). However, this type of editing raises many incredibly complex ethical and societal issues about the potential for dangerous human enhancements, long-term, unintended consequences, and permanent changes to the human gene pool (14). As a result, germline editing remains a controversial topic globally due to its profound implications for human evolution and identity and has been prohibited in many countries.

Translating editing tools into practically usable treatments, also known as a gene editing therapeutics, is a complex process (15). First, scientists use known genomic information about diseases to identify a faulty gene. Then, they must design a precise gRNA and editing strategy (e.g.

gene insertion or deletion) and, finally, safely deliver it to the right cells without causing side effects like toxicity, immune reactions, or off-target edits (15). Diseases caused by a single gene, such as cystic fibrosis, are more straightforward targets, but many conditions involve multiple genes or variants, complicating therapeutic development (16). Additional challenges include precision, which is crucial to ensure that the therapeutic creates accurate changes in the right part of the body (17). Delivery also remains a major hurdle, with viral vectors and lipid nanoparticles being common methods for transporting editing tools into cells (17).

Gene editing therapies are also categorized as *in vivo*, where the editing tools are delivered directly into the body, and *ex vivo*, where cells are extracted, edited outside the body, and transplanted (18). Ex vivo approaches offer greater control and have already shown clinical promise but can be very demanding with their many steps (19). For instance, Casgevy is the first approved CRISPR-based one-time therapy for sickle cell disease and beta-thalassemia and uses an *ex vivo* model (19). However, in vivo approaches may offer greater cost-effectiveness and broader applicability for more types of diseases (20). While much of the current focus is on treating inherited genetic disorders, gene editing also holds potential for tackling cancer, viral infections like Human Immunodeficiency Virus (HIV), and other complex diseases. However, these advancements come with significant challenges, including ensuring safety, minimizing off-target effects, and addressing ethical concerns such as informed consent and fair access (21). Moving forward, careful oversight, strong regulation, and collaboration across stakeholders will be essential for the responsible use of these powerful technologies.

6.3. Germline Gene Editing (GGE): Clinical and Research Uses

Because germline gene editing (GGE) is a high-risk and ethically complicated endeavor (as highlighted above), the permissibility of GGE is determined by whether it is being conducted for research purposes or as a clinical intervention. Currently, clinical uses of GGE are strictly forbidden; however, research uses of GGE are often vague and determined on a national basis.

6.3.1. Legal landscape for clinical applications

Current laws and regulations governing germline editing are largely straightforward in that they consider the clinical use of germline gene editing to be illegal as of the writing of this document in 2026. A key international document reinforcing this position is the Convention on Human Rights and Biomedicine, also known as the Oviedo Convention (22) which addresses both clinical and research uses of gene editing. Article 13 of the Convention permits interventions on the human genome only for preventive, diagnostic, or therapeutic purposes, and explicitly prohibits modifications that would affect future generations. While the Convention allows for somatic gene editing, it clearly bans germline interventions. However, it's important to note that not all European countries have ratified the Oviedo Convention, so its provisions are not universally binding across the continent. In addition to these international guidelines, many countries have also enacted their own national bans on the clinical use of GGE.

Additionally, the EU CTR (23) further restricts germline editing. Article 90 of the regulation states that gene therapy clinical trials must not result in changes to an individual's germline genetic identity, reinforcing a strong stance against heritable editing. Furthermore, professional societies, including

the European Society of Human Genetics and the European Society of Human Reproduction and Embryology, also oppose the clinical use of germline editing, deeming it premature and unacceptable at this time (24). Additionally, the World Health Organization (WHO) supports a temporary ban on germline editing for reproductive purposes, citing concerns about safety, inequality, human dignity, and insufficient long-term data. They also highlight the importance of continued international discussion before any clinical use of germline editing can be considered (25).

6.3.2. He Jiankui Experiment: Impacts of clinical research involving GGE

The sheer ethical complexities of clinical research involving GGE were brought into the limelight of the scientific community in 2018 when scientist He Jiankui announced that he had used CRISPR-Cas9 to modify the genomes of twin girls (26). He altered their CCR5 genes in an attempt to confer resistance to HIV, marking the first known case of clinical germline genome editing in humans (27). He presented his experiment at the second World Summit on Human Gene Editing and was swiftly met with strong backlash from the scientific community (26). In fact, researchers, scientific institutions, and national governments across the globe condemned his experiment, labeling He as a rogue scientist, extremely irresponsible, and in clear violation of regulatory and medical ethics standards. In addition to this ethical condemnation, He faced legal consequences: Chinese authorities investigated his work, and in 2019 he was sentenced to three years in prison and fined for conducting illegal medical practices, highlighting that clinical GGE can carry both ethical and legal repercussions (28).

6.3.2.1. Research Ethics Considerations for clinical research involving GGE

Firstly, He's experiment was not only a sharp wake-up call for scientists globally, but this case can be used to highlight serious research ethics concerns and missteps with clinical uses of germline gene editing. For instance, the safety and efficacy of germline intervention is widely considered to be unclear. Though gene editing techniques have improved significantly, especially with the advent of CRISPR editing tools, risks of the intervention are still high (e.g. off-target effects or unintended mutations) and still require considerable additional research (26). Furthermore, there is not sufficient documentation about the CCR5 gene to be able to adequately claim that modifying it could lead to a long-term health benefit (26). He also did not present sufficient pre-clinical evidence to prove the safety of the intervention (26).

Secondly, the clinical utility of genetic interventions must be clear and provide a sufficiently compelling reason to take on the risks involved with GGE. This was not achieved in He's experiment since HIV transmission to future offspring can be easily and effectively prevented through alternative methods, such as Assistive Reproductive Technology (26). Additionally, some argue that GGE itself does not offer greater medical benefit over other reproductive technologies since it can also be used negatively for human enhancement, which is widely understood to be impermissible. For instance, severe diseases can also be avoided using in-vitro fertilization in conjunction with preimplantation genetic diagnosis, prenatal testing, sperm donation, somatic gene therapies, or adoption (29).

Thirdly, the long-term effects of GGE are still unclear, further proving this experiment violated key research ethics standards. Currently, there is little to no understanding of the long-term consequences of germline editing, not just on the individual receiving the intervention but in the human gene pool as well (29). This is further complicated because there are no clear distinctions yet

about when GGE is being used as a therapeutic medical intervention or as human enhancement, which requires further and more extensive studies (29).

Fourthly, there is still no broad, societal consensus on the moral impacts of GGE, since altering the genome can be considered altering a fundamental aspect of humanity (29). Further discussions, including a wide range of voices, should have been established before He Jiankui's experiment.

Finally, one of the repercussions of He Jiankui's experiment on germline genome editing (GGE) was a call for a global moratorium. In 2019, leading scientists published a proposal in Nature advocating for a temporary halt of at least five years on clinical germline genome editing, pending the development of clearer scientific, ethical, and regulatory standards. Although this proposal was not legally binding, it significantly influenced international governance discussions. Since then, organizations such as the WHO have issued recommendations aimed at strengthening oversight and discouraging premature clinical use. As of 2026, no international consensus has emerged in favor of permitting clinical germline genome editing, and many jurisdictions continue to prohibit or strictly limit such applications. The moratorium has thus functioned less as a formal ban and more as a normative framework shaping ongoing regulatory and ethical deliberations.

6.3.3. Research Ethics Standards for Research Applications of GGE

Research considerations involving germline gene editing (GGE) are often vague and confusing because the legality of GGE research varies widely across countries (30). Some countries, such as the UK and Belgium, explicitly permit germline gene editing solely for research purposes and is codified through national policy (30). However, countries, such as Germany and Austria, explicitly prohibit germline genome editing for research (30). Other countries, such as Sweden and Norway, allow the research but in specified and controlled circumstances. Many more countries, especially within the EU, often have vague or indeterminate stances on GGE research (30). This is further confused since international laws, such as the Oviedo Convention, do not provide explicit guidance on the legality of GGE research. The lack of a unified international framework also raises concerns about "ethics dumping," where researchers may seek more permissive jurisdictions to conduct controversial work, undermining global responsible and transparent research (30).

The regulatory landscape of GGE research cannot be understood independently from embryo research regulation. Because heritable genome editing typically involves the modification of human embryos at early stages of development, national laws governing embryo research directly shape the permissibility and scope of GGE research. Globally, embryo research frameworks vary significantly and reflect diverse cultural, religious, and ethical traditions. GGE is closely linked to embryonic research because editing heritable DNA typically involves modifying embryos at many stages of development. Broadly, there are two principles followed when conducting research involving embryos (31). The first is to ensure edited embryos for research are not implanted in any human patients for investigative purposes (31). The second is the widely accepted 14-day rule that states embryos are not allowed to be cultured beyond 14 days (in countries that allows research on embryos) since it marks the beginning stages of individual development of embryos (32). However, some researchers are calling for the extension of this rule to at least 28 days to allow for more extensive studies (32).

Despite the confusion surrounding GGE research, there are still long-standing research ethics principles that can guide the future applications of GGE in research. For instance, since GGE would

require tissue donation (e.g. embryonic or fetal tissue), adequate consent must be obtained from donors, ensuring they fully understand the nature, purpose, and potential implications of the research (33). Additionally, measures must be taken to ensure donors' privacy as well, especially if their genetic data is made public at any time, Moreover, guidance on research values have been provided by the WHO in 2021. They emphasized that GGE must be guided by ethical values such as promoting well-being, transparency, due care, responsible science, respect for persons, and fairness. In its 2021 recommendations, the WHO called for strong global oversight, including an international registry for genome editing research and mechanisms to prevent unethical or unsafe practices (34). As scientific capabilities advance, there are increasing calls for robust oversight frameworks, not only to govern research but also to guide the potential clinical application of these technologies in a responsible and equitable manner.

6.3.4. Looking towards the future

As germline gene editing continues to evolve, research ethics guidelines and legal frameworks governing its use are undergoing dynamic and ongoing revision. With the rapid advancement of basic scientific research and increased public and professional discourse, there is growing recognition of both the potential benefits and profound ethical implications of altering the human germline. These discussions are prompting policymakers, ethicists, and scientists to continuously reassess existing standards, ensuring they reflect current scientific capabilities, societal values, and ethical considerations. As a result, the regulatory landscape for germline editing remains fluid, with laws and guidelines being updated or newly developed in response to emerging research, evolving norms, and shifting public attitudes. However, as of 2026, many researchers have implicitly agreed to extend the moratorium beyond 2024 as the technology has not reached a point where it can safely be used in humans.

6.3.5. Recommendations

- RECs should ensure that proposals explicitly state whether the GGE is intended for research or clinical application, as the ethical and legal implications differ significantly. RECs should not approve proposals involving clinical GGE, in line with current international and national prohibitions, including the Oviedo Convention and applicable EU regulations.
- RECs should require clarification as to whether the use of embryos for GGE will result in their destruction, particularly where national legislation prohibits such practices or where funding bodies, such as the European Commission, restrict funding for research involving embryo destruction.
- RECs should confirm that proposed GGE research is legally permissible in the country where it will be conducted and does not circumvent national or international bans. They should scrutinize cross-border research arrangements to prevent "ethics dumping" into more permissive jurisdictions.
- RECs should require comprehensive and understandable consent forms from all tissue donors (including embryonic or fetal tissue donors), clearly disclosing the research purpose, risks, and broader implications. They should also ensure appropriate safeguards for genetic data privacy.
- RECs should ensure compliance with the 14-day limit on embryo research, unless otherwise lawfully justified under evolving ethical guidelines, and should enforce a strict prohibition on implantation of genetically edited embryos in human subjects.

- In jurisdictions permitting GGE research, RECs should assess whether proposed modifications are ethically justifiable, for example where they target serious genetic diseases for which no alternative treatments exist.

6.4. Somatic Gene Editing

Somatic gene editing holds immense potential to transform medicine by precisely correcting disease-causing mutations, offering targeted, long-lasting treatments for a wide range of conditions (e.g. sickle cell disease, cystic fibrosis, and muscular dystrophy) (35). Beyond monogenic disorders, it also shows promise in enhancing cancer therapies, engineering immune cells, and combating viral infections like HIV (36). However, this form of gene editing presents many research ethics concerns as an emerging therapy with both high potential and high risks. Because it involves altering genes in non-reproductive cells, it requires rigorous ethical oversight to ensure that interventions are scientifically valid, and participants are adequately protected during clinical trials. As of 2026, there is only one gene-editing therapeutic intervention that has been approved (Casgevy) (37). However, many more similar therapeutics are in various stages of the clinical pipeline, making ethics considerations increasingly urgent to ensure that safety, informed consent, equitable access, and long-term oversight are prioritized as the field rapidly evolves (38).

Research using gene editing technologies, particularly in non-clinical and preclinical settings, is now well-established, with robust protocols and regulatory oversight guiding laboratory-based studies around the world. As such, in the following sections, this guidance document will be describing the key research ethics concerns related to somatic gene editing in clinical settings as well as potential recommendations for RECs to effectively ensure safe and ethical use of these therapeutics in clinical trials and research experiments. It is not the intention to provide an exhaustive list of issues to consider, but to provide an overview of the most important considerations for ethics committees.

6.4.1. Scientific and safety risks caused by somatic editing

Though gene editing offers immense potential for treating genetic disorders and advancing medicine, it also poses significant safety risks that warrant careful consideration. One such safety concern is the risk of off-target effects if gene editing tools unintentionally edit the wrong cells or a wrong section of DNA resulting in harmful mutations or disrupted gene function (14). In certain cases, the gene edits could unintentionally activate cancer-related genes, or oncogenes, or disrupt tumor suppressor genes, which could lead to uncontrolled cell growth and malignancies known as oncogenic events (39). Similarly, there is also a risk of mosaicism, which occurs if the gene editing intervention only successfully edits a portion of the target cells, which could create inconsistent treatment results or low efficiency of treatment (40). Moreover, these safety risks are often irreversible due to the permanent nature of gene editing, making thorough risk assessment even more critical. Broadly, the long-term effects of gene edits as a treatment are not properly understood yet, making it difficult to accurately predict both the potential benefits and consequences of gene editing therapeutics (41).

However, these risks only encompass concerns related to gene editing itself. A gene editing therapeutic presents additional risks if the delivery vector (typically a viral vector) triggers a patient's immune system or causes infection (42). Additionally, delivery mechanisms can contribute to insertional mutagenesis, a process in which the inserted genetic material disrupts normal cellular function by integrating into unintended sites within the genome. This risk is particularly associated

with integrating viral vectors, such as retroviruses or lentiviruses, which may insert near or within oncogenes or tumor suppressor genes, potentially leading to malignancy (43). Non-viral methods, such as lipid nanoparticles or electroporation, may also cause cellular stress, membrane damage, or inflammatory reactions (44).

To help prevent safety risks associated with gene editing therapies, several key strategies must be implemented across all stages of clinical development. These strategies broadly aim to prevent gene editing's safety concerns with thorough preparation or detect emerging risks early, allowing for timely intervention and mitigation should adverse effects arise. Foremost, extensive preclinical studies using the relevant cellular and animal models are essential to demonstrate that the therapeutic is effective at treating its target condition but also has a low frequency of safety risks, such as off-target effects, insertional mutagenesis, or immune reactions. These studies should incorporate comprehensive genomic analyses to assess potential unintended edits or structural variations. Additionally, during clinical trials, continuous monitoring and transparent reporting of results are crucial to promptly identify and respond to emerging risks. This is especially true for severe adverse events, such as sudden death, which may necessitate the early termination of a trial. Furthermore, reporting should include not only routine safety assessments but also deeper molecular profiling of patient samples when possible. Finally, long-term follow-up after the completion of a clinical trial is vital, as some complications, such as delayed oncogenesis or immune-related effects, may not manifest for years. By integrating robust preclinical evidence, vigilant clinical monitoring, and extended post-trial surveillance, gene editing therapeutic research can more responsibly advance from bench to bedside while prioritizing patient safety. Furthermore, it is important to create stricter standards, practices, and considerations for gene editing trials involving vulnerable pediatric populations.

RECs play an important role in assessing the ethical acceptability of gene editing trials, including the adequacy of the supporting preclinical evidence. While RECs do not duplicate the full scientific evaluation conducted by competent authorities, they must consider whether the available preclinical data are sufficiently robust to justify exposing participants to potential risks. For example, REC members may examine whether relevant animal models demonstrate acceptable safety profiles, whether off-target effects have been adequately assessed, whether dose-escalation strategies are justified, and whether long-term toxicity risks have been reasonably addressed. In first-in-human gene editing trials, particular attention may be given to the strength and reproducibility of preclinical findings and the plausibility of the proposed therapeutic mechanism.

REC members also evaluate whether the study design includes appropriate risk-minimization strategies and long-term monitoring plans, and whether the anticipated benefits reasonably outweigh the foreseeable risks. In addition, they assess the adequacy of the informed consent process, ensuring that participants understand the experimental and potentially irreversible nature of gene editing interventions. Although RECs are primarily involved in the initial ethics review and approval of research projects and do not conduct ongoing trial monitoring themselves, they may require periodic safety reports and review substantial protocol amendments during the course of the study.

REC members are responsible not only for ensuring that clinical trials are ethically sound and safe for participants, but also for verifying that studies comply with all relevant (local) national laws,

regulations, and ethics codes. This is particularly important in gene editing trials, where legal and ethical standards can vary widely between countries. As such, REC members should be well-informed about their country's specific regulations on gene editing, which are often published by national drug regulatory authorities, as well as additional laws related to data protection, patient rights, and biosafety. By staying up to date with these legal frameworks, RECs help ensure that clinical trials are both ethically and legally compliant, safeguarding participants and supporting responsible research conduct.

In vivo and *ex vivo* gene editing therapies carry differing safety and logistical considerations, mainly due to differences in how they are processed and delivered. *In vivo* therapies involve delivering gene editing tools directly into the patient's body, such as through intravenous infusion or localized injection (45). This method is generally less invasive and more patient-friendly since it avoids the need for surgical procedures or cell extraction. The single-step nature of in vivo editing reduces manufacturing complexity and time as well as potentially lowering costs (46). Additionally, because it does not rely on personalized cell manipulation, *in vivo* therapy may become more scalable and, thus, more accessible for more patients to receive potentially life-saving care (46). It also offers the advantage of targeting a wider range of organs, such as the liver, brain, or muscle, broadening its therapeutic applications (45). However, it is not without potential risks. The direct delivery of gene editing agents throughout the body raises concerns about off-target effects, immune reactions, and unintended edits in non-target tissues, which can be harder to control than in *ex vivo* settings.

In contrast, *ex vivo* gene editing involves removing a patient's cells, editing them in a laboratory, and then reintroducing them into the body (46). This process allows for more precise control and verification of the edits before the cells are returned, which can reduce some risks of unintended outcomes. However, the procedure itself introduces additional burdens. Patients must undergo chemotherapy or radiation to prepare their bodies for the edited cells, which can cause serious side effects such as immune suppression, organ damage, and infection (47). The process of cell extraction and transplantation is also painful, time-consuming, and carries risks like graft failure or infection (48). Furthermore, *ex vivo* therapies require specialized cell processing facilities and expert personnel, making them significantly more expensive and limiting their availability to well-resourced medical centers. As a result, while *ex vivo* therapies may offer greater control, their complexity and invasiveness pose additional safety and accessibility challenges compared to *in vivo* approaches that REC members should consider (49).

6.4.2. Concerns Involved with Patient Recruitment in Trials

Patient recruitment for clinical trials involving gene editing therapeutics presents a distinct set of ethical and logistical challenges. One of the primary concerns is the vulnerability of the patient population. Many gene editing interventions target severe, life-threatening, or rare genetic conditions (often monogenic in nature) for which there are few existing treatments or often no adequate treatment at all (50). As a result, patients and families affected by these conditions may face greater pressures to enroll in a study, which can compromise the voluntariness of given consent and their decision-making autonomy (51). Although the severity of a condition may create urgency for intervention, it does not ethically permit compromising participant safety. Efforts must be taken to ensure the fairness of the study and prevent exploitation, through what are known as collateral affective benefits, or feelings of hope or altruism that may motivate individuals to participate.(51)

These emotions, though genuine, can cloud judgment and make it harder for patients to fully weigh the risks. Researchers must prioritize the well-being and rights of current patients over speculative benefits for others in the future.

However, another complexity unique to gene editing trials is the absence of a healthy volunteer population in early-phase research. Unlike traditional clinical trials that often begin with healthy subjects to evaluate safety and dosage, gene editing trials typically involve only patients with the targeted condition. This is true for a couple of reasons, such as the lack of direct benefit of a gene editing intervention for healthy volunteers, high risks of unnecessary and irreversible invasive interventions, and the targeted nature of the therapy for correcting disease-causing genes that do not exist in healthy patient populations. This raises challenges in both designing fair recruitment protocols and ensuring equitable access to the trial. Furthermore, because of the high stakes involved and the scarcity of eligible participants, maintaining fairness and avoiding undue inducement or exploitation becomes a critical concern. Such pressure often occurs when the promise of a potentially life-saving therapy exerts strong emotional or psychological pressure on patients, leading them to participate without fully considering the risks or alternatives.

RECs play an important role in ensuring fair patient recruitment though they are not directly in charge of patient recruitment. Instead, a REC member will review the recruitment procedures and materials to ensure that they are both ethical and fair to potential trial participants. For instance, compensation for participants in gene editing clinical trials should be fair, reflecting the time, effort, and potential burdens involved, without being so high as to unduly influence or pressure individuals into participating. As such, it is important for a REC member to assess the voluntariness and vulnerability of participants, especially for rare conditions, and that they are adequately informed of the potential risks and irreversible outcomes of gene editing in humans. Additionally, REC members should mandate independent patient support, where independent patient advocates or ethics consultants are available to help participants understand the study to help safeguard patient autonomy. This would also include reviewing communication material, such as informational brochures and recruitment messages, to prevent misleading language or overpromising of benefits. Finally, RECs should require researchers to communicate clearly about post-trial care and access to treatment (if it is still needed after the gene editing intervention) as well as how results will be shared with participants. If there are cases where RECs are involved in any ongoing ethical re-evaluation or follow-up of studies, they should ensure that consent is an ongoing process and that participants have access to education, information, and the trial researchers both during and after the study.

6.4.3. Informed Consent and Therapeutic Misconception in Trials

These recruitment challenges can give rise to ethical pitfalls during first-in-human trials, such as therapeutic misconception, where participants mistakenly believe the primary purpose of the trial is to provide treatment rather than to conduct scientific investigation, such as to determine if there are any dosage related concerns (too high or too low) or toxicity effects of the intervention (52). Thus, participants may perceive they are receiving personalized treatment rather than contributing to an experimental study. This can also be compounded by the placebo effect, where participants experience perceived or real improvements in their condition simply due to the belief that they are receiving an effective therapy. This effect can be particularly strong in trials involving severe or rare genetic disorders, where patients may feel hopeful or emotionally invested in the outcome (51).

Addressing these challenges requires robust informed consent procedures and a strong commitment to upholding patient autonomy throughout the recruitment and trial process, which involves effective evaluation from RECs.

The researcher's purpose should be to uphold key ethical principles that ensure the safety, dignity, and rights of participants throughout the trial process. Independence is a foundational principle, achieved through oversight by ethics review committees (RECs), institutional review boards (IRBs), or data safety monitoring boards (DSMBs) who serve to review and evaluate the study's design, ethical implications, and progress (53)(54) (55). These bodies help ensure that the research adheres to established ethical standards and that potential risks to participants are minimized. Transparency is equally crucial since transparent reporting of both positive and negative outcomes, as well as long-term follow-up data, fosters trust and allows for the replication and critical evaluation of findings.(56) Lastly, accountability demands that all parties involved in the research, such as investigators, sponsors, and physicians, take full responsibility for the well-being of participants.(56) This includes ensuring that patients are adequately informed about risks, providing appropriate care during the trial, and ensuring that participants' rights are protected. These include the patients' right to be continuously informed about the progress of the treatment, the right to ask questions about the study, the right to privacy and data confidentiality, the right to withdraw from the study, the right to medical care if the procedure is harmful or has unanticipated effects, and the right to receive fair compensation for the trial. Through these ethical commitments, researchers can safeguard the integrity of the research process while respecting and protecting the rights of those who participate in these studies.

Informed consent in gene editing trials should be especially robust, focusing on fostering realistic expectations and ensuring patients are fully informed about available alternatives before participating in a clinical trial. This involves educating participants clearly and thoroughly about the experimental nature of the therapy, its risks and benefits, and what other options exist.(57) Effective strategies include tailoring consent procedures to the patient's level of understanding, recognizing and respecting their values such as altruism or a desire for empowerment, and engaging both patients and their caregivers in the co-development of study protocols. Open discussions about potential side effects, expected quality of life, and clearly outlining the stages at which withdrawal from the trial is possible are also crucial to ethical engagement.(57) Additionally, safeguards must be in place to prevent undue influence from physicians, who may unintentionally pressure patients due to their roles and perceptions as authority figures. When conducting clinical trials involving a pediatric population, ethical considerations become even more complex due to the inherent vulnerability of children. Informed consent procedures must be adapted to account for the fact that minors cannot provide full consent on their own, requiring both parental or guardian consent and, when appropriate, the child's assent.(58) Pediatric trials also raise unique concerns related to independence, as the power dynamics between researchers, parents, and healthcare providers can create pressures that might unduly influence the child's or parent's decision to participate.(58) Transparency remains just as critical, but it must be carefully tailored to avoid overwhelming parents or guardians with complex scientific information, focusing instead on clear and accessible explanations of what participation in the trial entails. Furthermore, ethical review processes, including oversight by RECs and IRBs, must consider the unique needs of pediatric populations, ensuring that any risk is minimized and that potential benefits are in the best interest of the child. In

pediatric trials, the focus should be on safeguarding the well-being of children, ensuring that their participation is in line with their best interests, while also considering the potential for long-term impacts on their development and health (58).

In the context of RECs, members play a vital role in ensuring that before being enrolled in gene editing clinical trials, participants, especially those from vulnerable populations (rare disease communities, pediatric populations, or marginalized groups), must be adequately informed, in order for consent to be specific, informed, unambiguous and freely given. This includes informing participants about all safety risks (short- and long-term) and taking additional measures to dispel potential therapeutic misconceptions. Because these trials often involve patients with severe or untreatable conditions, RECs must closely evaluate how consent materials and processes are designed and delivered as their role is to make sure that participants fully understand the experimental nature of the intervention. RECs ensure that consent forms clearly explain the goals of the trial, the distinction between care and research, all available alternatives to participation, they may also require that information is tailored to participants' comprehension levels and that extra protections are in place for vulnerable populations, such as independent patient advocates or opportunities for patients to discuss their decision outside the influence of clinical investigators. This also underscores the importance of long-term oversight mechanisms. While RECs do not themselves conduct follow-up studies or track real-world outcomes, they play a role in ensuring that appropriate long-term monitoring plans are incorporated into the study design. RECs may require researchers to include post-trial follow-up protocols, safety reporting obligations, and procedures for communicating new risk information to participants. Through continuing review and evaluation of protocol amendments, RECs contribute to ensuring that evolving scientific knowledge and emerging safety data are appropriately addressed.

6.4.4. Social Risks to patients involved in novel GE therapeutics

Additionally, patients may face several social risks, related to equity, access, and discrimination, by taking part in gene editing therapeutic clinical trials that extend beyond individual safety. As a result, individuals who participate in trials or are found to carry certain genetic traits related to disease may face biases in employment, insurance, or in social settings. Similarly, some individuals may be discouraged from participating in clinical trials or undergoing testing due to fears of genetic discrimination (59). To effectively combat these biases on a broader basis, ongoing legal efforts are needed to strengthen protections against structural discrimination and protect patients (60). On the level of the clinical trial itself, effective education about the social risks to patients can help inform them about risks of bias and provide support in cases of discrimination. Additionally, strong data protection mechanisms (e.g. secure data storage, controlled sharing of data, involving data monitoring and safety boards) can also help protect patients' privacy as a way of preventing potential discrimination (61).

It is also vital to note that many advanced therapies, which would include gene editing therapeutics, may be prohibitively expensive, creating a divide where only wealthy individuals or countries can benefit, while marginalized populations are left behind. In worse cases, marginalized communities may be tested on during clinical trials for a gene editing therapeutic but not have access to a treatment once it reaches the market. This raises ethical questions about fairness and the right to benefit from medical innovation, underscoring the need for policies that ensure equitable access to emerging genetic technologies. Hospital exemption and compassionate use programs in the EU can

serve as important pathways to addressing access and equity concerns in gene editing therapies. These pathways allow patients with serious or life-threatening conditions to receive investigational treatments outside of formal clinical trials, particularly when no alternatives exist. By enabling earlier access for individuals who might otherwise be excluded due to geography, socioeconomic status, or trial eligibility criteria, these programs can help bridge gaps in care.

RECs must ensure that patients are fully informed about the potential for genetic discrimination, particularly in areas such as employment, insurance, and social interactions, and that only certain legal protections are in place to safeguard against such biases. They must also ensure that data protection mechanisms are robust, securing participants' genetic and personal information to prevent misuse or discrimination. Although REC members do not play a direct role in determining therapeutic access once a gene editing product is commercially available, they do have responsibilities related to equity within the research context. RECs should promote fair participant selection, ensuring that marginalized populations are neither unjustly excluded from clinical trials nor disproportionately burdened by research risks. In this way, RECs contribute to distributive justice at the level of research participation, even though post-market access decisions lie outside their mandate. This includes evaluating the ethical implications of participation in trials by economically disadvantaged groups, ensuring that they are not exploited or disproportionately burdened. For instance, RECs can also recommend the integration of compassionate use programs and similar pathways that provide early access to investigational treatments for patients who may otherwise be excluded due to socioeconomic factors or geographic limitations. By addressing these ethical concerns, RECs help promote fairness, protect vulnerable populations, and ensure that the benefits of gene editing technologies are accessible to all.

6.4.5. Recommendations

Scientific & Safety Oversight:

- Ensure robust preclinical evidence supports safety and efficacy before human testing. Additionally, ensure that trials provide sufficient health care and insurance to patients during and after the trial.

Mandate long-term follow-up plans to detect delayed complications (e.g. oncogenesis, immune issues). Confirm that proposed monitoring protocols during trials are thorough and include plans for:

- Continuous clinical assessments
- Transparent reporting of adverse events
- Molecular profiling when appropriate
- Evaluate whether researchers have strategies to mitigate risks and justify potential benefits of the intervention.

Trial Design & Patient Recruitment:

- Ensure the trial adheres to all national laws and regulations (gene editing policies, patient rights, biosafety, data protection).
- Review recruitment plans for fairness and transparency, especially for rare and life-threatening conditions. Assess whether voluntariness is preserved despite emotional or psychological pressures. Ensure compensation is fair but not coercive.

Require that recruitment materials:

- Provide multiple sources of information for potential participants (Recommend inclusion of independent patient advocates or ethics consultants during recruitment).
- Use intentionally non-misleading language
- Clearly outline risks and experimental nature of intervention
- Confirm that researchers communicate post-trial care, follow-up, and access to therapy clearly.

Informed Consent:

Require clear, comprehensive consent procedures that:

- Emphasize the experimental nature and irreversible risks (the right to withdraw cannot be applied)
- Explain the difference between research and treatment
- Include alternatives to trial participation
- Promote ongoing consent rather than one-time documentation.
- Ensure that vulnerable populations (e.g. pediatric, rare disease, marginalized) are given extra safeguards.
- Confirm that information is tailored to participant comprehension levels and cultural context.
- Ensure procedures are in place to avoid undue influence by physicians or researchers.
- In pediatric trials, confirm that both parental consent and child assent are ethically handled.

Social Risks & Equity:

- Confirm that participants are informed about potential genetic discrimination in employment, insurance, or social settings.
- Require strong data protection and secure data-sharing protocols to protect participant privacy.
- Ensure equitable access to trial participation, especially for economically or geographically marginalized populations.
- Advocate for policies that support fair access to gene editing therapies post-trial (e.g., via hospital exemptions or compassionate use).
- Evaluate whether trials disproportionately burden disadvantaged communities without guaranteeing access to resulting treatments.

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7. Guideline 4: Artificial intelligence

7.1. Introduction

Artificial intelligence (AI) can be understood, for the purposes of this guidance document, as machine-based systems that are designed to operate with varying degrees of autonomy and that can, for explicit or implicit objectives, generate outputs such as predictions, recommendations, decisions, or content that influence physical or virtual environments (European Parliament and Council 2024; OECD 2024). This broad understanding is useful for research ethics review, because it captures not only prominent contemporary forms of AI, such as machine learning systems and generative AI models, but also a wider range of computational systems that may shape research practices, participant experiences, institutional decisions, and socially significant outcomes. At the same time, major international governance frameworks have emphasized that AI should be developed and used in ways that remain human-centered, rights-respecting, and attentive to fairness, transparency, accountability, safety, and societal well-being (UNESCO 2021; OECD 2024).

AI has become increasingly important in contemporary research both as an object of investigation and as a tool used in the production of knowledge. Researchers may develop, train, test, validate, or deploy AI systems in areas such as healthcare, education, public administration, and security, to name just a few of them. They may also use AI within the research process itself, for example to classify and analyze data, support prediction and decision-making, generate text or images, to assist in literature review and scientific writing, or to generate reasonable hypotheses. These developments create important opportunities for innovation and scientific progress. However, they also raise distinctive ethical concerns, including the risk of bias and discrimination, diminished transparency, weakened human oversight, privacy and data governance challenges, safety and security risks, and questions concerning accountability and responsibility. In addition, the use of AI in research may affect the reliability, interpretability, and integrity of scientific knowledge itself.

For Research Ethics Committees (RECs), these developments create a dual challenge. On the one hand, RECs must assess research *on* AI, including studies in which AI systems are developed, evaluated, or introduced into socially relevant settings. On the other hand, they must also assess research *with* AI, that is, research in which AI functions as a methodological, analytic, or epistemic tool. In both cases, the task of ethics review extends beyond narrow legal compliance. It requires examining whether the proposed training, design, use, and governance of AI are ethically justifiable in light of the potential effects on research participants, affected groups and communities, researchers, institutions, and society more broadly. This includes attention not only to individual harms, but also to structural unfairness, power asymmetries, epistemic risks, and the conditions under which meaningful human oversight can be sustained.

This guidance document is intended to support RECs, research ethics officers, administrators, and researchers in identifying and evaluating these issues in a structured and practically relevant way. It does not aim to replace existing legal or regulatory frameworks, but rather to complement them by highlighting the core ethical questions that arise when AI is developed or used in research. It also builds on current European discussions about how ethics review should adapt to AI-rich research environments. Work in the iRECS project has underlined the need for stronger AI-related expertise and more continuous forms of ethics review, while AIOLIA has shown how general principles such

as fairness, autonomy, safety, and accountability can be translated into operational and reviewable components (Aucouturier and Grinbaum et al. 2023; Aucouturier and Grinbaum 2024; Teo, Kyosovska, and Armengol 2025; Bayerl et al. 2026). The sections that follow therefore distinguish between key areas of concern that are particularly important in the ethics review of AI-related research: non-discrimination and algorithmic fairness, autonomy and meaningful human control, safety, security and well-being, and the implications of AI for research integrity and the changing shape of contemporary science.

7.1.1. The REC's role in the responsible governance of AI research

RECs are not substitutes for technical validators, data protection officers, cybersecurity specialists, or competent regulatory authorities. Their distinctive contribution lies elsewhere: ethically acceptable AI in research cannot be secured by legal compliance or benchmark performance alone. The REC is often the place within an institution where scientific validity, proportionality, participant protection, social consequences, and the conditions of responsible oversight are assessed together. That integrative role matters especially for AI because many of the most important ethical problems appear at the interfaces between domains: between data governance and fairness, between explainability and safety, between human oversight and responsibility, or between efficiency gains and research integrity.

In practice, this means that AI-related review asks RECs to address questions that may once have sat at the margins of ethics review. Is the training data appropriate for the population in which the system will be used? What forms of automation bias or over-reliance are foreseeable? Who is responsible for monitoring drift, failure, or harmful downstream effects after approval? Does the protocol contain a credible plan for human oversight, or only a symbolic reference to 'the human in the loop'? Are there communities that may absorb the burdens of error, exclusion, or surveillance without sharing in the benefits of the research? These are not merely technical or legal questions. They are normative questions about acceptable risk, distribution of burdens, respect for persons, and institutional accountability.

For these reasons, this guidance document treats RECs as bodies that should be able to identify when AI-specific expertise is required, request additional documentation, require proportionate safeguards, and insist on review pathways that extend beyond the first approval decision for dynamic or high-risk systems. This is consistent with recent recommendations from iRECS, which emphasize that AI-related research review requires stronger scientific expertise within or around RECs, and with the broader move in Europe toward more accountable and risk-sensitive AI governance (Aucouturier and Grinbaum et al. 2023; European Commission 2025a).

7.2. Framing the ethics review context for artificial intelligence

7.2.1. What do we mean when we speak of AI?

For the purposes of ethics review, "AI" should not be reduced to a single technical category. In research settings the term may refer to supervised, unsupervised, or reinforcement learning; to computer vision, natural language processing, recommender systems, large language models, world models, multimodal foundation models, predictive analytics, or generative systems; and to tools that operate as classifiers, ranking systems, decision-support systems, conversational agents, content generators, or autonomous optimization systems. The review question is therefore not simply whether a project "uses AI", but what kind of AI it uses, for what task, on what data, with what degree of adaptivity, opacity, autonomy, and specific consequence.

This matters because ethically relevant features vary substantially between AI systems. A static model validated on a closed dataset is different from a continuously updated model embedded in an institutional workflow. A generative model used for brainstorming research questions is different from an AI tool that supports triage decisions in a clinical trial, automates welfare eligibility assessments, or evaluates student performance. RECs therefore need conceptually precise descriptions of the system architecture, intended use, development stage, and interaction context. The AI Act itself reflects this by combining a risk-based framework with categories such as prohibited practices, high-risk systems, general-purpose AI models, and additional duties for specific uses (European Parliament and Council 2024).

A practical definition for REC work is that AI refers to computational systems that infer from data and produce outputs such as predictions, recommendations, classifications, rankings, or generated content that can shape research processes, participants' experiences, or socially relevant decisions. This definition keeps attention focused on probabilistic inference, output, context, and effect rather than on branding or novelty claims alone.

7.2.2. How AI research has shaped the world and may shape the future

AI research has already changed everyday life and institutional practice. It has altered how text, images, and data are processed; accelerated some forms of pattern recognition; and enabled new forms of automation in health care, education, policing, finance, social media governance, and science itself. In research contexts, AI can help analyze large datasets, detect patterns in imaging, draft code, cluster literature, support translation, and generate hypotheses. It may thereby improve efficiency and, in some domains, enable forms of inquiry that would otherwise be infeasible. At the same time, the same features that make AI attractive (scale, speed, adaptability, and data hunger) also amplify familiar ethical concerns: discrimination can occur at scale; security failures may propagate quickly; manipulation can become personalized; and flawed outputs may acquire unwarranted authority because they appear technically sophisticated (UNESCO 2021; OECD 2024).

The likely future impact of AI on research is not only methodological but also institutional and epistemic. AI systems may reorder who can do research, what counts as expertise, how results are justified, and which infrastructures become indispensable. Proprietary foundation models, cloud dependency, unequal compute access, and opaque model supply chains all have implications for scientific autonomy and fairness. The European Commission's work on generative AI in research rightly stresses that AI in science is not just a question of tool adoption but of research culture, integrity, accountability, and the public interest (European Commission 2025a).

For RECs, the future-oriented dimension is important because some AI harms are anticipatory. They involve not only actual current harms, but plausible pathways toward dependency, deskilling, lock-in, or normalization of ethically questionable practices. A good review therefore asks not only whether a system is currently lawful or beneficial, but whether the proposed research contributes to a trajectory that is ethically defensible.

7.2.3. Research on AI and research with AI

A distinction that is central both to the CHANGER MOOC and to this guidance document is the distinction between research on AI and research with AI. Research on AI includes the design, development, training, tuning, validation, testing, deployment, and evaluation of AI systems themselves. Here the AI system is the object of research, and the main ethical questions concern how it is built and introduced. Research with AI, by contrast, refers to the use of AI as a tool in the conduct of research: for instance, for literature review, coding, text production, image generation, data analysis,

participant interaction, or evaluation workflows. Here the AI system is part of the research process, and the ethical questions concern integrity, transparency, authorship, competence, reproducibility, and the reliability of the knowledge produced. Importantly, different ethical issues emerge when doing research with or on AI.

The distinction is analytically useful because it helps RECs identify which ethical issues are primary. If a study develops a predictive model for clinical deterioration, fairness, safety, oversight, and validation are likely to be central. If a research team uses generative AI to summarize literature, draft sections of a manuscript, or assist in qualitative coding, then disclosure, verification, accountability, epistemic quality, and the risk of deskilling become more salient. Many projects involve both dimensions at once. A study may, for example, develop a generative tool for research administration while simultaneously relying on AI-generated content during protocol preparation. RECs should therefore permit mixed classifications rather than forcing a project into only one category.

This distinction also clarifies why AI ethics review cannot be reduced to product safety or data protection review. Research with AI may raise serious integrity issues even where no participant-facing harm is obvious, while research on AI may raise participant and societal risks even where the project's publication practices are beyond any doubt.

7.2.4. Why AI poses distinctive problems for ethics review

AI presents distinctive challenges for ethics review because ethically relevant properties may be distributed across datasets, model architectures, prompts, interfaces, institutional workflows, users, and post-deployment conditions. Risk is therefore not always legible at the point of protocol submission. Data provenance may be uncertain. Model behaviour may be unstable across contexts. Feedback loops may emerge only after deployment. Human oversight may degrade over time as users become more reliant on automation. And harmful effects may be borne not only by identifiable participants, but also by indirectly affected groups who are absent from the study design.

Another challenge is that AI research often crosses conventional governance silos. A single project may raise questions about human subjects' protection, personal data processing, copyright, information security, clinical safety, discrimination, platform dependency, and scientific integrity. Existing institutional structures sometimes fragment these questions rather than integrating them. The result can be a form of ethical under-review in which each office assumes that another office is addressing the core risk. RECs can help counter this fragmentation by requiring protocols to clarify what has been reviewed elsewhere and what remains ethically open.

Finally, AI can make reviewing itself more difficult. Technical complexity, rapid change, uncertain terminology, and commercially mediated infrastructures can make it hard for non-specialists to interrogate system claims. iRECS has shown that this problem is already felt in REC practice and that relying on ordinary review procedures without strengthening expertise leaves committees poorly equipped to scrutinize AI-related research adequately (Aucouturier and Grinbaum 2024).

7.2.5. Legal and governance context

The ethical review of AI research takes place within a rapidly evolving governance landscape. In the European Union, the AI Act entered into force on 1 August 2024 and becomes fully applicable from 2 August 2026, with some obligations applying earlier or later depending on the category, including prohibited practices from February 2025, obligations for general-purpose AI from August 2025, and some high-risk product-related rules from August 2027 (European Commission 2025b; European Parliament and Council 2024). For RECs, the key point is not to act as AI Act enforcement bodies, but to recognize when a protocol touches categories of risk or governance addressed by the Act and to

require researchers to explain how legal duties intersect with their ethical safeguards. (Schmidt, M. W., Bagattini, A., Pfister, J., Martin, D., & Hillerbrand, R. 2026)

The AI Act does not exhaust the relevant framework. Depending on the project, RECs must also be attentive to data protection rules, anti-discrimination law, medical device regulation, product safety, research integrity standards, cybersecurity requirements, sector-specific governance, and institutional policies. At the level of principles and soft law, especially influential sources include the UNESCO Recommendation on the Ethics of Artificial Intelligence, the OECD AI Principles, the Ethics Guidelines for Trustworthy AI, ALTAI, NIST's AI Risk Management Framework and Generative AI Profile, and the European Research Area's living guidelines on the responsible use of generative AI in research (UNESCO 2021; OECD 2024; High-Level Expert Group on AI 2019, 2020; NIST 2023, 2024; European Commission 2025a).

The role of this guidance document is therefore complementary. Rather than restating high-level governance principles in the abstract, it translates them into REC-relevant questions about participant protection, fairness, control, safety, and integrity. In doing so, it also takes seriously a central lesson emphasized by AIOLIA: ethical guidance for AI is most useful when it moves beyond general commitments and is made operational through context-sensitive procedures, clearly assigned responsibilities, and practically usable indicators for evaluation and oversight. AIOLIA's work is particularly helpful in showing that principles such as fairness, human oversight, accountability, and transparency should not be treated as self-interpreting ideals, but as aims that must be specified in relation to the concrete research setting, the actors involved, the stage of the AI lifecycle, and the kinds of risks that may arise for individuals, groups, and institutions. For RECs, this means that ethical review should not stop at asking whether such principles are mentioned in a protocol, but should examine how they are implemented, monitored, and justified in practice (Teo, Kyosovska, and Armengol 2025; Bayerl et al. 2026).

7.3. Research on AI: Non-Discrimination and Algorithmic Fairness

7.3.1. Sources of bias across the AI lifecycle

Fairness problems in AI rarely arise at a single point. They can emerge in data collection, annotation, model design, evaluation, deployment, and institutional uptake. Training data may underrepresent certain groups, overrepresent historical disadvantage, rely on poor proxies, or reflect discriminatory institutional practices. Labels may encode contested or biased judgments. Feature selection may privilege variables correlated with protected characteristics. Benchmark datasets may not represent the population in which the system will be used. User interfaces may encourage uncritical uptake of model outputs, thereby turning moderate statistical bias into severe social harm. A fair ethics review must therefore examine the entire lifecycle rather than asking only whether the final model performs equally well on average (Chen et al. 2023; Koçak et al. 2025).

This lifecycle perspective is especially important in research settings because methodological decisions are often presented as purely technical even when they are value-laden. Decisions about what outcome to predict, which data to exclude, how to define error, and what counts as "ground truth" all have ethical significance. In health-related AI, for example, unequal access to care can distort the data from which models learn. In social data research, historical policing or content moderation patterns may encode structural bias. RECs should therefore ask researchers to explain the social provenance of their data and the normative assumptions built into labels, categories, and success metrics.

Recent literature in medicine and healthcare illustrates how easily fairness failures can become clinically relevant. Reviews by Chen et al. and Koçak et al. show that data imbalance, spectrum bias, site-specific bias, and hidden confounding can systematically disadvantage certain populations, even

where the model appears technically strong in aggregate evaluations. Similar concerns arise far beyond healthcare, including education, employment, and public administration, where population shifts and proxy labels may quietly magnify existing inequalities (Chen et al. 2023; Koçak et al. 2025).
A more explicitly research-ethics-oriented literature sharpens this point further. It has been argued that algorithmic bias should not be treated as an isolated technical defect, but as a socio-technical phenomenon that can emerge from problem formulation, proxy selection, temporal feedback loops, and institutional design choices. Their analysis is especially useful for RECs because it shows why fairness review must reach beyond dataset composition to the normative assumptions built into prediction targets, time horizons, and governance arrangements (Bagattini and Shao 2025).

7.3.2. Fairness metrics and normative trade-offs

There is no single fairness metric that solves all ethical concerns. Statistical parity, equalized odds, predictive parity, calibration, and individual fairness capture different ideas of what it means to treat persons or groups fairly. In some settings these metrics are mutually incompatible. This means that fairness is not a purely technical optimization problem, but a normative choice about which forms of inequality matter most in the context at hand. For RECs, the practical implication is that researchers should not be allowed to claim that a system is "fair" without specifying the fairness objective, why it was selected, what trade-offs it creates, and who bears the residual burdens. In high-stakes settings, committees should expect justification of the chosen metric in relation to the values and harms specific to the use case. A diagnostic tool, for example, may warrant special concern for false negatives in underdiagnosed populations. A triage or ranking tool may require scrutiny of error distribution across protected and vulnerable groups. Where fairness metrics conflict, researchers should explain whose interests are prioritized and why.
This is another area where AIOLIA is instructive. Its work underscores that principles such as fairness and non-discrimination become reviewable only when broken down into practical components, responsibilities, and evidence. An ethics guideline that stops at the word "fairness" without demanding operationalization leaves RECs with little to assess (Bayerl et al. 2026).

7.3.3. Individual and group harms

Fairness failures can produce both individual and group harms. At the individual level, model error may result in exclusion, delayed care, misclassification, denial of opportunity, denial of access to resources, or inappropriate intervention. At the group level, repeated small errors can stigmatize communities, reinforce stereotypes, shift institutional resources away from already disadvantaged populations, or legitimize unequal treatment under the appearance of objectivity. Some harms are direct and immediate; others are cumulative, symbolic, or structural.
Importantly, group harms may occur even where no single participant can show a large measurable loss. This poses a challenge for standard REC reasoning, which often focuses on identifiable participant risk. In AI-related studies, the relevant ethical question may instead concern the distribution of burdens across social groups, including those not directly enrolled in the study. RECs should therefore ask, in a reasonable way, whether the protocol includes impact assessment for affected groups, not merely for recruited individuals.
Recent literature and patient-oriented reviews also suggest that fairness, transparency, and voice affect public trust. Patients and other data subjects are often less concerned with AI in the abstract than with whether it will treat them as substitutable data points, whether it will obscure responsibility, and whether errors will fall unevenly on those who already experience disadvantage (Bashkin 2025).

7.3.4. Human rights, vulnerable groups, and shared values

Fairness review should not be detached from broader human rights and democratic values. The most pressing question is often not whether a model is equally accurate across predefined groups, but whether the research itself is compatible with dignity, non-discrimination, inclusion, due process, and contestability. This becomes particularly important for projects involving children, persons with disabilities, migrants, racialized minorities, linguistically marginalized groups, or socioeconomically disadvantaged communities. In these settings, a technically well-performing system may still be ethically problematic if it is imposed without meaningful consultation, does not permit challenge, or amplifies pre-existing asymmetries in voice and power (UNESCO 2021; OECD 2024).

The language of shared values is helpful here because it links fairness to legitimacy. RECs should ask not only whether a system avoids measurable bias, but whether the protocol is responsive to the values and expectations of the populations whose lives it may shape. Co-design, community consultation, and participatory methods may therefore be ethically important, especially where the social meaning of error or classification is contested. The iRECS and AIOLIA projects both reinforce the importance of context-sensitive ethical interpretation rather than generic principle recital (Aucouturier and Grinbaum et al. 2023; Teo, Kyosovska, and Armengol 2025).

7.3.5. Defining the scope: legal issues versus ethical issues

Many fairness-related concerns also have legal dimensions. Anti-discrimination law, equality duties, consumer protection, and sectoral regulation may all apply. But legal compliance is not identical to ethical acceptability. First, the law may lag behind technical practice or may not address cumulative and group-level harms adequately. Second, ethics review often asks questions about proportionality, respect, trustworthiness, and accountability that go beyond narrow compliance. Third, some legally permitted forms of optimization may still be ethically questionable because they exploit vulnerability, rely on opaque proxies, or offload risk onto groups with less institutional power.

RECs should therefore resist two errors: treating fairness as purely legal and hence somebody else's responsibility, or treating fairness as purely technical and therefore beyond ethical review. The right approach is integrative. Researchers should identify applicable legal requirements, but they should also articulate the ethical rationale for their fairness strategy, including the limits of that strategy.

7.3.6. Recommendations

- Require researchers to describe the full AI lifecycle relevant to the study, including data provenance, labelling, model development, evaluation, deployment context, and monitoring plans.
- Require explicit justification of the fairness objective used in the project. Claims that a system is "fair" should specify the metric, the reason for selecting it, and the trade-offs created.
- Ask for subgroup performance evidence where ethically relevant, especially in studies involving protected or vulnerable populations.
- Require discussion of individual and group harms, including reasonably foreseeable indirect harms to non-participating communities, while distinguishing them from remote or purely speculative risks. Where labels or proxies are socially contested, require researchers to explain their normative assumptions and the possible implications of those assumptions.

- Where risks of exclusion, stigmatization, or structural disadvantage are foreseeable, require participatory input, community consultation, or other context-sensitive forms of stakeholder engagement.
- Do not treat legal compliance as sufficient. Ask whether the fairness strategy is ethically proportionate to the stakes of the use case.
- Ensure that AI-related proposals are reviewed with access to appropriate ethics and domain expertise, either within the REC or through external consultation.4. Research on AI: Autonomy, agency and control.

7.4. Research on AI: Autonomy, agency and control

7.4.1. Meaningful human control

Autonomy questions in AI ethics are often framed in terms of "human oversight", but oversight is meaningful only if it is real, competent, and action-guiding. A human who cannot understand the system's role, cannot challenge its output, or is structurally pressured to defer to automation does not exercise meaningful control. Recent scholarship therefore asks whether human oversight is still possible in practice as systems become more complex, adaptive, and deeply embedded in institutional workflows (Holzinger, Zatloukal, and Müller 2025).

Scott Robbins's analysis is particularly helpful for ethics review because it makes clear that "meaningful human control" is not a single design feature but a family of questions: which humans count as relevant decision-makers, what exactly must be controlled, whether control is substantively meaningful rather than merely formal, and whether control extends beyond outputs to training data, inputs, institutional settings, and avenues of contestation. For RECs, that broader framing is valuable because it discourages the superficial equation of human control with the mere presence of a human operator somewhere in the loop (Robbins 2024). Meaningful human control should also be connected to the allocation of responsibility. In AI research, harms may result from distributed decisions across several actors, including model developers, data providers, platform vendors, deployers, research teams, and institutional users. A protocol should therefore identify who is responsible for anticipating, preventing, monitoring, explaining, and remedying reasonably foreseeable harms. For REC review, a "human in the loop" arrangement is insufficient if no responsible actor has the competence, authority, and resources to intervene when the system fails or produces harmful effects.

For RECs, meaningful human control should be analyzed in relation to the concrete task. Does the AI merely support judgment, or does it effectively structure the decision space? Are users given time, training, and authority to disagree with outputs? Is override possible and documented? Are there incentives that make deviation from AI recommendations costly? These questions matter because nominal "human in the loop" arrangements can conceal real deference to automation.

Meaningful control also has a participant-facing dimension. Research participants and affected persons should not be placed in interactions where they must accept AI outputs or AI-mediated decisions without avenues for explanation, challenge, or human recourse. This is especially important in high-stakes or asymmetrical settings such as healthcare, education, employment, law enforcement, and public administration.

7.4.2. Privacy and data governance

Autonomy is closely connected to informational self-determination. AI systems often rely on large, heterogeneous, and repurposed datasets, which can increase risks of excessive collection, secondary use, re-identification, context collapse, or unjustified inference. Even when data are lawfully processed, researchers should ask whether persons retain meaningful control over how information

about them is mobilized, combined, and interpreted. Privacy in AI research is therefore not only about confidentiality. It also concerns the ethical limits of inference: what may legitimately be inferred about participants or groups from the available data, whether such inferences remain within the purposes participants could reasonably expect, and whether AI-generated conclusions exceed what the data can responsibly support.

RECs should pay particular attention to context. A dataset collected in one relational setting may become ethically problematic when reused in another, especially when sensitive, behavioural, biometric, or health-related data are involved. Generative systems introduce additional concerns because prompts, uploads, and outputs may leak confidential information or intellectual property if researchers use untrusted tools. The European Commission's living guidelines on generative AI in research therefore stress privacy, confidentiality, and intellectual property as central dimensions of responsible use (European Commission 2025a).

Data governance review should cover necessity, minimization, provenance, access control, retention, de-identification limits, vendor dependence, cross-border transfer, and the governance of downstream reuse. It should also ask whether the protocol's promises to participants are compatible with the actual technical and contractual conditions of the AI infrastructure.

7.4.3. Manipulation, dependency, and behavioural steering

AI systems can shape autonomy not only by replacing judgment but by influencing behaviour. Personalization, nudging, conversational design, recommender logic, affective interfaces, and adaptive feedback can steer users' choices, attention, or trust.

In research contexts, this may affect recruitment, consent, adherence, participant behaviour during the study, or the behaviour of researchers themselves. The ethical issue is not simply whether influence occurs, because all interfaces influence behaviour to some extent, but whether the influence is transparent, proportionate, and compatible with voluntary and reflective agency. AI systems should influence people only in ways they can understand, reasonably resist, and evaluate for themselves. For example: RECs should assess whether the AI system's influence on users or affected persons is transparent, proportionate to the legitimate aim pursued, and compatible with individuals' ability to make informed, voluntary, and considered decisions.

This concern extends to dependency. Researchers and institutions may become dependent on AI systems that are hard to audit, difficult to replace, or embedded in routine workflows. Not every form of dependence is ethically problematic; some reliance on technical infrastructure is unavoidable in contemporary research. Dependence becomes ethically or institutionally concerning when it makes independent verification, replacement, refusal, or correction unrealistic; when commercial or technical infrastructures constrain researchers' methodological choices; when switching costs make ethically preferable alternatives practically unavailable; or when institutional expectations pressure researchers to rely on AI despite unresolved risks. RECs should therefore ask not only whether lock-in exists, but whether its degree is proportionate to the study's aims and accompanied by credible audit, fallback, and exit options.

7.4.4. Democracy, equity, and power asymmetries

Autonomy in AI research is not only an individual relation between a user and a system; it also depends on the institutional and infrastructural conditions under which that relation is organized. The primary concern remains the agency of participants, users, and affected persons: whether they can understand, refuse, contest, or seek human review of AI-mediated processes. However, this agency

can be constrained by decisions made by researchers and institutions, especially where research relies on commercial or proprietary AI infrastructures controlled by a small number of platform providers, model vendors, or highly specialized institutions. Such infrastructures may determine what data are processed, what explanations are available, what contestation routes exist, and how easily a system can be replaced. RECs should therefore examine whether commercial dependencies and infrastructural asymmetries undermine the practical autonomy of users, participants, or affected communities.

RECs should consider whether the study reproduces problematic asymmetries between developers and users, institutions and participants, or powerful and vulnerable communities. Equity concerns include language exclusion, disability access, unequal digital and AI literacy, and the differential ability to refuse participation or demand human review. A study can therefore raise autonomy concerns even when consent is formally obtained. The deeper question is whether affected persons have meaningful voice and whether the institutional context permits contestation.

7.4.5. Recommendations

- Require protocols to explain what "human oversight" means operationally: who reviews outputs, with what authority, at what stage, and under what time and workload conditions.
- Ask whether users can meaningfully override or contest AI outputs and whether deviations are institutionally supported rather than discouraged.
- Require a clear data governance plan addressing provenance, necessity, minimization, access control, confidentiality, retention, and vendor dependence.
- Require additional safeguards where AI is used in recruitment, consent support, conversational interaction, or other settings with heightened risks of behavioural steering or manipulation.
- Ask how the protocol addresses digital inequality, accessibility, language exclusion, and differential ability to exercise refusal or contestation rights.
- Where the system may meaningfully shape choices or judgments, ask whether the research design preserves reflective agency for participants, professionals, and researchers.
- Require protocols to assign responsibility for AI-related oversight, intervention, documentation, and remedy. Human oversight should not be accepted as meaningful unless responsible actors have the competence, authority, and resources to act on that responsibility.

7.5. Research on AI: Safety, Security and Well-Being

7.5.1. Safety and robustness

Safety concerns whether an AI system behaves acceptably under reasonably foreseeable conditions. Robustness concerns whether performance degrades gracefully when inputs, environments, or user behaviour change. In ethics review, safety is not exhausted by average performance in a development dataset. RECs should distinguish between adversarial conditions during training or development and adversarial conditions in deployment. The first concerns whether the model has been tested against challenging, biased, manipulated, rare, or edge-case data in order to improve robustness. The second concerns whether the system can withstand real-world attempts to game, manipulate, misuse, or strategically exploit it once it is in operation. Researchers are usually better able to anticipate adversarial conditions during development; adversarial conditions in deployment are often more context-dependent and harder to predict. Nevertheless, researchers should consider reasonably foreseeable forms of misuse, manipulation, and strategic behaviour in light of the intended

use context. The practical importance of these issues is clear from recent healthcare reviews, which stress the need for evaluation frameworks that connect validation, usefulness, transparency, and equity to ongoing monitoring after implementation (Wells et al. 2025; De Micco et al. 2025).
Safety should be judged in relation to foreseeable harm. In some research settings, hallucinations, unstable classifications, or silent failure modes may be minor annoyances. In others, the same technical behaviours may create serious welfare, health, reputational, or legal harms. A REC should therefore ask not simply whether the model is accurate, but what happens when it is wrong, how often those errors are likely to occur in practice, who notices them, and what mitigation pathway exists.
The burden of proof should rise with the stakes of the use case. Studies involving participant-facing decision support, health, behavioural intervention, social scoring, biometric inference, or vulnerable populations should be expected to present more substantial evidence of validation, fallback procedures, escalation pathways, and post-approval monitoring.

7.5.2. Security

AI security includes risks such as model theft, prompt injection, data poisoning, adversarial attacks, membership inference, extraction of sensitive information, and unauthorized access to model inputs or outputs. These are ethical concerns because security failures can harm participants, compromise confidentiality, distort research findings, and undermine trust. In some cases, weak security also converts otherwise proportionate research into unethical research because the residual risk becomes unjustifiable. Security review should be proportionate but concrete. Researchers should describe threat models, access controls, third-party dependencies, incident response, logging, patching, and the division of responsibility between the research team and external vendors. Where systems process sensitive data or are used in consequential settings, ethics review should expect clearer evidence that security has been considered from the design stage onward. Recent reviews emphasize that secure and trustworthy AI in healthcare depends not only on technical protection, but also on governance structures that connect innovation to accountability and ethical foresight (Khan et al. 2025).

7.5.3. Explainability and the need to understand AI

Explainability is sometimes discussed as if it were a universally required property. In fact, what matters ethically is whether the available understanding is sufficient for the specific review and use context. RECs should ask why understanding is needed in the case at hand: to contest decisions, to validate outputs, to detect failure, to assign responsibility, to support informed interaction, or to ensure that the model aligns with domain knowledge. A simple but opaque model may sometimes be more ethically acceptable than a badly explained but deeply consequential system. Conversely, a highly accurate system may remain ethically problematic if its operation cannot be interrogated where explanation is needed for accountability or safety.
The need to understand AI is therefore linked to the role the system plays in the research design. If the output merely suggests low-stakes hypotheses that are later independently verified, deep mechanistic explanation may be less important. If the output meaningfully structures participant treatment, recruitment, moderation, or resource allocation, then interpretability and traceability may become central ethical requirements. Here, AIOLIA's work on operationalizing transparency and accountability is useful because it connects explanation not to abstract intelligibility alone but to practical traceability, communication, and responsibility (Bayerl et al. 2026).

7.5.4. Dual use and misuse

AI research often has dual-use potential. A model, dataset, or method developed for beneficial purposes may later be repurposed for surveillance, deception, discrimination, cyber offence, or other harmful applications. Generative systems add further concerns because they can facilitate scale, speed, and plausibility in the creation of synthetic text, code, images, voice, or video. Dual-use risk does not automatically render research unethical, but it does require anticipatory reflection and proportionate safeguards. RECs should ask whether the protocol includes foreseeable misuse scenarios, whether access to models or data is appropriately governed, and whether publication or release decisions have been ethically considered. In some cases, staged access, redaction of sensitive implementation detail, or stronger governance around reuse may be appropriate. The goal is not to suppress research by default, but to ensure that the pathway from beneficial use to harmful reuse has been taken seriously.

7.5.5. Beneficence and non-maleficence

Classical research ethics principles remain relevant in AI research, but they require translation. Beneficence demands more than speculative claims of innovation or efficiency. Researchers should demonstrate plausible pathways by which the study could generate benefits, for whom those benefits are likely to accrue, and how those benefits compare with foreseeable risks. Non-maleficence requires more than avoiding obvious physical injury; it includes avoiding informational harm, dignitary harm, discriminatory harm, dependency, institutional distortion, and erosion of trust.
Recent practical frameworks, including FAIR-AI and European guidance on AI in science, support a view of beneficence that is inseparable from validation, governance, and post-implementation review. A system that appears promising but cannot be safely integrated, monitored, or contested may fail the ethical test even if its performance metrics are impressive (Wells et al. 2025; European Commission 2025a).

7.5.6. Recommendations

- Require validation evidence proportionate to the stakes of the use case, including plans for monitoring system drift, failure, and harmful unintended consequences after initial approval where relevant.
- Ask what happens when the system is wrong, who detects the error, and what escalation or fallback process is available.
- Require a security section covering threat models, access control, third-party dependencies, incident response, and protection of sensitive data and outputs.
- Where explainability is invoked, require researchers to specify for whom explanation is needed and what kind of understanding is sufficient for the use case.
- Require protocols to address foreseeable misuse or dual-use pathways, especially when models, datasets, or outputs may be repurposed in harmful ways.
- Do not accept vague claims of social benefit as sufficient. Ask who benefits, under what assumptions, and with what distribution of burdens.

7.6. Research with AI: Research Integrity, AI, and the Shapes of Contemporary Science

7.6.1. Research integrity and AI

The use of AI in research practice raises questions that are partly continuous with older integrity concerns and partly new. Long-standing duties of reliability, honesty, respect, and accountability remain in force, but generative AI and other AI tools make it easier to outsource drafting, coding, summarizing, classification, and review tasks in ways that blur the location of judgment and responsibility. The European Code of Conduct for Research Integrity remains a foundational reference, and the European Commission's living guidelines on generative AI in research build directly on it by articulating responsibilities for researchers, research organizations, and funders (ALLEA 2023; European Commission 2025a).

From an integrity perspective, the core question is not whether AI was used at all, but whether its use was transparent, verifiable, and consistent with responsible scholarship. A researcher may appropriately use AI for language support or coding assistance while remaining fully responsible for checking outputs, disclosing substantial use where relevant, protecting confidential material, and preserving the integrity of the research process. Problems arise when AI use obscures provenance, introduces fabricated or inaccurate material, compromises confidential inputs, or erodes the researcher's own control over claims and methods (Vasconcelos and Marušić 2025; Knöchel et al. 2025; Helmy et al. 2025).

A stronger research-ethics literature now gives these concerns sharper contours. Resnik and Hosseini argue in AI and Ethics that the established norms of science remain in force under AI use, but that they require more explicit guidance on bias control, disclosure, stakeholder engagement, synthetic data, authorship, and education. In Research Ethics, Hosseini, Resnik, and Holmes similarly reject blanket bans on large language models in scholarly writing and defend a transparency-oriented disclosure model tied to accountability and fair allocation of credit. Resnik and Hosseini later refine this position in Accountability in Research by distinguishing cases in which disclosure should be mandatory, optional, or unnecessary, a distinction that is highly relevant for REC expectations concerning protocol drafting, analytic assistance, and publication planning (Resnik and Hosseini 2025; Hosseini, Resnik, and Holmes 2023; Resnik and Hosseini 2026).

7.6.2. Research integrity and epistemic principles

Research integrity is not only procedural. It is also epistemic. The use of AI can affect how evidence is generated, filtered, interpreted, and justified. If researchers rely heavily on systems that produce plausible but weakly grounded text, code, or synthetic data, they may degrade the evidential quality of their work even while increasing productivity. Similarly, if AI systems shape the framing of questions, search strategies, coding categories, or hypothesis spaces, then epistemic bias can enter the research process before any explicit result is generated.

Recent work by Resnik, Hosseini, and Hauswald extends this concern by asking how scientific values should be protected as AI systems become more autonomous within research workflows. The more such systems participate in hypothesis generation, evidence ranking, or intermediate evaluative steps, the more important it becomes to preserve identifiable human responsibility, contestability, and alignment with the human values that justify scientific research in the first place (Resnik, Hosseini, and Hauswald 2026).

The emergence of AI agents adds a further layer to these concerns. AI agents used in research, including social and biomedical research, may not only generate outputs but also plan tasks, select tools, interact with datasets, trigger intermediate steps, and make preliminary research decisions. This can support scientific values such as efficiency, discovery, and methodological exploration. At

the same time, it may threaten transparency, epistemic accountability, validity, and respect for participants if human oversight is weak or merely formal. Researchers should therefore remain responsible for defining the aims, constraints, data uses, and acceptable forms of automation rather than treating agentic AI as an independent research actor. Particular attention should be paid to alignment: AI agents used in research should be aligned not only with task-specific goals, but also with scientific standards, ethical norms, participant protections, and institutional accountability.
The relevant concern is not only fraud or fabrication. It is also the more ordinary erosion of methodological vigilance when AI outputs are accepted too quickly because they look competent or save time. The literature increasingly warns that generative AI may challenge established concepts of originality, justification, and scholarly responsibility unless institutions insist on human verification and context-sensitive disclosure (Vasconcelos and Marušić 2025; European Commission 2025a).

7.6.3. Authorship, responsibility, and accountability

A central integrity issue concerns authorship and responsibility. Current journal and editorial guidance is clear on one point: AI systems cannot be authors because they cannot take responsibility for the work, approve the final version, or be accountable for integrity. This is reflected in the current recommendations of the International Committee of Medical Journal Editors and in COPE guidance. Human authors remain fully responsible for the content they submit, including material generated or supported by AI (ICMJE 2025; COPE 2023).
For RECs, the authorship issue is broader than publication policy. It concerns responsibility throughout the research lifecycle. If AI is used to generate protocol language, code, analytic suggestions, participant-facing content, or review summaries, the research team should specify who checks those outputs, how they are checked, and who remains accountable for them. The European Commission's guidance additionally advises against the use of generative AI for assessment or evaluation of scientific content where human judgment is essential, a point of direct relevance to peer review, grant evaluation, and some forms of REC support (European Commission 2025a).
The practical standard should be that AI may support work, but cannot bear responsibility for it. Accountability must remain human, named, and reviewable.

7.6.4. Deskilling and upskilling

AI may both support and erode expertise. On the one hand, tools can help researchers work across languages, automate repetitive tasks, and gain access to analytical capacities that would otherwise be unavailable. On the other hand, habitual reliance on AI may weaken domain judgment, writing ability, coding competence, interpretive skill, or methodological sensitivity. This concern is especially acute for early-career researchers and for institutional environments that normalize speed and output over reflective understanding.
Deskilling is ethically relevant because research quality depends not only on outputs but on trained human capacities. If AI use gradually substitutes for understanding, then the apparent efficiency gain may come at the cost of weaker scholarship and poorer supervision. AIOLIA explicitly identifies over-reliance and deskilling as practical governance concerns, and current research-integrity debates similarly emphasize the need for training and deliberate human competence development rather than uncritical tool adoption (Bayerl et al. 2026; Knöchel et al. 2025).
At the same time, responsible upskilling is possible. Institutions can train researchers to use AI critically, to disclose use proportionately, to validate outputs, to protect confidential materials, and to recognize when AI should not be used. RECs may therefore consider not only whether a protocol uses AI, but whether the research team is demonstrably competent to use it responsibly. In short, AI can

sharpen research practice or quietly hollow it out. The key ethical question is whether researchers use AI as a scaffold for developing and extending expertise, or as a substitute that erodes the skills needed to judge, challenge, and understand its outputs. RECs should therefore look for training, verification routines, and task boundaries that preserve the human competences on which research quality depends.

7.6.5. Missing understanding and black boxes in science

A final concern is that AI can produce useful outputs without yielding meaningful scientific understanding. In some settings, black-box systems may improve prediction while leaving underlying mechanisms opaque. This may be acceptable for certain exploratory or assistive purposes, but problematic when the research aim includes explanation, causal understanding, normative justification, or clinically or socially accountable decision-making. The ethical issue is not that all science must be mechanistically transparent, but that the role of understanding in the study should be explicit and not silently displaced by predictive convenience.

RECs should therefore ask whether the use of AI is compatible with the epistemic aims claimed in the protocol. If a project claims to improve understanding, explanation, or theory-building, yet relies on tools whose contribution cannot be meaningfully interrogated, there may be a mismatch between method and stated aim. Such mismatches can become integrity issues if they are hidden behind inflated claims of innovation or objectivity.

7.6.6. Recommendations

- Require transparent disclosure of substantial AI use in the research process, especially where it affects drafting, coding, analysis, synthesis, image generation, or evaluation.
- Require researchers to specify who checks AI-generated or AI-supported outputs and by what process.
- Treat human accountability as non-delegable: AI systems cannot be authors and cannot bear responsibility for the integrity of the work.
- Require safeguards for confidential, personal, proprietary, or unpublished material before generative AI tools are used in the research workflow.
- Ask whether AI use is compatible with the epistemic aims of the project, including explanation, interpretation, and reproducibility.
- Where reliance on AI may contribute to deskilling, require evidence of training, supervision, or workflow design that preserves human competence and reflective judgment.

7.7. Pulling the ethics review together

The preceding sections are intended to help RECs and researchers structure their ethical assessment rather than to produce an exhaustive checklist. In practice, an acceptable review integrates several questions at once: what kind of AI is involved, what role it plays in the study, who may be harmed, how control is distributed, whether the system is safe and secure enough for the use case, and whether the conduct of research remains transparent, accountable, and epistemically reliable. This integrated approach reflects both the iRECS recommendation to move beyond one-time compliance and the AIOLIA emphasis on operationalizing principles in context-specific ways (Aucouturier and Grinbaum et al. 2023; Bayerl et al. 2026).

7.7.1. Key questions for RECs

Dimension	Core REC question	Evidence to request
System and context	What kind of AI is used, for what task, and with what stakes?	System description; intended use; development stage; deployment context
Fairness	Who may be disadvantaged, and how was bias assessed?	Data provenance; subgroup evaluation; fairness rationale
Autonomy and control	Who is able to question or override the system?	Human oversight plan; recourse and contestation pathways
Safety and security	What happens when the system fails or is attacked?	Validation; monitoring; fallback procedures; threat model
Data governance	Are the data and infrastructure ethically and legally fit for purpose?	Data management plan; vendor and access information
Research integrity	How is AI used in the conduct of research itself?	Disclosure plan; verification workflow; authorship/accountability statement

7.7.2. What researchers should include in the protocol

A protocol involving AI should provide enough information for the committee to judge the ethical acceptability of the system in context. At a minimum, researchers should describe the AI system and its intended role; the data sources and their provenance; the populations represented and potentially affected; the performance and validation strategy; the fairness rationale; the plan for human oversight; the security and incident-response approach; and the conditions of post-approval monitoring where relevant. If generative AI is used in the conduct of the research, the protocol should also explain what was used, for what purpose, what safeguards were in place, and how human verification occurred.

It is often useful for RECs to require a short annex specifically devoted to AI-related ethical and governance matters. Such an annex can prevent the most ethically relevant information from being dispersed across data management, methodology, and dissemination sections.

7.7.3. Red flags

- Vague statements that the project uses “AI” without specifying the model type, task, data, or deployment setting.
- Claims that the system is “fair”, “robust”, or “trustworthy” without evidence, metrics, or justification.
- No discussion of affected groups beyond recruited participants, despite plausible wider social impact.
- Nominal references to human oversight without an operational account of who can review, challenge, or override outputs.
- No plan for monitoring drift, incidents, or harmful downstream effects in dynamic or consequential systems.
- Use of generative AI in protocol drafting, coding, analysis, or dissemination without disclosure and verification procedures.
- Dependence on third-party tools or vendors without explanation of confidentiality, security, access control, or intellectual property implications.

- Overstated claims about benefit or innovation with limited evidence of validation or proportionality.

7.7.4. Cross-cutting recommendations

- Ensure proposals distinguish clearly between research on AI and research with AI, while allowing for mixed cases.
- Ensure that the role of the AI system in the research design is described precisely enough for ethical review.
- Require proportionate evidence on data provenance, fairness, validation, oversight, security, and post-approval monitoring.
- Require a realistic account of human responsibility at every stage of the project, including publication and dissemination.
- Where AI-related expertise is lacking within the REC, seek internal or external expert input rather than defaulting to superficial review.
- Move beyond one-time compliance where the system is dynamic, adaptive, or likely to create ethically relevant effects after initial approval.
- Encourage ethics-by-design and ongoing ethical reflection throughout the project lifecycle, in line with insights from sister projects such as iRECS and AIOLIA.

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8. Conclusion

This deliverable presents the review guidelines developed within the CHANGER project to support researchers and Research Ethics Committees (RECs) in addressing ethical challenges arising from innovative research practices and emerging technologies. The guidance documents focus on four areas: electronic informed consent, gene editing, artificial intelligence, and organoids. Together, they provide practical recommendations and ethical considerations to support consistent, transparent, and well-informed ethics review processes.

Although each topic raises distinct ethical and regulatory questions, several common themes emerge across the review guidelines. These include the need for robust governance frameworks, meaningful stakeholder engagement, appropriate oversight mechanisms, transparency in research practices, and the protection of participants' rights and interests in rapidly evolving technological contexts. The guidance therefore not only addresses topic-specific challenges but also promotes a broader culture of responsible research and innovation.

Taken together, the review guidelines developed within CHANGER aim to facilitate ethically robust research and to support RECs in navigating areas where scientific and technological developments may outpace existing ethical and regulatory frameworks. By providing practical, evidence-informed recommendations, these resources contribute to the project's broader objective of enhancing the quality, consistency, and responsiveness of research ethics review across Europe.

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