



HYBRIDA

Policy brief No.2

Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies

Who is it for?

Policymakers at the European Union (EU) level: European Commission (EC), European Parliament, European Council, Council of the European Union; Policymakers at national, institutional, and funder levels.

Introduction

HYBRIDA developed a conceptual and regulatory framework able to overcome the classic person vs thing dualism covering all entities since Roman Law, by addressing how conceptual, epistemological, and regulatory uncertainties arise in organoid research. The main [outputs](#) of HYBRIDA are the following:

Highlights

1. To enable a reliable assessment of the quality of research reporting, each batch of organoids should be associated with standard information.

2. Scientific Committees must be well-equipped to evaluate the quality of organoid description in a grant application.

3. Two types of informed consent are the most appropriate for organoid research: the dynamic consent and the consent for governance model.

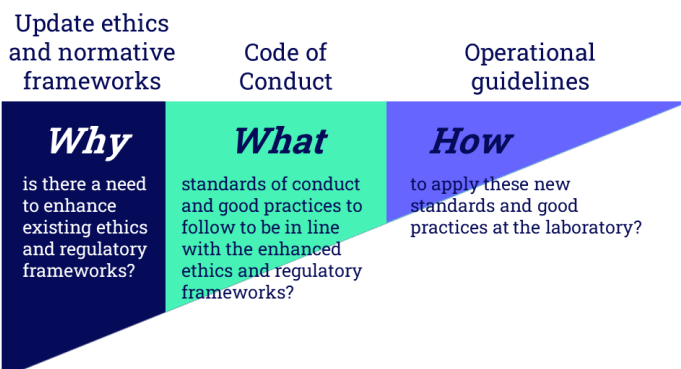
4. Educational and training programs should be developed to enhance ethical literacy among organoid researchers, stakeholders, and the broader public.

5. The latest version of the ALLEA European Code of Conduct for Research Integrity, should be augmented with content relevant to the organoid field.

6. HYBRIDA has compiled specific proposals for action for the agencies and/or actors best positioned to address each regulatory gap or uncertainty.

- [Operational guidelines](#): Recommendations to organoid researchers, designed to streamline certain working procedures according to best practices.
- [Code of Responsible Conduct for researchers](#): Ethical standards of good practice to guide organoid researchers.
- [Enhancement of existing ethics and normative frameworks](#): Compilation of the normative bedrock of the organoid field and analysis of the amount of risk and forms of uncertainty society is willing to accept in relation to different organoids.
- [Supplement to the ECOC](#): Criteria for proper research practice and self-regulation in the field of organoids.

These outputs address three types of questions:



This 2nd HYBRIDA policy brief outlines the main results that are developed in more detail in the outputs listed above.





Operational guidelines

The [HYBRIDA Operational Guidelines](#) aim to help researchers ensure reliable research, development and production of organoids and related technologies and provides advice on assessment and evaluation of organoid research projects.

1. To enable a reliable assessment of the quality of research reporting, each batch of organoids should be associated with standard information (structural, morphological, imaging, functional metadata).
2. Such information should be complemented by metadata related to regulatory aspects that have been complied within the relevant jurisdiction, noting that the recipient researcher may be subject to different regulations.
3. Scientific Committees must be well-equipped to evaluate the quality of organoid description in a grant application, in terms of reproducibility, replicability, and rationality of the proposed research.
4. Research Ethics Committees (RECs) and Research Integrity Offices (RIOs) should be provided with a tool that will ensure transparency and anticipate ethical issues in organoid research and related technologies.
5. The impossibility to anticipate all potential uses that might derive from a given biological sample, in the context of organoid research and related technologies, as well as the difficulty to assess the likelihood of a withdrawal of consent, due to the integration of donated biological samples in unanticipated types of biotechnological constructs, renders two types of informed consent as most appropriate: the **dynamic consent** and the **consent for governance model**.

Points 1 and 2 are covered by [MIAOU](#) (Minimal Information about Organoids and their Use for Researchers); point 3 is covered by [EChOES](#) (Evaluator Checklist for Organoid Experimental Studies). Point 4 is covered by [RICOCheck](#) (Research Integrity Committee Organoid Checklist). Point 5 is covered by [TRUSTED](#) (Donor's Tissue Research Under Secure Transparent Ethical Donation).

Recommendations

- **Anticipate and Address Ethical Concerns Proactively:** Stakeholders in the field of organoids are called to employ an Ethics by Design/Reflexivity, Anticipation, Deliberation (ED/RAD) framework to proactively anticipate ethical concerns, including the social implications of organoid research. MIAOU/EChOES should be used for these purposes.
- **Incorporate Responsible Research and Innovation (RRI) Practices:** Adhere to RRI principles by involving stakeholders early in the research process, promoting interdisciplinarity, including social sciences and humanities, and ensuring that research is conducted for and with society.
- **Ensure Continuous Ethical Engagement:** Maintain ongoing ethical dialogue among researchers, stakeholders, and society, from the initial stages of research to all conceivable applications.
- **Implement Ethical Reflection:** Combine RAD methodology with ED to allow for swift adaptations as ethical considerations and scientific knowledge evolve.
- **Foster Public deliberation and transparent regulation relating to Organoid Development:** Advocate for transparent oversight and regulation over the development and application of organoid technologies including a Public Advisory Committee for Organoid Research (PACOR) inside an existing agency.
- **Facilitate Ethical Literacy and Education in the field of organoids:** Develop educational resources and training programs to enhance ethical literacy among organoid researchers, stakeholders, and the broader public. This includes fostering an understanding of the ethical dimensions of organoid research and the importance of ethical design principles.
- **Commit to respecting the informed consent process:** including the TRUSTED questionnaire, enabling donors to explicitly authorize or prohibit specific potential uses and reuses of their biological material and data. Entrust the PACOR, mentioned above, to assess various consent forms and define the most appropriate consent options, as well as the modalities and consequences of a possible withdrawal of consent for all parties.





Code of Conduct for researchers

The [Code of Responsible Conduct for Researchers on Organoids and Related Fields](#) aims to develop and support Research Integrity (RI) within an ethical research ecosystem. While this framework must be operationalized locally and/or nationally in addition to the EU level, this document offers recommendations for institutions to consider for fostering a culture of research integrity.

It is essential to take into consideration that responsible conduct and integrity are not only a matter of individual behavior but also embedded collective practices, reason for which a systemic view involving research institutions and organizations is needed. Ethics, responsible conduct and integrity need to be part of the project from the planning stages to the end, both for researchers and their institutions, funding agencies and publishers.

The following recommendations should be considered as an [augmentation](#) of the latest version of the All European Academies (ALLEA) European Code of Conduct for Research Integrity (ECoC), with content relevant to the organoid field. The existing, generic framework of the ALLEA ECoC remains relevant to the organoid field.

Recommendations

1. Sensitive domains of RI more specific to organoid research

- **Ethical procurement and use of biological materials:** Guidelines on the ethical procurement of human tissues and cells for creating organoids must emphasize informed consent procedures and respect for donor rights.
- **Transparency and public engagement:** Initiatives to enhance public understanding of organoid research, including its potential benefits and ethical considerations, must foster an informed dialogue between researchers and the public.

2. Good Research Practices in organoid research

- **Data practices and management:** Confidentiality and privacy concerns, related to genetic information derived from organoids, should align with GDPR and other relevant data protection frameworks.

3. Violations of RI specific to organoid research

- **Misuse of organoids in research and therapy:** Potential misapplications of organoid technology, such as creating organoids with sentient potential or for purposes not aligned with ethical guidelines and societal values must be addressed.
- **Inequitable access to benefits:** Risks related to the commercialization of organoids, must be recognized and mitigated to ensure equitable access to advancements in organoid-based therapies and diagnostics.

4. Engagement with Stakeholders

- **Inclusion of Patient Advocacy Groups and Ethical Committees:** Ensure that organoid research addresses patient needs and ethical considerations by engaging with patient and donors advocacy groups and ethical committees in the research design and review process.
- **Regulatory and Legal Frameworks:** Develop specific guidelines for organoid research with collaboration with regulatory bodies, considering the rapid technological advancements and their societal implications.





Regulating organoid and organoid-related activities

While it is beyond HYBRIDA's remit to supply *substantive* answers to questions regarding the regulatory gaps or uncertainties, specific proposals for action for the agencies and/or actors best positioned to address each gap or uncertainty have been produced. This is a [compilation](#) of the acknowledged regulatory issues with the HYBRIDA's proposal.

- 1. Informed consent for organoid research:** The National Ethics Councils (NEC) Forum to determine whether and to what extent oversight practices for research-intended substances of human origin should be harmonized across Member States. Member States to assess domestic regulations governing informed consent for the donation and research use of human tissue and cells.
- 2. Normative Status of Organoids:** See proposals for other regulatory gaps and issues in this list.
- 3. Donor Withdrawals:** The NEC Forum to determine whether and to what extent oversight practices for research-intended substances of human origin should be harmonized across Member States. The NEC Forum and Member States to determine whether donor's right to withdraw consent extends to organoids as well as when the right to withdraw consent begins and ends.
- 4. Possibly Sentient and Conscious Neural Organoids:** No current need for further regulation.
- 5. Information Derived from the Analysis of Donated Cells:** Multi-stakeholder consultation coordinated by the EC to respond to the difficulties organoid researchers face when seeking to exchange organoids, human Embryonic Stem Cells (hESCs), and induced Pluripotent Stem Cells (iPSCs) with institutions outside of the EU/European Economic Area (EEA).
- 6. Material Transfer Agreements (MTAs):** The NEC Forum to determine whether and to what extent oversight practices for research-intended substances of human origin should be harmonized across Member States. The NEC Forum and the Commission to explore the possibility of introducing MTA templates and standard clauses for hESCs, iPSCs, and organoids.
- 7. Patentability of Organoids:** EC to collaborate with the NEC Forum and other named stakeholders to consider a harmonized regulatory definition of a human embryo and a harmonized regulatory definition of that which is produced through human embryo models.
- 8. Organoids and the Regulation of In Vitro Embryo Research:** EC to collaborate with the NEC Forum and other named stakeholders to consider a harmonized regulatory definition of a human embryo and a harmonized regulatory definition of that which is produced through human embryo models.
- 9. The NEC Forum deliberation:** will be based on HYBRIDA reports and further informed by the elaboration by the PACOR proposed at page 2.



Levels of uncertainty and HYBRIDA's responses

Since Roman times, all entities have been categorized and regulated either as persons or as things (subjects or objects). Organoids challenge this dualistic normative framework of health and life science research via three types of uncertainty:

Dualism of organoids and the resulting underlying levels of uncertainty



Conceptual

Persons or things?



Epistemological

Quantitative or qualitative uncertainty? Perhaps mere ignorance?



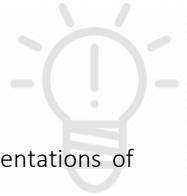
Regulatory

How to merge regulation dealing with persons and things?

HYBRIDA's workplan was structured along these three types of uncertainty, to study how they arise in organoid research, how they can inform the development of a conceptual and regulatory framework that overcomes this dualism, and how to communicate the potential and possible pitfalls of organoid research in ways that convey realistic, instead of hyped, scenarios.

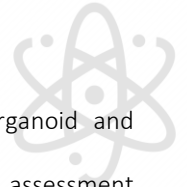
A compilation of HYBRIDA's mapping outputs is provided here (accessible at: <https://hybrida-project.eu/deliverables/>), broken down in the project's deliverables and to the types of uncertainty.

Conceptual



- D1.1 Mythological and artistic representations of chimeras and hybrids
- D1.2 Identification and discussion of conceptual uncertainties relating to organoids, chimeric entities, and hybrids
- D1.3 The challenging history of organoid research and its implications for ontology and ethics
- D1.4 Typology for artificial biological entities

Epistemological



- D2.1: The research landscape of organoid and organ-on-a-chip models
- D2.2 A traditional health technology assessment of organoids and organ-on-chips
- D2.3 Adaptation of health technology assessment -HTA- to evaluate organoids and organ-on-a-chip as emerging technologies in the clinic

Regulatory



- D3.1 Map report of Normative, Research Ethics and Research Integrity frameworks
- D3.2 Comparative analysis



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HYBRIDA Responsible Organoid-based research

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