HYBRIDA

D8.4 : Policy brief

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Executive summary

The HYBRIDA project aims to address how conceptual, epistemological and regulatory uncertainties arise in organoid research and to develop a conceptual and regulatory framework able to overcome the classic person vs thing dualism covering all entities since Roman Law. It also stresses the need to communicate the potential and possible pitfalls of organoid research in ways that convey realistic - instead of hyped - scenarios.

This policy brief contains an overview of the mappings conducted during the first 12 months of the project, as well as the exploration of public attitudes toward organoids conducted within the project's engagement activities. In addition it contains corresponding recommendations for policy makers and other stakeholders involved in the regulation of emerging technologies. Emphasis has been put on the language and its use in science and beyond, and for this reason a socially robust typology of the main concepts used in organoid research has been developed. The typology has the ambition to provide a common language for all stakeholders related to this type of research.

The policy brief also includes a brief description of the mapping of the field and its status in terms of translation, as well as a comprehensive health technology assessment (HTA) of organoids and related technologies (organs-on-chip) including evidence and epistemological issues related to these technologies in clinical settings. Furthermore, it contains a concise description of the conducted systematic scoping review of the debates that have occurred in the past with regard to similar technologies (i.e. induced pluripotent stem cell technologies, embryonic stem cell technologies, gene editing and cloning technologies) regarding the ethical, legal and research integrity-related dimensions of these technologies and their affiliations with organoid research.

Finally, this policy brief offers recommendations to be taken into account in future policy documents on organoids and organoid research, deriving from a series of deliberative workshops organised in order to explore attitudes, values and perspectives on organoid research among representatives from the general public, patients, donors, vulnerable groups and CSOs.

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1 Introduction

As described in the project's Grand Agreement in HYBRIDA's narrative starts from the fact that since Roman law all entities have been categorized and regulated either as persons or as things (subjects or objects). However, this conceptual, epistemological and regulatory dualism is currently being challenged by disruptive research and innovation, among which **organoid research** is a prominent example. The dualistic normative framework pertaining to health and life science research is disrupted by three different kinds of uncertainty. First, **conceptual uncertainty** (ontological uncertainty): how should one conceive entities that cannot be categorized as either persons or things? What are they? Second, **epistemological and methodological uncertainty**: How do we know the characteristics of these entities called organoids? How do we address forms of uncertainty that cannot be evaluated through the use of statistical methods, i.e. risk? In addition to quantitative uncertainty epistemological uncertainty comes in two additional kinds, which can be categorized as qualitative, or strict, uncertainty and ignorance or non-knowledge. In order to develop ethically and socially robust ways of assessing the effects of organoid research and related technologies, there is a need to include these additional forms of uncertainty in the Health Technology Assessment (HTA). Third, **regulatory uncertainty**: this uncertainty emerges because parts of regulatory frameworks concerning the rights and duties of persons have been merged with elements of regulation dealing with the stewardship of objects or things. These forms of uncertainty are of particular importance. The HYBRIDA project aims to address how these uncertainties arise in organoid research and develop a conceptual and regulatory framework able to overcome the aforementioned dualism. From this follows, also, the need to communicate the potential and possible pitfalls of organoid research in ways that convey realistic - instead of hyped - scenarios.

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2 Description of deliverable 8.4

On M18 and M36 of the project's timeline two short policy briefs will be compiled as a concise and comprehensive summary of the outcomes of the mapping and the engagement activities of HYBRIDA.. These policy briefs will primarily target research and government policy makers, as well as other stakeholders with the potential to influence policy making, and provide them the best options and recommendations in this respect.

The 1st policy brief (M18) situates HYBRIDA in the on-going policy context and reports on insights and lessons learned from the first 12 project months. More particularly, it includes an overview of the mappings conducted in WP 1, 2 and 3, the exploration of public attitudes toward organoids conducted in WP4 , and corresponding recommendations. Emphasis is put on the challenges of the communication with the public regarding organoid research as an example of issues that different types of stakeholders need to tackle when engaging in the regulation of emerging technologies. Extensive input and in-depth analysis of the results of the aforementioned mappings can be found in the corresponding reports which have been produced in WP 1, 2, 3, and 4, and will be made publicly available on HYBRIDA's website after the completion of the 1st reporting period of the project (autumn of 2022).

At the end of the project, on M36, there will be a 2nd policy brief issued with recommendations for policy makers deriving from the main outputs of the project; operational guidelines for the field of organoids and organoid-related technologies, a code of responsible conduct for organoid researchers, the possible provision of a supplement to the European Code of Conduct for Research Integrity (ECoC), and, a 'super map' of the gaps in existing ethics and normative frameworks.

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3 Engaging different stakeholder types in the regulation of emerging technologies

3.1. The challenge of identifying fundamental concepts and definitions

The exploration of **conceptual uncertainties** surrounding organoid research and related technologies is useful for deciding on the proper language to be used for communicating this type of technologies with different stakeholders. Conceptual uncertainty refers to the fact that organoids, as other productions of contemporary biotechnology, tend to blur traditional distinctions such as person/thing or object/subject on which common sense, philosophy, and the law rely to categorize entities.

The main issue revolves around **language and its use** in science and beyond. Indeed, "organoid" is only a generic notion that may conjure up various images and that, even in the lab, covers many kinds of entities. Intuitively, "organoid" refers to an entity that is similar to an organ or that has the shape of an organ. However, there are many uncertainties associated with this definition: what does it mean to be similar to something? When does something begin to look like an organ and when does it stop? HYBRIDA's approach on this issue was to provide a brief account of mythological and artistic representations of chimeric and hybrid entities as well as a conceptual mapping of main notions such as person, subject, nature, artefact, life, and so on. Furthermore, research has been conducted into the genealogy of the concept of an organoid, in an effort to discuss some of the uncertainties emerging in the scientific nomenclature.

One important outcome of this work is a **socially robust typology** of the main notions used in organoid research. The typology has the ambition to provide a **common language for all stakeholders** related to this type of research. With organoid research and the development of organoid-related technology, we are likely to see the emergence of ethically challenging entities, or entities that raise specific, new ethical issues. For instance, the debate on stem cells

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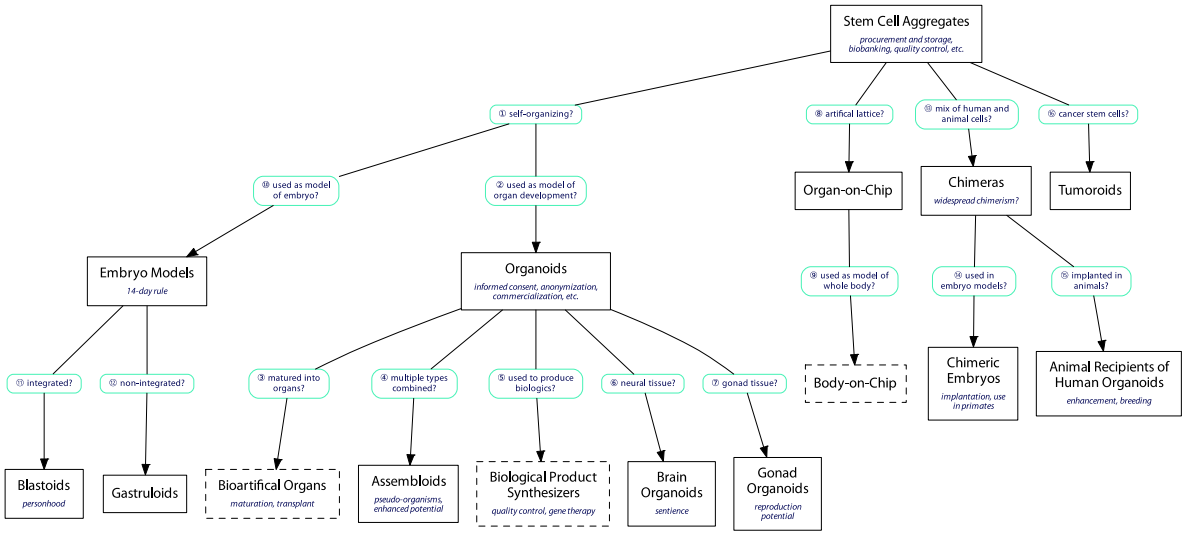
was focused for a long time on stem cell procurement, especially human embryonic stem cells. Now, as the entities in the laboratory turn into more and more complex hybrid structures, the question of the nature (some would say moral status) of the entities developed from stem cells is at the forefront. However, before assuming that new ethical issues emerge, we need to clarify the nature of the entities we are dealing with and discuss how they can be properly labelled. While presenting the main notions, our typology tries to convey the sense of uncertainty peculiar to ongoing research and evolving research objects. The purpose of the typology proposed is to go beyond the scientific uncertainties of ongoing research to chart a territory for bioethical discourse that refers not only to metaphors and theoretical constructs, but to actual biotechnological entities developed in the laboratory.



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3.2 Mapping Organoids and HTA for organoids

In order to reduce epistemological uncertainty in organoid research and produce improvements in impact assessment of organoïd-related technologies, a mapping of the field and its status in terms of translation has been conducted. Furthermore a comprehensive health technology assessment (HTA) of organoids and related technologies (organs-on-chip) has been carried out including evidence and epistemological issues with these technologies in clinical settings. This HTA consists of a "traditional" HTA looking at quantitative evidence from randomized controlled trials (RCTs), the development of an amended HTA and the application of this amended HTA methodology.

The mapping task is ongoing and provides a comprehensive, graphically depicted view of the organoid and organs-on-chip fields, looking at types of organoids, origins of cells, purpose of research, planned and potential translation, as well as trends in the research and patent literature. The mapping of such a field is challenging. An algorithm has been devised for extracting from a huge number of references data and trends of the field, providing a solution to a complex problem. It has been developed through a painstaking merger of computational and biological expertise, and the result can be used again and again to map the field in coming phases.

The HTA part includes a mapping and evaluation of the clinical evidence for the use of organoids that takes the form of RCTs. HYBRIDA had anticipated certain obstacles in the evidence production on organoids, and to confirm this no RCTs have been located through a systematically conducted search, but only some ongoing or planned studies of this kind.

These findings highlight the need to assess organoids and related technologies as applied to the clinic in other ways. Organoids and OOCs are new and emerging technologies (NESTs) that exist mainly as visions and plans for the future. The existing literature on methods for assessing such technologies early has been reviewed, taking epistemological, conceptual, social and ethical issues into account. This work has revealed a surprising number of publications, which have been reviewed and searched for methodological elements that are useful for the project's purposes. In the next phase of the project this methodology will be finished in a report

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and will be ready to be implemented, together with a vision assessment of organoids and OOC as emerging technologies for the clinic.

3.3 Mapping and comparing normative, RE and RI frameworks

3.3.1 The mapping

With the aim to collect and elaborate on the ongoing debates regarding the ethical, legal and research integrity-related dimensions of organoid research and compare them with the debates that have occurred in the past with regard to similar technologies (i.e. induced pluripotent stem cell technologies, embryonic stem cell technologies, gene editing and cloning technologies), a systematic scoping review has been conducted enriched with inputs from a series of interviews with experts (researchers in the field, RECs members, bioethicists, legal experts) . The findings indicate that:

i) the majority of **ethical issues** pertaining to these similar fields of research and technologies converge in organoid research and more acutely in the research on cerebroids and gastruloids:

- Issues related to the **moral status** of a gastruloid, the potential **consciousness** of a cerebroid, and the **naturalness** and **artificialness** of all types of organoids.
- Issues related to harvesting, storing and using for research purposes human-derived material. These last issues relate to both **research ethics**, like debates on the appropriate type of informed consent, and return of results/handling of incidental findings, as well as **research integrity**;how to strike the right balance between openess and privacy of data, FAIRification of data, harmonisation of data and metadata across biobanks, i.e. issues that fall under the umbrella of research data management.

ii) The main issue of the existing **legal framework** is that there is still uncertainty about the potential applications of organoids. Legislation is expected to provide protection and set the rules for scientific research. Legal provisions are general and abstract but, at the same time, very specific in the level of protection they provide. In general, new advancements in health

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research should be examined under the prism of existing legislation by taking into consideration the rapid growing scientific evidence while ensuring the protection of human life and human dignity as their main priority.

3.3.2 Recommendations

There is still no evidence that organoid research will raise any new ethical, legal or research integrity-related issues. However, exactly because it is a field of research that provides a substantial breadth of potential applications, the recognition of organoids' non-exceptionalism might not hold in ten or even in five years from now. Organoids may be exceptional due to the fact that they may provide answers to various questions, related to drug discovery, developmental biology, organogenesis, cognitive research, synthetic biology, bioengineering, and research on chimeras. They may be exceptional due to the fact that this breadth of potential applications renders organoid research a focal point, where virtually all ethical, legal and research integrity-related issues converge. Even if organoid research will prove to be non-exceptional, in the sense described above, it will be challenging to follow the transformations of old ethical and legal issues under a new perspective, as in the case of cloning.[1] Therefore, the following recommendations on Research Ethics, Regulatoryframeworks and Research Integrity could be taken into consideration when regulating organoid and organoid related technologies:

Research Ethics: Although organoid research does not raise substantially unique ethical concerns, it is important to continue to monitor its advancement and potential future applications that may require new and more detailed ethical analyses. The ultimate aim of this mapping has been to provide a guide to support researchers in integrating ethics into their research protocols in order to ensure the public and other stakeholders' trust and to be able through the continuation of their research to provide benefits for humans. Furthermore, and in view of most of the interviewees, it will be extremely helpful if Research Ethics Committees

[1] F. Neresini. "And man descended from the sheep: The public debate on cloning in the Italian press" *Public Understanding of Science* 9 (2000) 359-382.

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have members, or at least, will be able to consult with experts in various fields of research, if not directly related to organoid research.

Regulatory frameworks: New advancements in health research should be examined under the prism of existing regulations by taking into consideration the rapid growth of scientific research while ensuring the protection of human life and human dignity as their main priority. Finally, as the study of Bioethics in which organoids and relevant technologies are included, constitutes a broad area of research with an interdisciplinary character, the development of synergies between scholars and scientists from different disciplines is essential in order to provide answers to the debates raised by organoid research.

Research integrity: Regarding research integrity, we have not identified any particular issues specific to organoid research.

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3.4Co-creating and validating

3.4.1 Conceptions and attitudes towards organoid research by the public

In November 2021, the HYBRIDA project conducted a series of deliberative workshops to explore attitudes, values and perspectives on organoid research among representatives from the general public, patients, donors, vulnerable groups and CSOs. Three deliberative workshops with a total of 51 participants were held in Italy, Greece, and Denmark. Among other valuable results, the workshops ended with a number of recommendations to be taken into account in future policy documents on organoids and organoid research. Table 1 below summarises participants' recommendations regarding: 1) communication and research dissemination, 2) governance of organoids, and 3) ethical implications. There was a strong consensus across the three countries and across participant groups on the need to prioritise:

a) Thorough consent procedures and resources for careful patient information

b) Responsible, objective and transparent research dissemination

c) Ethical oversight and responsible governance structures

d) Strict data security and storage

e) Mitigation measures for unintended consequences and misuse

f) Promotion of equal access to research results and therapies

e) Focus on human value and improvement of the quality of life, not seeking immortality.

Additionally, the participants recommended that given the dynamic and changing nature of organoids and organoid research, there is a need for recurrently updating ethical guidelines, procedures and frameworks for this area.

In this way, the three deliberative workshops send a clear message to policy makers on what to think about in relation to patients, donors, vulnerable groups, and the public in general in policy documents (laws, guidelines, codes of conduct etc.). The workshop results are also relevant for

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other key stakeholders such as organoid researchers, research leaders, ethics committees, funders, communication and press units within research institutions, who have a responsibility for ensuring, e.g., responsible, objective and transparent communication around organoids and organoid research, data security, and a good internal governance structure at suchinstitutions.

3.4.2Recommendations

Table 1. Recommendations for key ethical issues to be addressed[2]

Communication and research dissemination	
Informed consent and patient information	Informed consent procedures and forms, as well as all relevant information provided to patients and donors, should be clear, concise, simple and understandable. Some participants suggest that this kind of information can and should be fully digitalised and available in advance to all interested parties, at any given time. Some participants suggest allocating resources to the specific purpose of patient information, e.g. to secure sufficient time to provide information. Some participants highlight the importance of specifying the purposes of the research or the final use of the materials. The consent should be reshaped if new technologies are discovered, and the destination of donated cells changes. Supervised consent through ethics committee that can advise patients can be considered.
Neutral, objective and transparent research dissemination	Clarity regarding how information on organoids is disclosed. It is important that information on organoids is disseminated in a clear, simple and above all, transparent way by competent authorities in order to strengthen the relationship between scientific research and civil society.

[2] This table as well as the introduction to it builds on the report "D4.3. Public attitudes, understandings and perspectives on organoid research" by Ravn et al. 2022.

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	Information on the potentialities of organoid research (stage of development, progress, potential applications) must be provided to the public to allow citizens to contemplate realistic rather than unrealisable scenarios. The terminology is important. Describing organoids as something human may cause fears and worries, while cell cultures or something similar to medication is more neutral. Transparency regarding stakeholders involved in organoid research (RPOs, RFOs, policymakers, public and private sector)
Governance of organoids	
Continuous evaluation of ethical guidelines	Regular review and evaluation of ethical guidelines. No agreement on how often this should be performed, since the progress of organoid research is unknown. The recommendation is to stay ahead and, as far as possible, avoid addressing potential issues after they become problematic.
Ethical oversight	The presence of ethics committees or public institutions to control how donated material and scientific discoveries are used is very important. The need for public control and transparency is highlighted by some participants in relation to the presence of the private sector in the research field. Some participants suggest a regularly updated list, a database of labs and research institutes that conduct organoid research and the current state of research. Strict regulation of organoid research to avoid misuse and maleficent applications, as those developed in other types of research. Transparency in organoid research and governance is important and will cause the public to feel safe and more trusting.
Governance responsibility	Regarding data collection, management and storage, participants broadly feel more comfortable with the perspective of these being governed by the state(s) and, in general, the public sector.

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	A suggestion is to involve the World Health Organization in the governance or monitoring of organoid research. WHO could be in charge of evaluating and monitoring the research and medical development based on organoid research or participate in a council with various stakeholders and citizens. Some participants warn against governance being too bureaucratic based on a worry that important decisions and actions will lag behind the development.
Adaptation of guidelines in alignment with type of organoids	Use of specific adjustments when needed based on the particular types of organoids, such as cerebral organoids.
Learning and best practices implemented from guidelines on related technologies	It would be advisable to follow the examples of other, well-established, analogous types of research/technologies and procedures, such as stem cell research, cloning, IVF, organ donation/transplantation, blood donation.
Data security and storage	Strict focus on data security and storage. This could be managed based on the consent given in the specific case.
Ethical implications	
Equal access to research results and therapies	The results of biomedical research on organoids must be distributed equally and globally based on the principles of solidarity, sociality and subsidiarity. Guidelines should support a development that will not increase inequality, e.g. by avoiding monopolising and commercialisation resulting in treatments being too expensive or non-accessible to the general public. As organoid research and potential applications focus on improvement of treatments, therapies and, in general, quality of life, it should be made sure that there will be no exclusions to access these benefits for society at large due to origin, sex, sexual orientation, religious orientation, economic status. Organoid research should not increase inequalities.
Human value and course of life	The guidelines should consider our current perception of human values and how organoid research might affect and change this.

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	The extent to which intervention to the course of life is desirable is open to discussion. The goal must be to improve quality of life but without aiming for eternal life and immortality. No participants expressed a desire for immortality.
Intended and unintended negative consequences	The legitimate goal of saving lives, curing disease and improving health must not affect other important ethical issues and harm others, such as the environment or other inhabitants of the earth. Carefully monitor uses to prevent activities against humanity. The guidelines should include rules regarding responsibility in case something goes wrong, e.g. unexpected results of organoid-based treatments.

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4. Next steps

It is acknowledged that there is a need to consider regulation of organoids in the general context of regulating high-impact technologies, while taking into consideration the interested parties' responses and reactions to this kind of technologies. Currently, in the second year/second stage of HYBRIDA, the initial versions of the project's main products are being developed and will be reviewed and revised through further co-creation and validation engagement activities.

A concise description of HYBRIDA's main products is presented below. Figure 3 supplements this description by differentiating between three different types of questions that have been addressed: "*Why is there a need to enhance existing ethics and regulatory frameworks*?", "*What standards of conduct and good practices should be followed to be in line with the enhanced ethics and regulatory frameworks*?", and, "*How should these new standards and good practices be implemented*?".

Description of HYBRIDA's products

- **Operational guidelines for the field:** Recommendations to organoid researchers. They are designed to streamline certain working procedures according to best practices. They should be open to interpretation, do not need to be followed by the letter and they should provide flexibility for unforeseen circumstances.
- **Code of Responsible Conduct for researchers:** Provides ethical standards of good practice to guide researchers in the organoid field, in compliance with the principles of the ECoC: Accountability, Honesty, Reliability and Respect.
- **Enhancement of existing ethics and normative frameworks:** They represent the normative bedrock of the organoid field, should reflect HYBRIDA's objectives and convey the amount of risk and forms of uncertainty society is willing to accept.
- Supplement to the ECoC: Will provide an add-on to the ECoC in the form of a set of criteria for proper research practices and self-regulation in the field of organoids.

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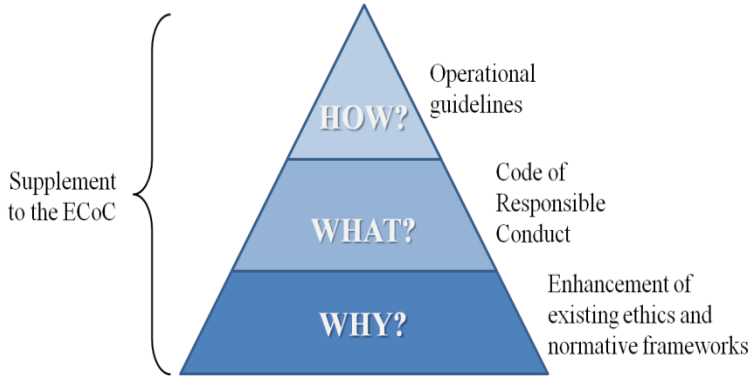

Figure 1: Types of questions addressed

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