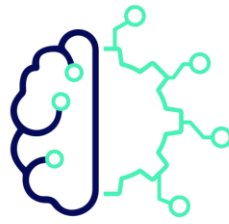




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D 6.2: Regulating organoid and organoid-related activities: Proposals to address regulatory gaps and areas of over-regulation

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HYBRIDA

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

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ABSTRACT:	This report provides specific proposals—co-created with expert stakeholders—to address the regulatory gaps and areas of over-regulation identified and detailed in our previous deliverable (D6.1). It is beyond HYBRIDA’s remit to supply <i>substantive</i> answers to questions regarding the regulatory gaps or uncertainties (i.e., in the form of legal advice, official, legally binding definitions or statutory provisions, or terms and conditions within legal documents). Therefore, in this report, we have produced specific proposals for action for the agencies and/or actors best positioned to address each gap or uncertainty. To inform the deliberations of regulatory actors and agencies, we also detail common arguments and considerations that have been employed within the relevant ethical and legal literature to address these regulatory issues as well as outline the relevant views of expert stakeholders captured during a series of focus groups conducted by WP4.
Keyword List:	advanced therapy medicinal product; biomaterial; blastoids; classification; consciousness; data protection law; dual regulation; embryo models; ethics; gastruloids; GDPR; human cells; human embryo; human pluripotent stem cells; human

	tissue use; in vitro; informed consent; material transfer agreement; medical device; moral status; normative framework; normative status; open science; organ-on-a-chip; organoids in healthcare; organoid regulation; organoid research; ownership; regulatory harmonization; regulation of research with human participants; sentience; stem cell patents; substances of human origin; withdrawal of consent
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1 Overview of the HYBRIDA project

The HYBRIDA project is a 3-year project, funded by the Horizon2020 framework programme. The main aim is to build a comprehensive ethical dimension for organoid-based research and related technologies¹.

An organoid is a self-organised cluster of cells generated *in vitro* from different kinds of stem cells (either pluripotent or derived from some types of adult tissue) through the use of 3D tissue culturing methods. By developing organ-specific cell types and structures, such entities might serve as “three-dimensional culture models” mimicking the structural and, especially, the functional properties of different organs from both humans and non-humans, such as the retina, heart, brain, intestine, kidney, pancreas, liver, inner ear and skin.

From Roman times, all entities have been categorized and regulated either as persons or as things (subjects or objects). However, organoids are entities – and organoid research and organoid-related technologies are examples of disruptive research and innovation – that challenge this conceptual, epistemological and regulatory dualism. More precisely, the dualistic normative framework pertaining to health and life science research is disrupted by three different kinds of uncertainty (**Figure 1**).

First, **conceptual uncertainty (ontological uncertainty)**: How should one conceive of entities that cannot be categorized as either persons or things? What *are* they? How do we *know* the characteristics of these entities called organoids?

Second, **epistemological and methodological uncertainty**: How do we address forms of uncertainty that cannot be evaluated through the use of statistical methods, i.e. risk assessment? This is particularly pertinent where organoids are intended for personalized or precision medicine, where the number of research subjects with a certain characteristic

Dualism of organoids



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?

Figure 1. Levels of uncertainty stemming from the dual nature of organoids.

¹ The HYBRIDA description in this section is reproduced from the project description (HYBRIDA Consortium, 2020, p. 2).



is too low for randomized controlled trials or other statistically based experiments. As precision medicine and related new technologies emerge, evidence-based medicine is challenged to find new footing. Epistemological uncertainty comes in two kinds, which can be categorized as i) qualitative, or strict, uncertainty and, ii) ignorance or non-knowledge. Qualitative, or strict, uncertainty is a form of uncertainty where possible positive and negative outcomes can be identified in advance but, contrary to risk assessments, the statistical magnitude of each possible outcome cannot be estimated. By contrast, ignorance or non-knowledge represents forms of uncertainty where neither possible outcomes nor the statistical magnitude of each can be identified in advance. 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.

HYBRIDA is addressing how these three kinds of uncertainties arise in organoid research and will develop a conceptual and regulatory framework able to overcome this dualism between persons and things. From this follows the need to communicate the potential and possible pitfalls of organoid research in ways that convey realistic, instead of hyped, scenarios.

2 Executive Summary

WP6's aim is to contribute to existing ethical and normative frameworks involving organoid research, organoid-related research (including research in which these models incorporate microfluidics as organs-on-chips), and the clinical applications of organoids and organoid-related technologies. In its previous D6.1 report (Lewis and Holm, 2022b), WP6, through systematic and structured mapping of the normative frameworks governing organoid activities, identified gaps in existing regulatory frameworks as well as those instances where current frameworks lead to over-regulation of organoid activities.²

For a summary of the regulatory issues, gaps, and areas of over-regulation identified and detailed in D6.1, see Table 1.

Where D6.1 sought to map the normative frameworks governing organoid and organoid-related research and applications and thereby identify potential regulatory gaps and areas of over-regulation, this report puts forward specific proposals—co-created with expert stakeholders—for appropriate regulatory agencies and actors to attend to these regulatory issues.

It is beyond HYBRIDA's remit to provide *substantive* answers to questions regarding the regulatory gaps or uncertainties (i.e., by providing legal advice, official, legally binding definitions or statutory provisions, or terms and conditions within legal documents). Thus, in this report, we limit ourselves to identifying and recommending *procedural* mechanisms, structures, and/or processes through which substantive answers to these regulatory issues can then be developed. In most cases, this involves identifying appropriate regulatory agencies and/or actors and providing specific proposals for action for those agencies or actors best positioned to address each gap or uncertainty. In order to inform the deliberations of regulatory actors and agencies, we have also identified and detailed common arguments and considerations that have been employed within the relevant ethical and legal literature when considering how these regulatory issues should be addressed.

In terms of the regulatory issues, gaps, and areas of over-regulation listed in Table 1, the most pressing and substantive in terms of their immediate practical and regulatory implications, and which require significant domain-specific knowledge and expertise to address, are those that concern the following issues (listed in the order that they appear in Table 1):

1. Informed Consent for Organoid Research
2. Normative Status of Organoids
3. Donor Withdrawals
4. Information Derived from the Analysis of Donated Cells
5. Classifying Organoid-based Technologies for Medical Use

² In this report, when we refer to “organoid activities”, this should be taken to include, unless specified, organoid derivation, organoid research, organoid-based technologies, and (potential or planned) clinical translations of organoid research.

6. Organoids and the Regulation of In Vitro Embryo Research

For the regulatory issues associated with these specific topics, the proposals detailed in this report have been co-created with, and validated by, expert stakeholders through a series of Focus Groups organised and conducted by WP4.³

For a summary of the proposals, see Table 1.

In terms of the “Normative Status of Organoids” (see section 4.2), the problem we identified in D6.1 is a general problem in the sense that it is not based on any single piece of legislation or parts thereof. It concerns the tension between treating organoids as “objective” biomaterial, over which those that have donated the required cells and tissue have limited normative claims, and responding to organoids as “hybrids”, thereby granting donors more rights and control over how their donated tissue and/or cells are used. This tension forms the basis of several of the other regulatory issues in this report (see “Informed Consent for Organoid Research” (4.1), “Donor Withdrawals” (4.3), “Sentient and Conscious Neural Organoids” (4.4), “Information Derived from the Analysis of Donated Cells” (4.5), “Material Transfer Agreements” (4.6), and “Organoids and the Regulation of In Vitro Embryonic Research” (4.9)). Thus, it is extremely difficult, if not impossible, to address and resolve this tension in a single regulation. For that reason, the proposals that bear on the question of the normative status of organoids can be found in sections 4.1, 4.3, 4.4, 4.5, 4.6, and 4.9.

The regulatory issues pertaining to the classification of organoid and organoid-based technologies for medical use (see section 4.8) were presented to a focus group organized by WP4, whose members included several regulatory experts (Ravn, Falkenberg and Sørensen, 2024). They were able to adequately answer our questions and address the regulatory uncertainties thereby making it clear that these issues did not require regulatory action. We reached the same conclusion when considering the issues associated with “Sentient and Conscious Neural Organoids”, albeit for different reasons (see section 4.4).

A common feature of the issues associated with the regulation of organoid research is that they arise predominantly because the EU and the EC do not have jurisdiction over the research ethics standards, processes, and practices of individual Member States except where the research pertains to interventions or products explicitly covered by EU/EC regulations and directives, such as clinical trials and research pertaining to medicinal products and medical devices. This means that the EU/EC cannot *directly* regulate the overwhelming majority of organoid and organoid-related research activities that involve the donation and use of human tissue and cells. It is also important to note that the regulatory issues surrounding research-intended human biomaterials cannot be resolved by the proposed EC regulation on the standards of quality and safety for substances of human origin (“SoHO”), which only extends to human

³ In terms of the proposals co-created and validated by stakeholders during WP4’s Focus Groups, full details of participant selection, the views and attitudes expressed by the participants, the format, structure, and data-gathering processes, and the associated ethics assessment and approval can be found in Ravn, Falkenberg and Sørensen, 2024. In this report, we do not directly quote individual participant views, identify individual participants, or mention the capacities in which participants attended the workshop (beyond referring to some of those participants as “organoid researchers”, “industry representatives”, and “regulators”). As a result, ethics approval was not required for this report.



tissue and cells *intended for human application*. Nevertheless, given that the EC (2022) considers the strengthening in harmonization of oversight practices among Member States to be a necessary condition for reforming its current BTC (blood, tissue, and cells) Directives, the problems pertaining to organoid research, particularly those concerning “Informed Consent for Organoid Research” (section 4.1), “Donor Withdrawals” (section 4.3), and “Material Transfer Agreements (MTAs)” (section 4.6), provide good, stakeholder-approved reasons to explore the possibility of encouraging harmonization of the current domestic differences in the formal legal requirements for the research use of human tissue and cells. This is reflected in the proposals in sections 4.1, 4.3, and 4.6. However, as far as the proposals for “Informed Consent for Organoid Research” (section 4.1) and “Donor Withdrawals” (section 4.3) are concerned, the pursuit of regulatory harmonization will necessarily require collaboration and agreement between Member States rather than the “top-down” supply of legislation, provisions, and legal instruments from the EC/EU.

The remaining proposals contained in this report are primarily aimed at the EC and/or individual Member States, and are intended to motivate the provision of specific guidance or legal clarity in the face of specific regulatory uncertainties and/or filling specific gaps resulting from limitations in current regulatory frameworks (i.e., by providing legal advice, template legal documents, official, legally binding definitions or statutory provisions, or terms and conditions within legal documents). Where specific regulatory uncertainties and gaps are concerned, the proposals in this report justify the need for:

- The European Commission to consult with the European Data Protection Board (and other named stakeholders) on specific aspects of GDPR interpretation and, as appropriate, to provide guidance for the research community (sections 4.1, 4.3, 4.5, and 4.6)
- Authoritative – ideally harmonized – national decisions about whether a donor’s right to withdraw consent extends to organoids as well as when the right to withdraw consent begins and ends (section 4.3);
- MTA templates and standard clauses for transfers of human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and organoids i) between different legal entities that make up a consortium funded by the EU/EC; and ii) between EU/EC-funded research projects (section 4.6);
- Authoritative – ideally harmonized – regulatory definitions of a human embryo.

Table 1: Summary of Regulatory Issues and Proposals

REGULATORY ISSUE	SOURCE OF REGULATORY ISSUE	IMPLICATIONS OF REGULATORY ISSUE	PROPOSAL
Informed Consent, Donor Rights, and User Rights			
Informed Consent for Organoid Research	<p>1. Regulatory standards for informed consent do not explicitly include research using human tissue and cells</p> <p>2. Genuine informed consent for the depositing and use of human biomaterials is difficult to obtain owing to unknown future research uses and risks</p>	<p>1. National differences in the formal legal requirements for the research use of human tissue, cells, and associated data</p> <p>2. If valid informed consent is to be obtained, then alternative models of consent should be considered</p>	<p>The National Ethics Councils (NEC) Forum to discuss whether and to what extent oversight practices for research-intended substances of human origin should be harmonized across Member States</p> <p>Member States to assess domestic regulations governing informed consent for the donation and research use of human tissue and cells</p>
Normative Status of Organoids	Organoids complicate the issue of what does and does not form part of the human body and thereby seem to be an exception to regulatory assumptions concerning the “objective” status of donated biomaterial	Question of whether regulators need to reconsider the normative (i.e., legal and moral) status of organoids	See proposals for other regulatory gaps and issues in this table
Donor Withdrawals	Regulations guiding donor withdrawals only extend to the donated cells and tissues. However, donors may have legitimate moral and legal claims over the organoids that have been derived from cells and tissues	Not clear that a donor’s right to withdraw consent extends to the organoids that have been derived from donated cells	<p>i) The NEC Forum to discuss whether and to what extent oversight practices for research-intended substances of human origin should be harmonized across Member States</p> <p>ii) The NEC Forum, Member States, and EC to determine whether a donor’s right to withdraw consent extends to cell lines and organoids and when the right to withdraw consent begins and ends</p>
Sentient and Conscious Neural Organoids	Extensive debates regarding the ethical permissibility of generating or using organoids with sensory, cognitive, and/or consciousness capacities. However, there is no evidence to suggest that the neural organoids that have been established resemble a fully functioning brain or integrated parts of the brain	As neural organoids mature and become more complex, regulatory questions regarding ownership, the normative status of these entities, and user’s obligations to them may arise	None
Information Derived from the Analysis of Donated Cells	Problematic interaction between the regulation of donated cells and cell lines and the regulation of information derived from the analysis of that material	Complicates the exchange of organoids between research institutions	Multi-stakeholder consultation coordinated by the EC to respond to the difficulties organoid researchers face when seeking to exchange organoids, hESCs, and iPSCs with institutions outside of the EU/EEA

Open Science (OS) and Benefit Sharing

<p>Material Transfer Agreements (MTAs)</p>	<p>Process of drafting and agreeing an MTA between two parties based in different jurisdictions is complex owing to multiple international laws and separate multi-national and national laws and regulations</p> <p>The European Commission (EC) has produced standard contractual clauses for data associated with material under an MTA. However, there are no such clauses covering the material component of the MTA</p>	<p>Legal uncertainty as to the applicable legislative and regulatory requirements for MTAs. Organoid researchers also report experiencing significant delays in executing MTAs because institutional legal teams interpret the terms differently</p> <p>Organoid researchers have requested MTA templates and standard clauses for human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and organoids</p>	<p>The NEC Forum to discuss whether and to what extent oversight practices for research-intended substances of human origin should be harmonized across Member States</p> <p>EC to explore the possibility of introducing MTA templates and standard clauses for EU/EC-funded projects</p>
<p>Patentability of Organoids</p>	<p>In Europe, human embryonic stem cells (hESCs) and their derivatives generally cannot be patented. However, in their judgments regarding the non-patentability of hESC lines and their derivatives, the European Court of Justice (CJEU) and the European Patent Office (EPO) employed very broad definitions of a human embryo and a hESC</p>	<p>Organoid researchers are uncertain as to whether Europe's non-patentability restrictions would extend to some blastoids, gastruloids, and resulting technologies</p>	<p>EC to collaborate with the NEC Forum and other named stakeholders to consider a harmonized regulatory definition of a human embryo</p>

Organoid Research and Use

<p>Classifying Organoid Technologies for Medical Use</p>	<p>The European Medicines Agency (EMA) recognizes that there is substantial regulatory scrutiny of those seeking to apply for market authorization for new Advanced Therapy Medicinal Products (ATMPs)</p> <p>In Europe, legally binding definitions, which determine whether a technology can be classed as a medical device or a medicinal product, lack sufficient clarity. Some advice has been provided but it is not legally binding, nor does it reflect the official position of the EC</p>	<p>Extremely difficult for applicants to demonstrate and provide evidence for how they have fulfilled the requirements for marketing authorization of new ATMPs</p> <p>Significant regulatory uncertainty when new technologies do not clearly fall under the current legally binding definitions of a medicinal product or a medical device or when new technologies incorporate elements of both medicinal products and medical devices</p>	<p>None</p> <p>None</p>
<p>Organoids and the Regulation of In Vitro Embryo Research</p>	<p>A prohibition on the creation of human embryos for research purposes is enforced by EU/EC research funding regulations and by national laws in most EU Member States. But an adequate definition of a human embryo is absent in these regulations</p>	<p>Organoid researchers are uncertain as to whether the EC would deem certain types of organoid research – especially that lead to the formation of putative gametes – to be creating human embryos</p>	<p>EC to collaborate with the NEC Forum and other named stakeholders to consider a harmonized regulatory definition of a human embryo</p>



3 Introduction to D6.2

WP6’s primary aim is to contribute to existing ethical and normative frameworks involving organoid and organoid-related research (including research involving organs-on-chips) and the potential clinical applications of organoids.⁴ To this end, we previously identified regulatory gaps in existing normative frameworks as well as identified those regulatory areas where current frameworks lead to instances of over-regulation of organoid and organoid-related activities, including cell/tissue procurement, organoid derivation, modelling, experimental, preclinical, and clinical research, and healthcare application activities (see Lewis and Holm, 2022b).⁵ The central aim of this current report is to provide specific proposals—co-created with expert stakeholders—for appropriate regulatory agencies and actors to attend to these gaps and areas of over-regulation.

3.1 Scope of D6.2

It is beyond HYBRIDA’s remit to provide *substantive* answers to questions regarding the regulatory gaps or uncertainties (i.e., by providing legal advice, official, legally binding definitions or statutory provisions, or terms and conditions within legal documents). Thus, in this report, we limit ourselves to identifying and recommending *procedural* mechanisms, structures, and/or processes through which substantive answers to these regulatory issues can then be developed. In most cases, this involves identifying appropriate regulatory agencies and/or actors and providing specific proposals for action for those agencies or actors best positioned to address each gap or uncertainty. In order to inform the deliberations of regulatory actors and agencies, we have also identified and detailed common arguments and considerations that have been employed within the relevant ethical and legal literature when considering how these regulatory issues should be addressed.

In terms of the regulatory issues, gaps, and areas of over-regulation listed in Table 1, the most pressing and substantive in terms of their immediate practical and regulatory implications, and which require significant domain-specific knowledge and expertise to address, are those that concern the following issues (listed in the order that they appear in Table 1):

⁴ Unless specified, when we refer to “organoids”, this should be understood as including organs-on-chips.

⁵ In this report, when we refer to “organoid activities”, this should be taken to include, unless specified, organoid derivation, organoid research, organoid-based technologies, and (potential or planned) clinical translations of organoid research. When we refer to “organoid-related activities”, this notably includes organ-on-a-chip derivation, research, and any potential clinical applications.

1. Informed Consent for Organoid Research
2. Normative Status of Organoids
3. Donor Withdrawals
4. Information Derived from the Analysis of Donated Cells
5. Classifying Organoid-based Technologies for Medical Use
6. Organoids and the Regulation of In Vitro Embryo Research

For the regulatory issues associated with these specific topics, the proposals detailed in this report have been co-created with, and validated by, expert stakeholders through a series of recent Focus Groups organized and conducted by WP4.⁶

3.2 Outline of D6.2

Section 4 provides specific proposals to address each regulatory gap, uncertainty, or instance of over-regulation listed in Table 1 along with appropriate justifications for each of the proposals.

⁶ In terms of the proposals co-created and validated by stakeholders during WP4's Focus Groups, full details of participant selection, the views and attitudes expressed by the participants, the format, structure, and data-gathering processes, and the associated ethics assessment and approval can be found in Ravn, Falkenberg and Sørensen, 2024. In this report, we do not directly quote individual participant views, identify individual participants, or mention the capacities in which participants attended the workshop (beyond referring to some of those participants as "organoid researchers", "industry representatives", and "regulators"). As a result, ethics approval was not required for this report.



4 Proposals to Address Regulatory Issues, Gaps, and Areas of Over-regulation

In this section, for each of the regulatory issues listed in Table 1, we provide:

1. An outline of the relevant regulatory gap, uncertainty, or instance of over-regulation in question together with an explanation of ethical, legal, classificatory, and practical issues posed by certain organoid and organoid-related activities that highlight these regulatory problems (for comprehensive details of each regulatory issue, see Lewis and Holm, 2022b);
2. An overview of common arguments and considerations that have been employed within the relevant ethical and legal literature to address these regulatory issues (where relevant);
3. A specific proposal for action for those agencies or actors best positioned to address the relevant regulatory gap or uncertainty;
4. Suitable justification, based on regulatory analysis and the mapping of the normative frameworks that govern organoid and organoid-related research and application in D6.1, for why the named regulatory agencies and/or actors should be the ones to substantively address the regulatory issue in question.

In those few instances where what was initially identified as a regulatory gap or area of over-regulation in D6.1 is now—in the light of expert stakeholder insight and/or other evidence—no longer deemed to be relevant, we provide details of such insight and evidence and thereby justify our decision not to provide a specific proposal.

4.1 Informed Consent for Organoid Research

4.1.1 Regulatory Gap

- Current EU/EC regulations regarding standards of informed consent for the donation and use of human tissue and cells do not explicitly cover research-intended uses outside of a clinical trial setting. Directive 2004/23/EC (on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells) only covers the standards for informed consent for human tissues and cells *intended for human applications, manufactured products, and medical devices*. In addition, the Clinical Trials Regulation (EU) 536/2014 does not explicitly cover preclinical, experimental, in vitro, or animal research involving donated human tissue and cells. Furthermore, with the proposed EC regulation on the standards of quality and safety for substances of human origin (“SoHO”), which is set to repeal Directive 2004/23/EC, the proposals contained therein only extend to SoHO *intended for human application*. Thus, where informed consent is specifically concerned, the overwhelming majority of organoid and organoid-related research that involves the donation and use of human tissue and cells would not be covered by legally binding EU instruments. This has led to individual Member States adopting different domestic approaches with national differences in the formal legal requirements for the research use of human tissue and cells.
- Genuine informed consent for the depositing and use of human biomaterials is often difficult (if not impossible) to obtain owing to unknown future organoid and organoid-related research uses and risks. This issue could be addressed by allowing blanket consent for all possible uses or very broad consent for all healthcare related uses. Alternatively, donors could be allowed to provide consent on a regular and ongoing basis for specific organoid and organoid-related research studies and/or organoid-based clinical applications. A third option is to adopt a “consent for governance” framework, whereby, rather than consenting to a general and unspecified range of research uses, or in addition to consenting to a broadly specified range of healthcare-related uses, donors are asked to consent to a specified governance infrastructure (and associated governance obligations).

For full details of these regulatory gaps and uncertainties, see Lewis and Holm, 2022b, section 5.1.1.

4.1.2 Arguments and Considerations in Addressing the Gaps

On the issue of a lack of specific legally binding EU instruments covering the standards of informed consent for SoHO intended for research outside of a clinical trial, it is worth noting that one of the reasons the EC has sought to update its legislation for SoHO intended for human applications is that “Member States



have divergent approaches to oversight that hampers cross-border exchanges of BTC [blood, tissue, and cells]” (European Commission, 2022). If the EC considers the strengthening in harmonization of oversight practices among Member States as a necessary condition for reforming its current BTC Directives, then there may also be a case for encouraging harmonization of the current national differences in the formal legal requirements for the research use of human tissue and cells. As we detail below with regards to the regulatory gaps and uncertainties concerning “Information Derived from the Analysis of Donated Cells” (4.5) and “Material Transfer Agreements” (4.6), the practice of exchanging cells and organoids between research institutions is complex and subject to significant delays. A greater level of regulatory harmonization would, in principle, mitigate at least some of these issues, and thus seeking to develop specific legal instruments harmonized across individual Member States for research-intended SoHO could be a key part of developing easier and more efficient cross-border exchanges of SoHO and organoids in particular.

However, it is important to note that the EU and the EC do not have jurisdiction over the research ethics standards, processes, and practices of individual Member States except where the research pertains to interventions or products explicitly covered by EU/EC regulations and directives, such as clinical trials and research pertaining to medicinal products, medical devices, and other human applications. This means that the EU/EC cannot *directly* regulate the overwhelming majority of organoid and organoid-related research activities that involve the donation and use of human tissue and cells. Therefore, the pursuit of regulatory harmonization with regards to research-intended human biomaterials will necessarily require collaboration and agreement between individual Member States.

With that in mind, one of the proposals detailed in section 4.1.3 below is specifically directed at the National Ethics Councils (“NEC”) Forum, a network made up of the national research ethics bodies from all Member States and formed under EU’s fifth Framework Programme for Research and Innovation to facilitate the exchange of information and best practice in the area of research ethics. As well as providing a space for representatives of Member States’ national ethics organizations to collaborate, the NEC Forum brings together representatives from Associated Countries to the Research and Innovation Framework Programme, the EC’s Directorate-General for Research and Innovation, the European Group on Ethics in Science and New Technologies (“EGE”), the Council of Europe (“CoE”), the United Nations Educational, Scientific and Cultural Organization (“UNESCO”) and the World Health Organization (“WHO”). This makes the NEC Forum the ideal context in which issues concerning regulatory harmonization between Member States and Associated Countries can be initially considered and explored before, ideally, becoming enshrined in domestic legislation.

When it comes to an individual donating their cells and tissue for organoid research or medical applications, consent is the mechanism through which they articulate the boundaries for what they consider to be permissible use of their bodily material (Manson, 2019; Lewis and Holm, 2022a). However, one of the issues facing regulatory approaches to cell/tissue donation for organoid research or organoid-based medical applications is that an individual’s consent to donate often cannot be fully informed because samples are collected for future research uses that may not yet be formulated and, most importantly, the personal data risks are not adequately known. Furthermore, in the case of organoid



research and, more so, in future cases involving clinical trials and clinical application of organoids, there are significant epistemic limits to predicting how and in what ways a donor's cells, tissue, and associated data will be used.

The risks to a donor and the nature of those risks, which, in these instances, are primarily concerned with personal data (European Commission - Directorate-General for Research and Innovation Science in Society, 2012, p. 36), are morally and legally relevant, but assessment of those risks requires specific knowledge about the ways in which biospecimens will be used in organoid research and clinical applications. If an understanding of what the research or translation involves and entails is necessary for consent in terms of determining risk, then consent—of a general and unspecified kind—to donation and subsequent use cannot be obtained (Hofmann, Solbakk and Holm, 2009, 13). In other words, organoid researchers, biobanks, or those manufacturing medical products or devices derived from or using organoids may consider that a donor's initial consent extends to or entails specific uses unforeseen at the time of obtaining initial consent, but there is no warrant for such an extension.

One way of addressing the risks associated with personal data is to obtain complete anonymization of donated human materials and any associated personal data. However, advances in high throughput genetic sequencing and “big data” research have led some to question the practical feasibility of achieving full anonymization (Lowrance and Collins, 2007; Mostert et al., 2016; Kasperbauer et al., 2018, Lensink et al., 2020) as well as the value of complete anonymization for those patients who are also research participants (Eriksson and Helgesson, 2005, Lensink et al., 2020).

Faced with the challenges of obtaining genuinely informed, general, and unspecified consent and the issues concerning anonymization in an age of big data and genetic sequencing, which is regularly applied in organoid-based research, there is a case to be made for the regulatory adoption of alternative consent frameworks, of which there are five main general approaches (with associated variations/specifications thereof):

1. Blanket consent for all possible research uses;
2. Broad consent for all healthcare-related uses;
3. Specific consent for a single, specified use;
4. Case-specific consent (including dynamic consent and meta-consent) when human cells and tissue are intended for multiple downstream research uses and/or clinical applications (see, e.g., European Commission - Directorate-General for Research and Innovation Science in Society, 2012, pp. 51-2, 57-8; Lewis and Holm, 2022a); or
5. Rather than consenting to a general and unspecified range of research uses, or in addition to consenting to a broadly specified range of healthcare-related uses, donors are asked to consent to a specified governance infrastructure (and associated governance obligations)—“consent for governance”—the purpose of which is to decide on the use of the donated material if and when new questions arise after the initial consent is given (see, e.g., Boers and Bredenoord, 2018; Lensink et al., 2020).

All five general approaches to informed consent have their own strengths and weaknesses, and the relative pros and cons of each model have been extensively debated in the fields of bioethics and research ethics for the past twenty years (for further details, see Lewis and Holm, 2022a).

In terms of their principal limitations, blanket and broad consent delineate types of material risk and benefit disclosure that fall below the appropriate standard for *genuinely* informed consent and also downplay donor autonomy to the extent that they limit downstream opportunities for donors to control which research projects and clinical applications can permissibly use their tissues, cells, and associated organoids (O'Neill, 2004; Hanson et al., 2006; Karlsen, Solbakk, and Holm, 2011; Sheehan, 2011; Lewis and Holm, 2022a). By contrast, critics have argued that case-specific consent, including dynamic consent and meta-consent, risks impeding the utility of research, for example, by creating delays, by diverting research resources to consent acquisition, and through the increased likelihood of donor unresponsiveness (Helgesson, 2012; Manson, 2019; Mikkelsen et al., 2019).

A consent for governance framework aims to deal with the problem of obtaining genuinely informed individual consent without resorting to case-specific consent by combining ongoing collectivized ethical oversight and active research participant involvement (Boers and Bredenoord, 2018; Lensink et al., 2020). Depending on the case and context, participant involvement can consist of, on the one hand, informing donors about planned, ongoing, and finalized projects, or, on the other hand, groups of donors or the wider public engaging directly, deliberatively, or representatively in the design and continuous adaptation of research governance (Boers and Bredenoord, 2018; Boers, van Delden, and Bredenoord, 2019). Within a consent for governance framework, not only do participant engagement and ethical oversight function as safeguards to ensure that the risks associated with a research project are managed and the interests of different stakeholders are taken into account, but also the governance body can contribute to decisions about which research activities require individual donors to provide new consent (O'Doherty et al., 2011).

From a regulatory perspective, perhaps the most pertinent challenge to the adoption of consent for governance within the context of organoid research is that a participant's consent to such a framework would not, in and of itself, form a legal basis for consent to data processing under the GDPR (EU) 2016/679. Given that sequencing techniques are routinely applied in organoid research to reveal the donor's genetic make-up, given that the risks to donors with organoid research are primarily concerned with personal data, and given that several other regulatory gaps and uncertainties discussed in this report turn on the correct interpretation or operationalization of the GDPR (see sections 4.3, 4.5, and 4.6), there is a need to ensure that there is a legal basis for a research project to process a participant's personal data in order to be compliant with the GDPR. If this legal basis is donor consent, then a consent for governance framework cannot, in and of itself, make the processing of a donor's data GDPR compliant.

From an ethical perspective, one of the downsides to the consent for governance model is that, like blanket and broad consent, it can limit a donor's individual autonomy in terms of the control they have over which research projects can use their donated biomaterial downstream of the initial consent (Lewis and Holm, 2022a). As Prainsack and Buyx (2013) acknowledge in their case in support of the model of consent for governance, a governance model comes at a cost. Specifically, it requires a participant to



voluntarily accept the risk that their ability to exercise their autonomy over how their donated biomaterial is used may be limited, and that this risk, therefore, comes with a degree of uncertainty. Simply put, depending on, for instance, whether commercial interests are involved, whether organoid research stands to yield participant health benefits, or whether a research project has controversial or culturally sensitive aims, the governance body may decide to allow individual donors to consent to these new, and previously unforeseen, uses of their donated biomaterial. But this isn't guaranteed. Instead, participants may be merely informed of these new developments and, if applicable, afforded an opportunity to withdraw their consent (though whether a participant is entitled to withdraw is itself a matter of regulatory uncertainty as we discuss in section 4.3).

Thus, even though, at a recent HYBRIDA focus group (Ravn, Falkenberg and Sørensen, 2024), stakeholders expressed their support for a consent framework that combines a model of dynamic consent with consent for governance, such a framework would be incoherent, at least in principle. Case-specific consent, which would be one of the options under a dynamic consent model, cannot be guaranteed within a governance-based framework (for further details, see Lewis and Holm, 2022a).

4.1.3 Proposals

1. Given the concerns that organoid researchers have raised regarding the transfer of organoids between institutions (see “Information Derived from the Analysis of Donated Cells” (4.5) and “Material Transfer Agreements” (4.6)), we propose that the National Ethics Councils (NEC) Forum considers and explores the possibility of introducing greater levels of regulatory harmonization in the domestic legislation of Member States and Associated Countries for substances of human origin (SoHO) specifically intended for research.
2. Until such time as the regulatory standards of informed consent for research-intended SoHO become harmonized across Member States, we propose that individual Member States should consider whether their domestic regulations governing informed consent for the donation and research use of human tissue and cells are adequate given the challenges that organoid and organoid-related research present to obtaining *genuine* informed consent. In addition, given that the risks associated with future organoid research undisclosed and/or unforeseen at the time donation is made (and consent is sought) are primarily concerned with personal data (European Commission - Directorate-General for Research and Innovation Science in Society, 2012, p. 36), we also propose that the European Commission should consult with the European Data Protection Board to determine whether current domestic informed consent regulations covering the donation and non-clinical-trial research use of human tissue and cells are in line with the GDPR.

4.2 Normative Status of Organoids

4.2.1 Regulatory Gap

- Current regulation of donated cells and cell lines operate on the assumption that deposited biomaterial and any derivatives are “objective” material (i.e., material that is no longer significantly part of the donor’s body such that they have severely limited moral and legal claims over that material). However, as a matter of both principle and practice, organoids complicate the issue of what does and does not form part of the human body thereby calling into the question their categorization as purely “objective” material.⁷ Thus, there is a question of whether the normative (i.e., legal and moral) status of organoids needs to be (re)considered at the regulatory level.

For full details of these regulatory gaps and uncertainties, see Lewis and Holm, 2022b, section 5.1.2.

4.2.2 Arguments and Considerations in Addressing the Gaps

Current regulation of donated cells and cell lines operate on the basis that biomaterial is deemed to be “objective” material (Boers et al., 2018; Boers, van Delden and Bredenoord, 2019), that is, material that does not have *intrinsic* normative value yet possesses instrumental value such that it can be used in research and human applications.

In one sense, organoids seem to affirm this “object” paradigm (Gaillard, Pence, and Botbol-Baum, 2021). Although organoids are, in part, defined by their self-organizing capacities (Lancaster and Knoblich, 2014; Vogt, Gaillard, and Green, 2023), their development requires the manipulation of donated cells or tissues and considerable expertise, effort, and investment applied to those biospecimens (Boers et al., 2016; Bartfeld and Clevers, 2017). They are also instruments that serve scientific and, potentially, clinical purposes (Bartfeld and Clevers, 2017; Bredenoord, Clevers and Knoblich, 2017). In addition, if clinical translation proves to be successful, then organoid-based medicinal products and devices could become commercially available.⁸

⁷ This claim can also be said to apply to all cultured human cells, including tumour cells and immortalized cell lines.

⁸ Some commentators have argued that if donated biomaterial is purely “objective”, then it should be permissible to treat that material as a commodity that can be exchanged in the private domain (Erin and Harris, 2003; Wilkinson, 2011; Hoeyer, 2013). By contrast, current regulations operate on the principle that because donated cells and cell lines have been gifted, they should not give rise to financial gain (Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, 1997, Article 21).

At the same time, the relationship between a donor and organoids derived from their biospecimens can have moral value for functional, genetic, and meaning-based reasons (Boers et al., 2018; Boers, van Delden and Bredenoord, 2019; Lewis and Holm, 2022a).

Firstly, as organoid researchers have acknowledged, organoids relate to the bodily integrity of donors in the sense that they represent the (dys)functioning of donors' bodies (Lancaster and Knoblich, 2014).

Second, organoids relate to the personal identity of donors. For instance, given that sequencing techniques are routinely applied, organoid-based research is likely to reveal the donor's genetic make-up. This requires a lawful basis for data processing in addition to informed consent to research participation. Not only can genetic sequencing generate study-specific information about a donor's present medical conditions, but it can also uncover findings unrelated to the study question, such as a donor's risk of hereditary disease derived from the presence of certain genetic risk or protective factors (Boers et al., 2016; Bartfeld and Clevers, 2017).

Thirdly, the results from the analysis of donated cells and tissue and subsequent experimental and clinical research with organoids derived from those cells can shape and reshape the meanings and attitudes that donors attribute to their disorders. For that reason, organoids can be perceived to form both a literal and a symbolic representation of donors and their bodies (Boers, van Delden and Bredenoord, 2019; Lewis and Holm, 2022a). Empirical studies have also shown that research participants perceive a value-based connection to their organoids and, more importantly, that the strength and qualitative nature of that connection depend on the type of organoid derived from their cells (e.g., stronger connections would likely exist for neural and gonadal organoids) (Boers et al., 2018; Bollinger et al., 2021; Lensink et al., 2021).

Given the current stage of organoid derivation and research, some donors may relate to organoids derived from their biospecimens only as tissue samples or living cell lines (Boers et al., 2016; Bredenoord, Clevers and Knoblich, 2017; Lewis and Holm, 2022a). However, as empirical studies indicate, such relations are likely to become increasingly complicated and the boundary between organoid and body increasingly blurred when, as researchers anticipate, organoids become increasingly more mature and complex (Hyun, 2017; Boers, van Delden and Bredenoord, 2019) and when certain models, e.g., recent human embryo models, offer the possibility of more advanced development and thereby begin to challenge legal definitions and currently accepted regulatory standards (see, e.g., Rivron et al., 2023).

There is, thus, a tension between categorizing and treating organoids (and, indeed, cultured human cells, including tumour cells and immortalized cell lines) as "objective" biomaterial (i.e., as biotechnological artefacts) over which those that have donated cells and tissue have limited moral and/or legal claims, and responding to them as, in a sense, "hybrids" (Boers, van Delden and Bredenoord, 2019) whose status is such that donors should be accorded more rights and control over their use than is currently afforded by regulations governing donated cells and cell lines (Lewis and Holm, 2022a).

As is the case with the issues regarding informed consent when donating human tissue and cells for non-clinical research purposes (see section 4.1), and as we shall explain in the context of "Donor Withdrawals"(4.3), the question of the normative status of organoids highlights a longstanding debate in

bioethics regarding the tension between respecting donor autonomy and promoting scientific utility (for further details regarding this debate, see Lewis and Holm, 2022a).

4.2.3 *Proposals*

At a very general level, the question of the normative status of organoids seems simple enough: Should regulators treat organoids as “objective” biomaterial or should they respond to organoids as “hybrids” and thereby grant donors more rights and control over how their donated tissue and/or cells are used?

This question arises in the contexts surrounding many of the identified regulatory gaps, uncertainties, and areas of over-regulation discussed in this report (see “Informed Consent for Organoid Research” (4.1), “Donor Withdrawals” (4.3), “Sentient and Conscious Neural Organoids” (4.4), “Information Derived from the Analysis of Donated Cells” (4.5), “Material Transfer Agreements” (4.6), and “Organoids and the Regulation of In Vitro Embryo Research” (4.9)). However, how that question is addressed in these different contexts will depend on a number of factors, including:

- The epistemic state of the research
- Whether the research is dependent on biomaterials that have already been donated or whether it will make use of new material that has not yet been donated
- The diversity in the origin of the biomaterial being used to develop organoids and the diversity in the origin of the organoids being used in subsequent research (e.g., the dependency of the field of organoid development and research on a limited pool of “standard” or “paradigmatic” cell lines versus activities seeking to develop and use patient-specific organoids)
- The type, nature, and function of the organoid or model being developed and used
- The current regulation of different types of research
- The principled and promised anticipations about how specific types of research might or will develop in the future.

The presence of, and interactions between, all these factors in different organoid research contexts not only impede any principled attempt to answer the question of the normative status of organoids at the general level, but also make the successful governance of organoid research practices according to a single principle or standard extremely unlikely.

Having considered the regulatory gaps and uncertainties as they pertain to different organoids and organoid activities (see 4.1-4.9), it is clear that regulatory proposals that bear on the question of an organoid’s normative status require a considered appraisal of how the previously mentioned factors contribute to the state, practice, and regulation of specific forms of organoid research. Thus, specific proposals will be presented in 4.3, 4.4, 4.5, 4.6, and 4.9.

4.3 Donor Withdrawals

4.3.1 Regulatory Gap

- Given that regulators have not considered the ways in which organoids may be an exception to regulatory assumptions concerning the “objective” status of donated biomaterial, regulations guiding donor withdrawals only extend to the donated cells and tissues under certain conditions. It is not clear that a donor’s right to withdraw consent extends to the organoids that have been derived from those cells. In addition, there is disagreement about the extent to which cell donors can withdraw their cells, especially if turned into a cell line.

For full details of these regulatory gaps and uncertainties, see Lewis and Holm, 2022b, section 5.1.3.

4.3.2 Arguments and Considerations in Addressing the Gaps

As detailed in Lewis and Holm, 2022b, section 5.1.1, although EU/EC regulations regarding standards of informed consent for the donation and use of human tissue and cells do not explicitly cover research-intended uses outside of a clinical trial setting, organoid research is expected to meet the general standards for informed consent provided in the Clinical Trials Regulation (EU) 536/2014 (European Commission - Directorate-General for Research and Innovation Science in Society, 2012, p. 36). As well as requiring that consent must be obtained from participants before the research commences, Regulation (EU) 536/2014 provides for a participants’ right to withdraw. These standards reflect the longstanding international consensus expressed in, for instance, the World Medical Association’s Declaration of Helsinki first issued in 1964, which, with regards to a participant’s right to withdraw, states under Article 26 that “the potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal”.

The regulatory uncertainty regarding whether, to what extent, and under what conditions a cell or tissue donor can withdraw their cells and, in particular, the organoids that have been derived from those cells is based on an important distinction between having the right to withdraw the “basic” tissue and cells from future use (Holm, 2006; 2011) and withdrawing a cell line or biotechnology that has been produced from the donated cells (Holm and Lewis, 2022).

As already discussed, organoids possess, in part, the features of biotechnological artefacts (Gaillard, Pence, and Botbol-Baum, 2021; Lewis and Holm, 2022b), that is, “objective” material produced by researchers through specialized, technical processes (Parry and Gere, 2006). Organoids are not merely or simply self-organizing entities that spontaneously arise from a collection of cells – though self-organization is considered to be a core feature that defines an organoid *as* an organoid (Lancaster and



Knoblich, 2014; Vogt, Gaillard, and Green, 2023). Organoids also require manipulation of donated cells and tissues and substantial amounts of expertise, effort, and investment. Furthermore, many organoid-derivation processes, drug screening protocols, disease models, organs-on-chips, and organoid-based therapeutics will have been patented (see D2.1, section 10).

The fact that organoids are, in part, biotechnological artefacts undermines a donor's claim to exclusive control through a putative right to withdraw. Thus, in relation to organoids that have already been created from donated biomaterial, the donor's right to withdraw may either be non-existent or it only applies when organoids are produced or used outside of the terms of the original consent (Holm and Lewis, 2022).

However, in light of the discussions concerning the normative status of organoids (section 4.2), the "hybrid" status of organoids may be considered a moral reason for according greater levels of recognition to a donor's normative claims to organoids derived from their cells, and, more specifically, for extending a right to withdrawal from the "basic" cells and tissues that have been donated to the derived biotechnological artefacts as well as some control over their future use (Holm 2006, Lewis and Holm, 2022a). Note that such an extension to a donor's right to withdrawal would, for the reasons already mentioned in the previous paragraph, only appear to apply to organoids yet to be created.

Even if withdrawal were to only apply to organoids yet to be created (i.e., as opposed to cell lines and organoids that have already been established and potentially widely shared among different laboratories and research institutions), organoid researchers still question the feasibility of such a policy. Within the HYBRIDA project, organoid researchers have raised concerns about level of monitoring compliance required, the logistics and costs involved in tracing samples, the capacity and resource demands associated with obtaining ongoing case-specific or dynamic donor consent, and the costs involved in destroying organoids and any organoid-based technologies.

These questions regarding the ethics and practical feasibility of organoid withdrawal, as well as the question of when the right to withdrawal begins and ends, are further complicated if the lawful basis for data processing is consent, where the question arises of until which point one can withdraw this consent and hence the personal data associated with or derived from the donated material (for further details, see section 4.5).

On this specific issue, it was reported at a recent HYBRIDA focus group (Ravn, Falkenberg and Sørensen, 2024) that, according to the European Data Protection Board, if a data controller chooses to rely on donor consent for any part of the data processing, then they must be prepared to respect the terms of consent associated with that choice. Accordingly, when such terms include a right to withdraw, data processing must be terminated in the event that withdrawal is requested. Thus, in spite of the claims regarding the legitimate interests of the research community in limiting a donor's right to withdraw, one interpretation is that, in the event of a data subject's withdrawal, it is not permissible to switch from relying on consent for the processing of Material Associated Data (in the name of legitimate scientific interests) to ignoring the rights associated with the terms of consent.



Once again, these questions highlight and, ultimately, turn on the tension between respecting donor autonomy and promoting scientific utility, a tension that was illustrated in the discussions concerning donor withdrawal at a recent HYBRIDA focus group facilitated by WP4 (see Ravn, Falkenberg and Sørensen, 2024).

4.3.3 *Proposals*

At the European Union/European Commission level, regulatory standards for informed consent and withdrawal do not explicitly extend to research using human tissue and cells (unless the research is part of a clinical trial). Thus, it is up to individual Member States to determine the formal legal requirements for the research use of human tissue and cells.

We repeat the proposal presented in section 4.1.3; specifically, we propose that the National Ethics Councils (NEC) Forum considers and explores the possibility of introducing greater levels of regulatory harmonization in the domestic legislation of Member States and Associated Countries for substances of human origin (SoHO) specifically intended for research.

Given the concerns that organoid researchers have raised regarding the transfer of organoids between institutions (see “Information Derived from the Analysis of Donated Cells” (4.5) and “Material Transfer Agreements” (4.6)), the regulatory approaches to donor withdrawal should be harmonized across Member States. Thus, we propose that the NEC Forum, in the context of any discussions it has regarding the question of regulatory harmonization, also considers the questions of whether a cell donor’s right to withdraw consent extends to the organoids that have been derived from their cells as well as when the right to withdraw consent begins and ends. If regulatory harmonization cannot be achieved or delivered in reasonable timeframe, then individual Member States should seek to answer these questions of donor withdrawal. Any determinations should be enshrined in domestic regulation such that a donor’s right to withdrawal is legally explicit.

For research projects funded by the EU/EC, the European Commission should seek to answer these questions of donor withdrawal.

In addition, in terms of the question of until which point a donor can withdraw their consent to the use and processing of personal data associated with or derived from the donated material, we propose that the European Commission should consult with the European Data Protection Board as this is a matter of GDPR interpretation.

4.4 Sentient and Conscious Neural Organoids

4.4.1 Regulatory Gap

- For the past few years, there has been extensive debate in the fields of bioethics and neuroethics concerning ownership, normative status, and researcher’s obligations if certain neural organoids were found to have, or were likely to develop, sentience and/or higher levels of consciousness.⁹

For full details of these regulatory gaps and uncertainties, see Lewis and Holm, 2022b, section 5.1.4.

4.4.2 Arguments and Considerations in Addressing the Gaps

In recent years, there has been much speculation concerning the possible consciousness of neural (or cerebral) organoids. This has led to debates regarding the ethical permissibility of conducting research that may, intentionally or not, yield organoids with sensory and/or cognitive capacities (see, e.g., Farahany et al., 2018; Lavazza and Massimini, 2018; Koplin and Savulescu, 2019; Sawai et al., 2019; Hyun, Scharf-Deering and Lunshof, 2020; Bollinger et al., 2021; Niikawa et al., 2022; Sawai et al., 2022; Kataoka et al., 2023; Zilio and Lavazza, 2023). To a much lesser degree, some have also raised such concerns regarding research with human “brain slices” of tissue extracted from the neocortex or hippocampus regions from patients undergoing surgery (Farahany et al., 2018), though they suggest that the possibility of consciousness or other higher-order perceptive properties seems extremely remote given that, currently, *ex vivo* brain tissue does not have sensory inputs. As we shall illustrate below, there are good reasons to suggest that a similar conclusion can be drawn in relation to neural organoids.

Consciousness, as an object of empirical study, as a philosophical concept whose nature and conditions have been theorized, and as a term of ordinary language, is hugely complicated and highly varied in terms of the way in which it is used and the inferences it underlies. As Levy and Savulescu (2009, p.362) state, “different thinkers denote different properties when they refer to ‘consciousness,’ and different concepts of consciousness underlie different kinds of moral value”. Where the debates regarding neural organoids are concerned, they have tended to invoke two forms, levels, or types of consciousness and thereby distinguish two different levels of moral obligation depending on what “consciousness” they consider a neural organoid might manifest:

- *Sentience or Phenomenal Consciousness*. It may be conscious in the generic sense of simply being a *sentient* creature (Armstrong, 1981), one capable of *phenomenally conscious* (i.e., subjective) experience, whereby to be in a phenomenally conscious state is to experience “what it is like to

⁹ Neural assembloids are organoids that combine multiple cell types or lineages (i.e., cells from different regions of the brain) in 3D culture or co-culture and connect several neural organoids modelling different brain regions.



be in that state” (Block, 1995). In other words, phenomenally conscious experience necessarily means that there is something it is like for the subject to have that experience (Nagel, 1974). In bioethics, the typical experiences that are invoked as representative of this form of consciousness are those of pleasure and pain. Being conscious in this sense may admit of degrees, and just what sort of sensory capacities are sufficient are not sharply defined.

- *Cognitivist Consciousness.* The term “cognitivist consciousness” is not a philosophical term of art, at least not in mainstream Anglophone philosophy of mind, though it is employed to refer to the object of study of most theories of consciousness in analytic philosophy by those working in fields whose theories of, or approaches to, the nature and study of consciousness take their bearings from principles in phenomenology. We use the term here as a “catch all” concept for those theories of consciousness developed on the basis that theories and conceptions of sentience or phenomenal consciousness are taken to be limited in terms of their ability to capture all of what it means to be “conscious”. Broadly speaking, the “higher” levels of consciousness to which “cognitivist consciousness” refers – no matter how each of these types or forms of consciousness are individually defined, characterized, or theorized in philosophy of mind – are employed by bioethicists and neuroethicists for explicitly moral ends. In short, following John Locke’s conception of consciousness as a necessary condition of an entity being a “person” (see, e.g., Locke, 1975, II.xxvii.17), these higher levels of consciousness are used as premises in moral arguments that bear on questions of moral personhood (Levy and Savulescu, 2009). As such, discussions of these sorts of consciousness are intricately bound up with claims about certain advanced cognitive abilities and capacities that are typically invoked in conceptualizations of the conditions for full moral status (i.e., roughly the status of a cognitively normal adult human being), such as the capacity for self-awareness (McMahan, 2002), consciousness of oneself as a continuing subject (Tooley, 1983), the ability to rationalize one’s preferences for how one’s life goes (Singer, 1993), or the capacity to value (Buss, 2012).

Given these two forms or levels of consciousness, some have argued that possessing sentience is sufficient to underwrite moral status and would entitle an entity to morally appropriate treatment (see, e.g., Warren, 1997; Levy and Savulescu, 2009). However, in relation to perhaps the most pressing ethical issue when it comes to moral status, i.e., that of who should own and control the use of a sentient neural organoid, speculation that it has obtained or will obtain phenomenal consciousness which confers it *some* moral status is not of any genuine legal concern. Currently, the overwhelming majority of legal systems have no issue with the ownership of non-human, phenomenally conscious organisms *per se* (e.g., as we find with pets and livestock). The traditional legal point of departure is that all non-human animals can be owned, irrespective of their cognitive abilities, including degree and type of consciousness (Holm and Lewis, 2022). However, what legal ownership permits the owner to do with a non-human animal will vary between jurisdictions depending on the laws governing non-human animal rights, including whether a legal system recognizes non-human animal sentience and/or suffering and whether laws prohibit or place limitations on animal cruelty. Nevertheless, when it comes to the question of what cannot be legally owned, the law recognizes only one type of natural person (i.e., the human being).



In addition, speculation that a neural organoid could obtain phenomenal consciousness does not raise any significant ethical concerns when it comes to the questions of its ownership or its right to life. There is broad philosophical agreement that phenomenally conscious entities have *some* moral status. However, in general, having *some* moral status is not sufficient to guarantee an entity's right to life or to stop it from being owned (Holm and Lewis, 2022). If we agree with the philosophical consensus that possession of sentience is sufficient to underwrite some – but not full – moral status, then the questions of who should own a sentient neural organoid and how such an organoid should be used in a research context could, in principle, be considered within the context of the ongoing ethical debates concerning non-human animal research and animal rights in general.

Now, one may argue that the fact that the sentient neural organoid is made from human cells makes a difference because it is a *human* organoid and, therefore, somehow special in terms of both the consciousness it manifests and the regulations that should govern its use. There is, however, a risk of equivocation concerning the term “human” here (see, e.g., Holm and Lewis, 2022). The fact that an organoid is, in part, biologically human does not support the conclusion that its phenomenally conscious states must also be qualitatively human (for further details, see pp.30-31). A merely sentient human organoid would still be merely sentient and to categorize this as human sentience purely on the basis that the neural organoid has been formed from the self-organization of human cells is an inferential mistake. Furthermore, a merely sentient human organoid would still only be in possession of *some* moral status, and thereby not entitled to the full protections afforded natural persons. In short, if consciousness and its theoretical relationships to moral status are the basis for determining the ethical permissibility of creating, controlling, and owning neural organoids, then the origin of the cells used to produce the organoid have no direct bearing on these debates.

On the basis of broad philosophical consensus concerning the limited moral status of entities that are merely phenomenally conscious, the contentious questions, and the ones on which the ethical permissibility of neural organoid research could turn, are: i) whether neural organoids could possess certain “higher” levels of consciousness, which, as mentioned previously, tend to be philosophically cashed out in terms of the advanced cognitive abilities and capacities; and ii) whether these “higher” levels of consciousness are sufficient for ascribing moral personhood or full moral status to these entities. It is argued by some, or at least assumed by way of an appeal to personhood theory, that in the event of the creation of neural organoids with higher levels of consciousness, their moral status should be equivalent to that of humans, and they ought to be treated in an appropriate manner (see, e.g., Koplin and Savulescu 2019; Niikawa et al., 2022; Kataoka et al., 2023).

The legitimacy of that sort of argument, however, turns on how we answer questions i) and ii) in the previous paragraph. Addressing those questions requires: i) an understanding of the state of neural organoid research and its promises for future development; and ii) an understanding of the state of empirical, as opposed to philosophical, research into the nature of consciousness. We cannot do justice to these two issues within the confines of this report. However, we can articulate some of the main developments in both fields in order to determine whether there is an immediate or impending need for a regulatory response to the recent bioethical and neuroethical debates concerning neural organoids.

While neural organoids can model regions of the human brain remarkably well, the current methods for generating neural organoids do not result in an *in vitro* organoid that matures beyond the equivalent of (parts of) an early prenatal brain. Indeed, most studies using neural organoids have focused on studying early developmental events in the brain. Although organoid researchers have claimed that it is conceptually possible to combine multiple cell types or lineages (i.e., cells from different regions of the brain) in 3D culture or co-culture to produce neural assembloids (i.e., an assembly of several neural organoids modelling different brain regions), there are major limitations to neural organoid development in terms of modelling the entirety of the human brain – e.g., the problems of oxygen and nutrient diffusion, the absence of a peripheral nervous system, and the problems of modelling interactions between different parts of the brain and understanding the neural activity of neural organoids (Chen et al., 2019).

It is the current state of neural organoid research, and the major challenges it faces, that recently led the International Society for Stem Cell Research (ISSCR) (2021) to argue that there is no reason to believe, or evidence to suggest, that isolated neural cell organoids or brainstem, hindbrain, choroid plexus, and forebrain organoids (i.e., those neural organoids that have currently been established – see D2.1, p. 25) resemble a fully functioning brain or integrated parts of the brain. Therefore, there is no reason to believe that such organoids are sentient let alone capable of possessing the “higher” levels of consciousness that warrant special ethical or legal concern.

Turning now to the current state of scientific research into the nature of consciousness, it is important to note that the most widespread consciousness-related research programme in neuroscience (often also drawing on cognitive science, evolutionary biology, comparative psychology, and analytic philosophy) has consisted of attempts to uncover the “neural correlates of consciousness”, i.e., the neurological activity, structures, and/or substrates correlated with conscious experience. The shift towards advancing understanding of the “neural correlates of consciousness” occurred during the 1990s and broadened into the area of non-human animal consciousness during the 2000s.

This singular focus on the neurological dimension of consciousness has led critics, particularly those in the fields of embodied cognitive science and neurophenomenology, to decry research programmes focused on investigating the neural correlates of consciousness for their narrow-minded “brain-“ or “neurocentrism” (see, e.g., Varela, Thompson, and Rosch, 1991; Gallagher, 2018).

In terms of whether such criticisms possess a degree of empirical – as opposed to conceptual – legitimacy, one of the most important, and widely publicized, events in consciousness research occurred in June 2023, when the COGITATE consortium reported on its “adversarial”, theory-neutral study to evaluate two of the most prominent theories of consciousness - Integrated Information Theory (“IIT”) and Global Neuronal Workspace Theory (“GNWT”) (COGITATE Consortium et al., 2023). The study failed to confirm its two central hypotheses: 1) that certain forms of consciousness-related neural activity would be observed toward the back of the brain; and 2) that consciousness-related activity would be found in the front of the brain.



The results of COGITATE collaboration led neuroscientist Christof Koch, one of the study's principal investigators, to concede, at the 2023 meeting of the Association for the Scientific Study of Consciousness in New York, that he had lost his longstanding bet with philosopher David Chalmers, as part of which Koch bet Chalmers a case of very expensive Madeira wine that 25 years was more than enough time for scientists to uncover the patterns of brain activity that underlie each and every one of our conscious experiences.

Relatedly, in light of the publicity one of the theories tested in the COGITATE study has received – Integrated Information Theory (“IIT”) – and its prominence in the field of neuroscience, 124 scholars posted a letter in September 2023 labelling IIT as pseudoscience; “something that is not very scientifically supported, that masquerades as if it is already very scientifically established” (Lenharo, 2023).

The inability of neuroscience to empirically validate prominent theories of consciousness has a direct impact on the legitimacy of certain arguments in the debates regarding neural organoids in bioethics and neuroethics (see also Diner and Gaillard, 2023). Those involved in the ethical debates concerning neural organoids have referred to studies in neuroscience whereby complex neural activity similar to that of preterm neonates has been seen in in vitro human cerebral organoids (see, e.g., Sawai et al., 2022; Zilio and Lavazza, 2023). According to certain theories of consciousness, such neural activity may be deemed to be sufficient for attributing consciousness to an in vitro neural organoid (Sawai et al., 2022). The problem here, however, is that these theories of consciousness, which are also often referred to by those who speculate as to the consciousness of *future* cerebral organoids (see, e.g., Lavazza and Massimini, 2018; Koplin and Savulescu, 2019; Zilio and Lavazza, 2023), are the same ones which the COGITATE consortium were unable to confirm and which led to David Chalmers receiving his expensive case of Madeira in New York earlier this year.

In contrast to the dominant and widely publicized “brain-“ or “neuro-centric” theories and studies of consciousness in current neuroscience, cognitive science, evolutionary biology, comparative psychology, and analytic philosophy of mind, there is a rich and relatively side-lined body of principled, and increasingly tested, scholarship in neuroscience and cognitive science that takes its bearings from the principles and concepts of classical phenomenology. Broadly speaking, what characterizes these investigations into the nature, conditions, and origins of consciousness is a commitment to the idea that the brain is not the central and almost exclusive mechanism of cognition. Conceptions of brain function, and, hence, our understanding of consciousness and its neural correlates, cannot “ignore the dynamical relations among brain, body and environment” (Gallagher, 2018, 8).

As Francisco Varela, Evan Thompson, and Eleanor Rosch – three pioneers of embodied neuroscience/cognitive science – asserted in 1991:

We hold with Merleau-Ponty that Western scientific culture requires that we see our bodies both as physical structures and as lived, experiential structures-in short, as both "outer" and "inner," biological and phenomenological. These two sides of embodiment are obviously not opposed. Instead, we continuously circulate back and forth between them. Merleau-Ponty



recognized that we cannot understand this circulation without a detailed investigation of its fundamental axis, namely, *the embodiment of knowledge, cognition, and consciousness*. For Merleau-Ponty, as for us, embodiment has this double sense: it encompasses both the body as a lived, experiential structure and the body as the context or milieu of cognitive mechanisms [emphasis added] (Varela, Thompson, and Rosch 1991, xv-xvi)

For accounts that hold that consciousness is intimately bound up with the body-brain-environment complex, it is conceptually impossible that an in vitro neural organoid will ever be able to attain conscious states that are qualitatively the same as those of a human being such that they would be sufficient for full, or near full, moral status. The point is that if human consciousness is an embodied phenomenon, then we cannot ignore the role of the human body in determining the content of a specific type of consciousness, that is, human consciousness (Clark, 2008; Damasio, 1994; Gallagher, 2005; Lakoff and Johnson, 1999; Merleau-Ponty, 1962). This argument has been applied specifically to neural organoids (see Hyun, Scharf-Deering and Lunshof, 2020).

4.4.3 Proposals

In accordance with the ISSCR's (2021) most recent guidelines and recommendations, the state of current neural organoid research and the challenges it faces in developing sufficiently complex organoids are such that we have no reason to believe that currently established in vitro neural organoids are sentient or possess levels of consciousness that warrant special regulatory attention. This conclusion can also be drawn on the basis of the current lack of consensus within neuroscience concerning the neural correlates of consciousness and, more specifically, the absence of empirical validation for competing theories of consciousness.

Until such time as significant progress is achieved in the fields of neural organoid research and empirical research on the nature of consciousness, there is no evidence to support a change in policy governing neural organoid research.

We, therefore, have no proposals or recommendations for regulatory action at this time.

4.5 Information Derived from the Analysis of Donated Cells

4.5.1 Over-regulation

- When it comes to the exchange of research-intended donated biomaterials between institutions, it is, simultaneously, an exchange of donated research material, which, as discussed in section 4.1, is governed by the laws of individual Member States (with standards of best practice drawn from the Clinical Trials Regulation (EU) 536/2014), and an (implicit) exchange of personal data about the cell or tissue donor's genetics, governed by the GDPR (EU) 2016/679. The genetic data may, in turn, also constitute genetic data about the donor's family members. The problem is that the dual nature and regulation of the exchange significantly complicates such exchanges and hinders collaboration in practice, especially exchanges of personal data and collaborations between EU/EEA and non-EU/EEA research institutions, biobanks, and regulatory bodies.

For full details of this regulatory issue, see Lewis and Holm, 2022b, section 5.1.5.

4.5.2 Arguments and Considerations in Addressing the Over-regulation

The problem of over-regulation presented above manifests in different ways depending on whether the exchange of organoids is between institutions within the EU/EEA or between EU/EEA and non-EU/EEA institutions (see Lewis and Holm, 2022b, sections 5.1.5-5.1.6; Ravn et al., 2022; Ravn, Falkenberg and Sørensen, 2023; Ravn, Falkenberg and Sørensen, 2024). In this section, we focus on the issues reportedly experienced by organoid researchers concerning exchanges of biomaterials between EU/EEA and non-EU/EEA institutions, issues which largely turn on the divergences between the GDPR and data protection laws in “third” (i.e., non-EEA) jurisdictions. In section 4.6, we will address this issue of over-regulation, and the specific forms in which it manifests in research, in the context of intra-EU/EEA biomaterial exchanges.

The exchange of donated research-intended biomaterials, including associated personal data, between EU/EEA-based institutions and institutions based in third jurisdictions is widely considered to be a public good (All European Academies et al., 2021), with the importance of such exchanges enshrined in various national laws and international legal instruments, including the International Health Regulations (2005) (e.g., Articles 6 and 46), the Convention on Biological Diversity (Article 15) on access to genetic resources, and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity.

At a WP4 stakeholder workshop in Copenhagen in 2022 (Ravn et al., 2022) and also at a more recent stakeholder focus group (Ravn, Falkenberg and Sørensen, 2024), EU-based organoid researchers raised a

concern that, where an exchange of donated biomaterial involved institutions in countries without an Article 45 decision of data protection adequacy from the EU, the dual regulation of the exchange (i.e., as an explicit exchange of biomaterial governed by the laws of individual Member States and an implicit exchange of personal data governed by the GDPR (EU) 2016/679) placed significant obligations on recipient parties. On the basis that third-country data importers are required to ensure a GDPR-equivalent level of protection for personal data, organoid researchers reported experiencing laborious, complex, and time-consuming processes.

Suffice it to say that such experiences are not confined to those organoid researchers interviewed by the HYBRIDA project. As All European Academies (ALLEA), the European Academies Science Advisory Council (EASAC), and the Federation of European Academies of Medicine (FEAM) (2021) have explained, it is apparent that international transfers of data to outside the EU/EEA involve overly complex and inefficient processes, and these impediments, as the FEAM (2018) have previously reported, have largely stemmed from the inadequate operationalization of the GDPR.

Free movement of data from the EEA is permissible provided there is an Article 45 “adequacy” decision for the recipient jurisdiction. If a decision concerning whether a jurisdiction is able to offer a GDPR-equivalent level of protection for personal data is absent, Article 46 of the GDPR allows for a controller/processor to “transfer personal data to a third country or an international organization only if the controller or processor has provided appropriate safeguards, and on condition that enforceable data subject rights and effective legal remedies for data subjects are available”. Under Article 46, safeguards would include Standard Contractual Clauses (“SCCs”), administrative arrangements between public bodies, or specific contractual clauses, with authorization by the competent supervisory authority.

However, as ALLEA et al. (2021) observe, where the operationalization of the GDPR in data transfers to outside the EU/EEA is concerned, there are a distinct lack of *suitable* Article 46 transfer mechanisms. It is currently the case that the mechanisms provided under Article 46 conflict with national laws (e.g., certain US federal laws), lack adequate guidance from the European Data Protection Board, and are ill-suited to the specific demands of biomedical research (All European Academies et al., 2021, 28-31).

As a means of addressing the research-specific issues concerning the operationalization of the GDPR in exchanges of personal data between the EU/EEA and third countries, the FEAM (2018) and ALLEA et al., (2021) argued that there would be value in constituting a cross-Directorate-General multi-stakeholder group to monitor the implementation of the GDPR in research with health data, and as a mechanism to receive feedback from the medical and science communities.

In terms of the other issues, the majority of the ALLEA, EASAC, and FEAM (2021, 33-34) recommendations involve calls for greater and more appropriate guidance from the European Data Protection Board.



4.5.3 *Proposals*

We propose that the European Commission should consider and respond explicitly to the difficulties organoid researchers face (see Ravn et al., 2022; Ravn, Falkenberg and Sørensen 2023; Ravn et al., 2023) when seeking to exchange organoids, embryonic stem cells, and induced pluripotent stem cells with institutions outside of the EU/EEA. Following the previous recommendations made by the FEAM (2018), this could involve dialogue between the Directorate-General for Research and Innovation, the International Data Flows and Protection Unit of the Directorate-General for Justice and Consumers, the European Group on Ethics in Science and New Technologies, the European Data Protection Board, and Rapporteurs and Shadow Rapporteurs for the proposed EC regulation on the standards of quality and safety for substances of human origin.

The European Data Protection Board is currently in the process of providing guidance for the scientific research field, and this is one of the topics that ought to be considered in their guidelines.

4.6 Material Transfer Agreements (MTAs)

4.6.1 Regulatory Issues

- Organoid researchers have raised concerns regarding current regulatory standards and procedural rules relating to Material Transfer Agreements (MTAs) for transfers between institutions based in the EU/EEA.¹⁰ The process of drafting and agreeing an MTA between two parties in different countries is complex due to legal differences in states' domestic laws and the fact that domestic laws may or may not refer to international laws and regulations. This can lead to legal uncertainty as to the applicable legislative and regulatory requirements. The differences in domestic laws may also partly explain why institutional legal teams interpret the terms of the MTA differently and, thus, why organoid researchers have reported experiencing significant delays in executing MTAs.
- Although the European Commission (EC) has produced Standard Contractual Clauses (“SCCs”) for data associated with material under a MTA, there are no such clauses covering the material component of the MTA. This is because the transfer of material is legislated by the domestic laws of individual Member States. However, given the value of these SCCs for those seeking to transfer Material Associated Data, organoid researchers have indicated that it would be useful to have MTA templates and SCCs for human embryonic stem cells (hESCs),¹¹ induced pluripotent stem cells (iPSCs),¹² and organoids.

For full details of these regulatory issues, see Lewis and Holm, 2022b, section 5.2.1.

4.6.2 Arguments and Considerations in Addressing the Regulatory Issues

Whereas the issues discussed in section 4.5 regarding the exchange of organoids between EU/EEA-based institutions and those in third countries primarily turn on the problems of operationalizing the GDPR for

¹⁰ MTAs are legal contracts that set out the terms and conditions of the transfer and use of materials and/or data between the owner or provider (e.g., a specific research institution) and a recipient (i.e., a different research institution). They also set out any relevant legislative and/or regulatory requirements which the recipient and provider must comply with.

¹¹ Human embryonic stem cells (hESCs) are stem cells derived from early-stage, preimplantation embryos. They are pluripotent meaning that they are capable of differentiating into germ cells and any of the three primary layers of cells that form during embryonic development.

¹² Induced pluripotent stem cells (iPSCs) are stem cells that have been generated directly from cells that make up the body of an organism (i.e., somatic cells). Like hESCs, they are pluripotent, meaning that they are capable of differentiating into germ cells and any of the three primary layers of cells that form during embryonic development.

the transfers of data associated with research-intended donated biomaterial, the harmonization of data protection law across the EU/EEA should, in principle, mean that any regulatory issues concerning the transfer of organoids within the EU/EEA will primarily depend on the material component of the transfer. However, as noted by organoid researchers at a WP4 stakeholder workshop in Copenhagen in 2022 (Ravn et al., 2022) and also at a more recent stakeholder focus group (Ravn, Falkenberg and Sørensen, 2024), intra-EU/EEA exchanges pose difficulties in terms of being laborious, complex, and time-consuming. This is, in part, because institutional legal teams vary in their interpretations of the GDPR and because of excessive risk-aversion on the part of data processors in their interpretations of the scope and nature of donor consent. As these stakeholders note, there still seems to be a tension between the regulatory harmonization which the GDPR, in principle, provides and the everyday practice of interpreting and applying the GDPR to data transfers in biomedical research settings.

To address these difficulties in intra-EU/EEA exchanges of personal data associated with a material transfer (“Material Associated Data”), stakeholders at these workshops and focus groups suggested the possibility of introducing standardized consent forms and/or standardized “data clauses” within consent forms (Ravn, Falkenberg and Sørensen, 2024).

In terms of the material component of the transfer of human tissues, cells, stem cell lines, and derivatives of those materials (e.g., organoids), when such biomaterials are not intended for human applications or use in a clinical trial, they are not covered by legally binding EU instruments. As we detailed in section 4.1 above and in Lewis and Holm, 2022b, section 5.1.1, this has led to a lack of regulatory harmonization, with individual Member States adopting different domestic approaches with national differences in the formal legal requirements for the research use of donated human biomaterial.

When it comes to MTAs, which are required for the export of samples from one jurisdiction in the EU/EEA to another and for domestic movement of samples and associated data to a separate legal entity (or, in some cases, to different parts of the same legal entity), HYBRIDA stakeholders reported that not only did the differences between domestic laws and the complex relationships between international and national laws generate legal uncertainty, but also institutional legal teams interpret the terms of the MTA differently, leading to significant delays in execution (Ravn et al., 2022; Ravn, Falkenberg and Sørensen, 2024).

As detailed in section 4.1, a greater level of regulatory harmonization could, in principle, be a means of increasing the level of legal certainty about the applicable principles and provisions within Member State legislation governing research-intended human tissues and cells. In that sense, attaining regulatory harmonization could be a key part of facilitating easier and more efficient cross-border exchanges of human tissue, cells, and their derivatives.

In the shorter term, and to address the issue of variation in the interpretation of the terms of MTAs by different institutional legal teams, organoid researchers have stated that it would be useful to have MTA templates and standard clauses for human embryonic stem cells, induced pluripotent stem cells, and organoids (Ravn et al., 2022).



4.6.3 *Proposals*

When considered in the light of the regulatory issues surrounding informed consent discussed in section 4.1, the case for greater regulatory harmonization across Member States is strengthened by the challenges experienced by organoid researchers in executing MTAs for transfers of research-intended human biomaterial between legal entities in the EU/EEA. Thus, we repeat the proposal presented in section 4.1.3; specifically, we propose that the National Ethics Councils (NEC) Forum considers and explores the possibility of introducing greater levels of regulatory harmonization in the domestic legislation of Member States and Associated Countries for substances of human origin (SoHO) specifically intended for research.

In terms of the challenges experienced by organoid researchers with intra-EU/EEA transfers of Material Associated Data, these issues specifically involve variation in legal interpretations of the GDPR. Thus, we propose that the European Data Protection Board, in collaboration with the Directorate-General for Research and Innovation, the European Group on Ethics in Science and New Technologies, and academic researchers representing individual Member States, explore the possibility of introducing “data passports”, standardized consent forms, and/or standardized “data clauses” within consent forms for research-intended human biomaterials.

Given the challenges experienced by organoid researchers arising from the variation in the interpretation of the terms of MTAs by different institutional legal teams within the EU/EEA, we propose that the European Commission explores the possibility of introducing MTA templates and standard clauses for transfers of human embryonic stem cells, induced pluripotent stem cells, and organoids i) between different legal entities that make up a consortium funded by the EU/EC; and ii) between EU/EC-funded research projects.

4.7 Patentability of Organoids

4.7.1 Regulatory Gap

- Organoid researchers have concerns regarding the implications of Europe’s patent laws for the patentability of iPSCs, organoids, and resulting applications. In Europe, hESCs and their derivatives cannot be patented if the hESC lines have been obtained by the prior destruction of human embryos. Given the definitions of a human embryo and a hESC used by the European Court of Justice (CJEU) and the European Patent Office (EPO) in their respective judgments regarding the non-patentability of hESC lines and their derivatives, it is unclear whether technologies derived from certain gastruloids and blastoids would fall under the non-patentability restrictions.¹³

For full details of these regulatory issues, see Lewis and Holm, 2022b, section 5.2.2.

4.7.2 Arguments and Considerations in Addressing the Gaps

In 1999, Oliver Brüstle was granted a patent for the generation and therapeutic use of neural cells derived from human embryonic stem cells (hESCs). The patent was challenged and put before the European Court of Justice (CJEU) (*Oliver Brüstle v Greenpeace eV*), which ruled that inventions involving the prior destruction of human embryos cannot be patented.

Subsequently, in 2014, the Technion Research and Development Foundation applied to obtain a European patent on a cell culture comprising both human foreskin cells and hESCs as well as on methods of maintaining hESCs in an undifferentiated state. Technion appealed the European Patent Office’s (EPO) decision to refuse the patent. The Technical Board of Appeal of the EPO maintained the patent’s refusal on the basis that establishment of cells lines necessarily involved the prior destruction of human embryos.

The exclusion from patentability of hESC lines that have been obtained through the destruction of human embryos is now a legal certainty in Europe, having been based on two distinct legal frameworks—those of the CJEU and the EPO (Mahalatchimy et al., 2015). Such an exclusion also extends to: i) derivative products and technologies if their development requires prior destruction of human embryos; and ii)

¹³ Gastruloids are embryo-like structures cultured from pluripotent stem cells that recapitulate the early stages of development of post-implantation embryos. Unlike true embryos, gastruloids are devoid of the tissue (“primitive streak”) that forms on day 15 of embryo development and which marks the point at which an embryo transforms from a one-dimensional layer of cells into a multidimensional cell structure (“gastrulation”). Blastoids are stem-cell-derived embryo models that contain inner cell mass and embryonic and extra-embryonic cell types. They model the early pre-implantation stages of embryo development.

processes that require base material obtained by the destruction of human embryos (Nielen, de Vries and Geijsen, 2013).

Where organoid research and the clinical application of organoid-related technologies are specifically concerned, the legal maneuvering around these cases also demonstrates that the future of stem cell-based patents in Europe is unsettled. Specifically, novel technologies, products, and derivation processes that could be deemed to require or involve the destruction of human embryos risk being included under the CJEU/EPO's non-patentability rulings (Nielen, de Vries and Geijsen, 2013; Mahalatchimy et al., 2015).

Given the widespread publicity human embryo models have received in the past 12 months, and given the significant advances in the field of human embryo model research since the HYBRIDA project commenced in February 2021, what is particularly pertinent in the context of future organoid-based medical technologies is the question of the patentability of technologies and processes that could incorporate, or require the destruction of, blastoids and gastruloids (for further details, see, e.g., Rivron et al., 2023). However, it is important to acknowledge that such technologies do not yet exist, meaning that material conditions do not necessarily require an immediate legal response.

In reaching its decision in *Brüstle*, the CJEU applied a broad definition of a human embryo as an entity that is "capable of commencing the development of a human being". Relatedly, in a further judgement on 18 December 2014 concerning a patent application from International Stem Cell Corporation, the CJEU stated that parthenotes, developed from unfertilized ova that have entered a process similar to embryonic development due to chemical or electrical activation, are not human embryos, as they do not possess the "inherent capacity of developing into a human being".

The patentability rulings stemming from the CJEU's definitions of a human embryo are, at least in principle, potentially legally significant where blastoids and gastruloids are concerned, precisely because they recapitulate the organization, and early stages of development of pre- and post-implantation embryos, respectively (Pera et al., 2015; Munsie, Hyun and Sugarman, 2017; Hyun, Munsie et al., 2020; Piotrowska, 2020; Bollinger et al., 2021; Niemann and Seamark, 2021). Moreover, such in vitro human embryo models have recently begun to challenge legal definitions of a human embryo as well as raise important ethical questions regarding their use (Rivron et al., 2023).

The point is that if medical technologies were to be developed in the future that required or involved the destruction of embryo models, then, in light of CJEU's and EPO's extant rulings and definitions, the question of the patentability of such technologies in the EU/EEA may be considered as turning on whether these human embryo models are deemed to be human embryos (in terms of the biological, technical, and normative complexities involved in addressing this question, see, for instance, Denker, 2006; Holm, 2008; Rivron et al., 2023).

Whether an entity is or is not a human embryo, how we know whether it is a human embryo, and how we ought to regulate the use of such entities are questions that involve a high level of conceptual, epistemological, and regulatory uncertainty. This is not the only time that we consider the normative status of human embryo models in this report. Currently, the question of the patentability of embryo-



model-derived technologies is a hypothetical one (since there is no reason to believe or evidence to suggest that such technologies are already within the developmental pipeline). By contrast, there is a pressing regulatory need to address the question of whether and to what extent it is permissible to conduct research with human embryo models. On that basis, we will address this issue further, and in greater detail, in section 4.9.

4.7.3 *Proposals*

The current state of R&D is such that the question of the patentability of embryo-model-derived technologies is a hypothetical one. Thus, we have no reason to believe or evidence to suggest that this specific question requires an immediate legal or regulatory response. Nevertheless, given the precedents established by the CJEU and the EPO, the answer to this question is likely to involve consideration about whether (some) embryo models are human embryos. This is currently the subject of intense academic debate in the context of organoid research, and there are good reasons to suggest that a research-focused regulatory response is imminently required. Thus, the imperative is to develop specific proposals to address this more pressing regulatory gap (see section 4.9).

Nevertheless, and despite the fact that there are obvious differences between EU patent law and the law governing human embryo research, it would be prudent for the Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, European Patent Office, and regulatory bodies and groups charged with the review and implementation of the EC's "Biotech" Directive 98/44/EC to remain active in apprising themselves of regulatory developments concerning the EC's position on the funding of research involving human embryo models (for further details, see section 4.9).

4.8 Classifying Organoid-based Technologies for Medical Use

4.8.1 Regulatory Issues

- Organoid research is still firmly at the preclinical stage, no precedents have been set in terms of the classification of organoid-based medical products or devices, and even the most recent guidelines developed by competent authorities at the EU level do not mention organoids. The European Medicines Agency (EMA) recognizes that the correct characterization of future organoid-based technologies for healthcare applications will prove particularly challenging given that they could contain a mix of cells, substances, matrices, scaffolds, and/or medical devices.¹⁴ As a result, depending on what these technologies contain and what their functions, effects, and modes of action are, they may be characterized as medicinal products, medical devices, or combination technologies that incorporate elements of both medicinal products and medical devices. At this stage, it appears that the main regulatory uncertainty concerns the correct classification of ATMPs and combination products/devices that achieve their primary therapeutic effect not principally through the pharmacological, immunological, or metabolic action of its cells or tissues but through *functional integration*.
- In principle, organoids could be used to develop Advanced Therapy Medicinal Products (ATMPs).¹⁵ The European Medicines Agency (EMA) has recognized the concerns raised by researchers seeking to develop ATMPs, those applying for market authorization of ATMPs, and manufacturers of ATMPs regarding the significant levels of regulatory scrutiny, the burdens placed on applicants regarding clinical testing, and the problems applicants may face in demonstrating and providing evidence for how they have met regulatory standards for marketing authorization.

For full details of these regulatory issues, see Lewis and Holm, 2022b, section 5.3.1.

¹⁴ Medical devices are instruments, apparatuses, appliances, materials, or other articles to be used, alone or in combination, on humans for a medical purpose. Medicinal products are substances or combinations of substances to be used on humans for a medical purpose. In general, according to EU/EC regulations, what distinguishes a medical device from a medicinal product is that the former does not contain or is not derived from viable cells or tissues and does not achieve a functional or anatomical change in a patient *primarily* by pharmacological (e.g., a drug), immunological (i.e., the body's defence system), or metabolic (i.e., energy generating) means.

¹⁵ Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, cells, or tissue engineering.

4.8.2 Arguments and Considerations in Addressing the Regulatory Issues

When organoid technologies are finally developed for medical use, they may be employed as medicinal products, medical devices, or combination technologies that incorporate elements of both medicinal products and medical devices.

Correctly characterizing a future organoid technology for medical use is not only vital for determining which of the large number of EU/EC regulations and directives the technology is governed by (see Lewis and Holm, 2022b, section 5.3.1), but it is also a necessary part of applying for market authorization, including which standards for clinical testing the technology must comply with and what evidence needs to be provided to meet the relevant marketing authorization standards.

The EMA (2008) recognizes that characterization will prove particularly challenging for new products containing cells, substances, matrices, scaffolds, and medical devices. In part, this is because products may be combination technologies that incorporate elements of both medicinal products and medical devices, and, in part, because of the complex interactions within the product, ranging from biochemical, metabolic, or immunological actions, which are difficult to pinpoint and depend more on the functionality of the cellular components, to the structural replacement of damaged tissue or (parts of) organs. In addition, there is a degree of overlap in the respective definitions of a medicinal product and a medical device (see Medical Device Coordination Group, 2022, p.4). For instance, one of the two defining characteristics of a medicinal product is that it is “any substance or combination of substances *presented as having properties for treating or preventing disease in human beings*”. In terms of medical devices, the definition includes those materials that are *intended by the manufacturer to be used for “diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease”*. For a technology that is employed to treat or prevent disease, much, therefore, turns on the respective meanings of “presented as having properties for” and “intended by the manufacturer to be used for”. Unfortunately, further specifications are not provided either in the medical device regulations, medicinal products directives/regulations or by the MDCG.

The problems with characterization are compounded by the fact that organoid research is still firmly at the preclinical stage (see D2.1), no precedents have been set in terms of the classification of organoid-based medical products or devices, and even the most recent guidelines developed by competent authorities at the EU level do not mention organoids (see, e.g., Medical Device Coordination Group, 2022).

At this stage, it appears that the main regulatory uncertainty – where correct characterization is concerned – pertains to potential organoid technologies that achieve their primary therapeutic effect principally through *functional integration*. For example, as has been discussed by HYBRIDA in an analysis of the applications of organoids for regenerative medicine (Vogt, Gaillard, and Green 2023, pp. 140-141), two clinical trials are currently underway; the first seeks to culture salivary gland organoids for transplantation into head-and/or-neck cancer patients in order partially restore salivary gland function after radiation therapy; and the second aims to develop patient-derived intestinal organoids that can be

transplanted back into the intestine of patients suffering from inflammatory bowel disease or ulcerative colitis in order to repair the function to damaged mucosa.

Regulators attended a recent focus group organized by WP4 for the purpose of providing expert insight not only into the question of the correct characterization of future organoid technologies in general, but also the question of which regulations (if any) would be able to capture the integrative application of organoids (Ravn, Falkenberg and Sørensen, 2024).

Firstly, they stated that all the potential medical applications of organoids that they could envisage would constitute applications that fall under the medicinal product regulations. Specifically, because organoids for human application would: i) contain viable cells or tissues, which exclude them from the criteria for medical devices as provided by Directive 93/42/EEC (repealed by Regulation (EU) 2017/745);¹⁶ and ii) because those cells or tissues would be deemed to have been subjected to “substantial manipulation” (i.e., a necessary condition for an ATMP) organoid technologies would fall under Regulation (EC) 1394/2007 (on ATMPs).

On that basis, the regulators who attended the recent HYBRIDA focus group said that they have no reason to believe that the issue concerning the general characterization and regulation of future organoid technologies (i.e., as either medicinal products or medical devices), which we identified previously (see Lewis and Holm, 2022b), would require additional regulatory proposals or action.

On the question of functional integration, regulators at the recent HYBRIDA focus group made a comparison between the potential transplantation of human organoids for structural replacement and functional integration with the recent trials in tissue replacement for Parkinson's disease. Again, it was their considered opinion that an organoid technology that achieves its primary therapeutic effect principally through functional integration would fall under the ATMP regulations (Regulation (EC) 1394/2007) on the basis that it would be considered as being administered to human patients with a view to regenerating, repairing, or replacing a human tissue.

It is worth noting that the reasons given to support the governance of organoids by the ATMP regulations would mean that organoids used for functional integration would likely be classed as “Tissue Engineered Products” (TEPs) (under Article 2(1)(b) of Regulation (EC) 1394/2007). To be considered as a TEP, a product must contain cells or tissues that either i) have been subject to substantial manipulation, so that biological

¹⁶ *Active implantable devices* fell under Directive 90/385/EEC before it was repealed by Regulation (EU) 2017/745. An “active implantable device” means any medical device which: i) depends on a source of energy other than that generated by the human body or gravity for operation; and ii) is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure.

Regulation (EU) 2017/745 does not extend to *in vitro diagnostic medical devices*, which are covered by Regulation (EU) 2017/746. These are classed as tests that provide information on the predisposition to a medical condition or a disease, such as genetic tests, and tests that provide information to predict treatment response or reactions, such as companion diagnostics. (Note: this definition does not include devices that are used to monitor treatment with a medicinal product).



characteristics, physiological functions, or structural properties relevant for the intended regeneration, repair, or replacement are achieved; or ii) are not intended to be used for the same essential function or functions in the recipient as in the donor. In addition, according to the ATMP regulations, a TEP presents as having properties for, is used in, or administered to human patients with a view to *regenerating, repairing, or replacing a human tissue*, and may also contain additional substances, such as cellular products, biomolecules, biomaterials, chemical substances, scaffolds, or matrices.

By contrast, according to Part IV of Annex I to Directive 2001/83/EC on the Community code relating to medicinal products for human use (as amended), a “Somatic Cell Therapy Medicinal Product” (SCTMP) must meet either i) or ii) for TEPs above *and* have the properties for, is used in, or administered to human beings with a view to *treating, preventing, or diagnosing a disease through the pharmacological, immunological, or metabolic action of its cells or tissues*. An organoid product achieving a therapeutic effect principally through functional integration and not principally by pharmacological, immunological, or metabolic action will, thus, *prima facie* not be classifiable as a SCTMP.

It is also worth noting that according to Article 2(5) of Regulation (EC) 1394/2007, a TEP can also be classified as a Gene Therapy Medicinal Product (GTMP) (see Part IV of Annex I to Directive 2001/83/EC, as amended) if it contains recombinant nucleic acid(s) directly involved in the mechanism of action or employs genetically modified cells as part of the manufacturing process (e.g., to generate iPSCs that are later differentiated into organoids and subsequent TEPs).

In light of the expert regulatory insight provided at a recent HYBRIDA focus group, and the subsequent regulatory analysis we carried out concerning the characterization of organoid technologies as TEPs, it appears that the regulatory question of the status of organoid technologies that achieve their primary therapeutic effect principally through *functional integration* has been sufficiently addressed.

On the issue of potential over-regulation of ATMPs (i.e., concerns regarding the level of regulatory scrutiny, the burdens placed on applicants regarding the clinical testing, and the problems applicants may face in evidencing how they have met regulatory standards for marketing authorization), the EMA (2014) has attributed the concerns to the heterogenous character of ATMPs, the origin and nature of the starting materials, and the unique influences their therapeutic indication have on the risk profile.

What this means is that although comparisons with similar ATMPs are possible, applicants under Regulation (EC) 1394/2007 may be required to develop and validate new analytical test methods in order to investigate risks and therapeutic effects unique to a given ATMP. In addition, if an organoid-based product fulfils the criteria for an ATMP and, simultaneously, incorporates one or more medical devices as integral parts of the final product to produce a “Combined Advanced Therapy Medicinal Product” (see Article 2(1)(d) of Regulation (EC) 1394/2007), then, in the context of marketing authorization, the device part should also comply with the general safety and performance requirements laid down in Regulation (EU) 2017/745 on medical devices. In practice, this means that the success of an application for a new ATMP will turn on the applicant’s ability to successfully characterize all the components present in the



finished product, including single components (cellular and non-cellular), the combined product, and any changes to the characteristics of both the single and combined components because of the integration.¹⁷

Relatedly, for ATMPs containing, or developed from genetically modified cells, applicants must fulfil not only the standards set in Regulation (EC) 1394/2007, but also the principles of “Good Medical Practice” and the scientific recommendations provided by the EMA.¹⁸

The consensus among regulators at a recent HYBRIDA focus group was that the approach to approving ATMPs must necessarily be risk-based - even when organoid technologies start being approved and more precedents are set (Ravn, Falkenberg and Sørensen, 2024). Characterization should be proportionate to the knowledge about, and complexity of, the product. With organoid technologies, and ATMPs in general, there is a need to know what it is and what it intends to do; answering these questions will be comparatively more burdensome for organoid technologies/ATMPs than for other products given their complexity and the fact that assessments will need to be made on a case-by-case basis. Because of the risk-based approach, it is highly unlikely that applications for organoid products will ever be "tick-box"-based or substantively streamlined.

4.8.3 Proposals

In light of the discussions in section 4.8.2, and taking into consideration the expert insight provided by regulators at a recent HYBRIDA focus group (Ravn, Falkenberg and Sørensen, 2024), the two regulatory issues relating to the classification of organoid-based technologies for medical applications do not require proposals at this stage. Indeed, it is our considered judgment that these two issues have been sufficiently addressed by HYBRIDA’s regulatory stakeholders.

Nevertheless, in the future, should market authorizations be sought with respect to organoid technologies that challenge their (presumed) classification as ATMPs, there will be a need for the European Medicines Agency and/or the Directorate-General for Health and Food Safety’s Medical Device Coordination Group to respond to any unanticipated issues in such applications and issue guidance for the purpose of providing greater clarity for manufacturers and the European pharmaceutical industry in general.

¹⁷ Further to the implementation of Article 17 (Regulation (EC) 1394/2007), potential applicants have the opportunity to obtain the scientific recommendation of the Committee for Advanced Therapies for the classification of ATMPs.

¹⁸ Specifically, the issue here, as the EMA (2020) acknowledges, is that the early steps of deriving genetically modified cells may be affected by the availability of cell material, which, in turn, may make it difficult for an applicant to adequately qualify how they have fulfilled these standards.

4.9 Organoids and the Regulation of In Vitro Embryo Research

4.9.1 Regulatory Gap

- A prohibition on the funding of research that involves the creation of human embryos for research purposes is enforced by EU/EC regulations and by national laws in most Member States. In light of this regulatory framework, there is uncertainty as to whether certain types of organoid research (e.g., involving blastoids and gastruloids) would be deemed to be creating human embryos. Consequently, organoid researchers have requested EC-approved regulatory definitions of a human embryo and whatever it is that is generated through human embryo models.

For full details of this regulatory issue, see Lewis and Holm, 2022b, section 5.3.2.

4.9.2 Arguments and Considerations in Addressing the Gap

As the legal instrument for establishing the EU's most recent Framework Programme for Research and Innovation (Horizon Europe), Regulation (EU) 2021/695 explicitly excludes from funding eligibility all research activities intended to create human embryos solely for the purpose of research (or for the purpose of stem cell procurement).

That said, the creation of human embryos for research purposes (within defined boundaries) is permitted by national laws within several jurisdictions in the EEA, including Belgium, Spain, Netherlands, and Denmark.

In its Statements on Regulation (EU) 2021/695 (2021/C 185/01), the European Parliament, Council, and Commission state that the EC will continue not to fund research activities which destroy human embryos, including for the procurement of stem cells.

Up to now, the EU's regulations regarding the funding of in vitro embryo research have not explicitly relied on a definition of a human embryo. However, at a HYBRIDA workshop organized by WP4 in Copenhagen in 2022, organoid researchers raised concerns about whether certain types of organoid research (e.g., the recent production of post-blastocyst embryo models or research that could produce increasingly advanced gastruloids) would be deemed to be creating human embryos and thereby excluded from EC funding programmes (Ravn et al., 2022).

Since the HYBRIDA project commenced in February 2021, there have been substantial developments that have fueled the calls made by organoid researchers for legally explicit definitions.



The first relates to developments in the field of human embryo model research. Human embryo models intended to recapitulate post-implantation embryogenesis, including gastruloids (embryonic stem cell-derived embryo-like structures devoid of a primitive streak that marks the start of gastrulation), have generally lacked the essential extraembryonic tissues and cells needed to recapitulate embryo development and morphology (Weatherbee et al., 2023). However, research involving gastruloids is becoming increasingly advanced, with human and animal gastruloids being developed to model increasingly later stages of embryogenesis where: i) somitogenesis occurs (van den Brink et al., 2020); ii) the heart field starts to develop at early stages of cardiac primordia (Rossi et al., 2021); and iii) extra-embryonic structures develop in vitro (Mackinlay et al., 2021). Most recently, Liu and colleagues (2023) developed a method to derive “peri-gastruloids”, encompassing both embryonic and extraembryonic tissues, and which recapitulate critical stages of human peri-gastrulation development.

At least in the past 12 months, developments in the research of stem cell-derived blastocyst-like structures that represent the integrated development of the entire embryo, including its extraembryonic membranes (Niemann and Seamark, 2021), have received significant amounts of media attention. As Weatherbee et al. (2023) note, generating a sufficiently integrated human embryo model with relevant embryonic and extraembryonic cell types that can develop to post-implantation stages has been challenging, with significant developmental limitations in those blastocyst-like structures that have been developed from human embryonic stem cells. But the issue has always been that, at least in principle, such embryo models have the potential to achieve the complexity by which they might realistically undergo further integrated development if cultured for additional time in appropriate conditions, or, theoretically, if transferred to a uterus (Lovell-Badge et al., 2021). It is against this background that, in the summer of 2023, teams led by Magdalena Zernicka-Goetz (Weatherbee et al., 2023) and Jacob Hanna (Oldak et al., 2023), respectively, received significant global press coverage when they reported establishing separate models of a human post-implantation embryo comprising embryonic and extraembryonic tissues which could mimic several critical stages of post-implantation development. However, it is important to note that the findings presented by Zernicka-Goetz and her team, and, to a lesser extent, those by Hanna et al. have been the subject of criticism in the field (Martinez Arias et al., 2023), and the publicity which these studies have received has also been criticized, largely on the basis that the initial wave of global “media frenzy” was based on two preprints that had not been subjected to peer review (Ball, 2023).

Closely bound up with these recent developments in the field of blastoid and gastruloid research is the issue of the regulation of human embryo model research (or lack thereof). The limitations in the regulation of this field of research have been thrown into focus as the above-mentioned advances in the complexity and developmental capacity of these models have reduced the conceptual and biological gaps to real human embryos. At the same time as these gaps have narrowed, human embryo models have, as a result, increasingly challenged legal definitions of the human embryo (see Rivron et al., 2023)

Traditionally, many legal definitions of the embryo have incorporated fertilization of an ovum by sperm, or cloning, as a necessary condition. IVF embryos satisfy this condition and, in many jurisdictions, are protected with a prohibition on research beyond 14 days culture (or the appearance of the primitive



streak). Despite some jurisdictions revising their initial definitions of the human embryo to accommodate features such as potentiality and/or critical developmental stages (e.g., gastrulation), fertilization has generally remained a constant (though not the case in Germany, Belgium, and the Netherlands, for example). The key point to consider here is that the fertilization condition would exclude human embryo models formed from human stem cells, meaning that they would not, as a matter of principle, be subject to the legal protections afforded IVF embryos.

The point that Rivron and colleagues (2023) have made is that as the biological gap between human embryo model and human embryo continues to narrow, so too – but for ethical reasons – should the legal gap.

Thus, there is a need to ensure that human embryo model research is regulated such that these models – at the point at which the biological and ethical gaps to real human embryos disappear – can be captured within regulatory frameworks for in vitro embryo research.

Notably, this does not necessarily require that we reach a consensus about what a human embryo is, i.e., biologically, naturalistically, or metaphysically. Nor do we need to know for certain whether an embryo model being generated really is a human embryo proper. Instead, to regulate research with human embryo models accordingly, what is needed is a *normative* definition of a human embryo that would include some possible embryo models, i.e., those models where the ethical and/or legal distinctions with a human embryo disappear.

For example, Rivron et al. (2023) have proposed a definition of a human embryo as “*a group of human cells supported by external elements fulfilling extraembryonic and uterine functions that, combined, have the potential to develop into a fetus*”.

Again, Rivron et al. are not saying that this biologically defines a human embryo nor are they claiming to know what a human embryo is. In fact, they acknowledge that their definition diverges in several ways from those offered by biologists. Furthermore, they recognize that current methods for developing embryo models require the use of cells that rapidly accumulate genetic abnormalities and are too abnormal to form a fetus. On that basis, they acknowledge that they do not know whether human embryo models are, or will ever be, more than models.

Rather, one of the purposes of a normative definition, of which Rivron and colleagues’ is an example, is to function as a means of demarcating an entity – in this case, a *possible* embryo model – whose characteristics, functions, and capacities are normatively (i.e., ethically and/or legally) comparable to those of real human embryo such that the entity can be afforded legal protections comparable to those of a real human embryo. And the entity should be afforded such legal protections precisely because we have good reasons to believe that the similarities between the characteristics, functions, and capacities of the entity and those of a real human embryo ethically and/or legally matter.

A second function of a normative definition of a human embryo is that it provides scope for individual jurisdictions to set the boundaries for permissible research according to their local values, charters, and



other legislation. For instance, as Rivron et al. (2023) demonstrate, by defining a human embryo, in part, as something with “the potential to develop into a fetus”, individual jurisdictions can then set their own “tipping point” for the stage at which they consider that potential to be sufficiently demonstrated.

Rivron et al.’s proposed regulatory definition is by no means perfect. There are still uncertainties underlining it: for instance; it is unclear precisely which fetal stage is referred to; and there is a lack of clarity about what distinguishes a genuine human embryo model from a mere tissue culture. It follows, as noted by organoid researchers at a recent HYBRIDA focus group (Ravn, Falkenberg and Sørensen, 2024), that future proposals for a normative definition of a human embryo should seek to establish a clear normative definition of a human embryo model such that there is adequate clarity about the “tipping point” at which an in vitro model and a real human embryo should be treated as normatively comparable.

It is worth acknowledging that Rivron et al.’s proposed normative definition demonstrates the possibility that regulators can respond to the speed at which embryo model research is progressing without there being any consensus or certainty as to what these entities, in fact, are and with significant limitations on what scientists know about them.

4.9.3 *Proposals*

In light of Article 18 of Regulation (EU) 2021/695 – prohibiting the EU’s financing of activities intended to create human embryos solely for the purpose of research – we propose that the European Commission should provide a definition of a human embryo for this purpose, which, at the request of HYBRIDA’s stakeholders, should also clarify the “tipping point”; i.e., the stage at which an in vitro model will be excluded from funding (Ravn et al., 2023). However, given that the EU’s competence with regards to this issue only extends to legal provisions pertaining to the funding of research, rather than regulations that set the ethical standards for research, the questions of whether and to what extent certain forms of human embryo model research are legally permissible will need to be answered by individual Member States. In effect, this means that regulatory definitions of a human embryo will need to be provided by the European Commission (for funding purposes) and individual Member States (for research ethics purposes). We, therefore, propose that the European Commission, represented by the Directorate-General for Research and Innovation and the European Group on Ethics in Science and New Technologies, collaborate with the NEC Forum in developing these definitions, which, ideally, would result in a harmonized definition of a human embryo (even if individual Member States were then to set their own regulatory boundaries for human embryo model research). As part of the collaborative process, external expert opinion should be sought from the International Society for Stem Cell Research.



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