



**HYBRIDA**

## **D4.5. Report on Focus Group Consultation concerning an Ethical and Legal Framework for Organoid-based Technologies**

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**HYBRIDA**

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

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<b>Abstract:</b>	<p>The report presents the main results from a focus group consultation concerning an ethical and legal framework for organoid technologies. Six focus group interviews were conducted, wherein experts were consulted to help validate issues related to the latest version of the HYBRIDA Operational Guidelines for the Field of Organoids and Organoid-Related Technologies (Chneiweiss et al. 2023) and a regulatory framework for the field (Lewis and Holm 2022). In all, 35 key experts in the field participated in the consultation process, with representation from the research community, industry, patient organizations, biobank networks, stem cell registries, donor organizations, European agencies, research ethics committees, and research integrity offices. The experts represented 17 different European countries. The report addresses the following main topics and provides several recommendations to be addressed for the ethical and legal guidelines produced in HYBRIDA: i) the overall set of Operational Guidelines; ii) Informed Consent; iii) Existing Cell Lines and Ownership; iv) Classification and Regulation of Organoids for Medical Use; and v) Embryo Models and Neural Organoids.</p>
<b>Keyword List:</b>	<p>Focus group consultation, organoid-based technologies, legal and ethical aspects, operational guidelines, informed consent procedures, commercialisation, existing cell lines, ownership, material transfer agreements (MTAs), classification, new Advanced Therapy Medicinal Products (ATMPs), human stem cell-derived embryo models, neural organoids.</p>

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## Executive Summary

The main objective of work package 4 in the HYBRIDA project has been to consult with and engage a broad spectrum of citizens and professional stakeholders throughout the process of developing, designing, and producing ethical and legal guidelines and frameworks concerning organoid and organoid-related technologies. The primary aim of this process has been to help ensure that the documents and guidelines produced in HYBRIDA are responsive to the diverse requirements, concerns, and recommendations of citizens, professional stakeholders, and the research community, while remaining adaptable to scientific advancements and current and emerging ethical and legal concern.

The engagement and consultation process has comprised three stages. The last stage, reported in the current report, includes a focus group consultation. A total of six focus group interviews have been conducted, wherein experts and professional stakeholders were consulted to help validate the latest version of the HYBRIDA products. A total of 35 key experts in the field have participated in the consultation process, with representation from the research community, industry, patient organizations, biobank networks, stem cell registries, donor organizations, European agencies, research ethics committees, and research integrity offices. The experts have represented a total of 17 different European countries, including Austria, Belgium, the Czech Republic, Denmark, England, Finland, France, Germany, Greece, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Spain, Sweden, and Switzerland.

Each focus group interview has addressed different key ethical and regulatory issues through collective discussion, reflection, and idea generation and has provided a structured exploration and assessment of the remaining open questions and unresolved concerns related to the latest draft versions of the ethical and regulatory guidelines produced in WP5 and WP6 of the project. The six focus group discussions have addressed the following main topics:

- Validation of the existing set of ‘Operational Guidelines for the Field of Organoids and Organoid-related Technologies’, their relation to a Code of Conduct for the field, and ethics by design
- Donor’s Organoid Wish List and informed consent
- Informed consent, withdrawal, and exchange of material (MTAs)
- Commercialisation, existing cell lines, ownership and intellectual property rights
- Classification and regulation of organoid-based technologies for medical use
- Embryo models and neural organoids

The deliverable reports on expert observations and recommendations, stemming from a validation and consultation process primarily based on existing materials and related open questions. A summary of these main empirical findings and recommendations concludes each main section in the report and is summarized in the tables below.

Operational Guidelines		
TOPICS	ISSUES	RECOMMENDATIONS
<b>Ethics by Design</b>	Consistency in how ethics by design is described	<ul style="list-style-type: none"> <li>Currently, ethics by design is described inconsistently in the guidelines. To improve clarity, it should be consistently defined throughout the document as a continuous anticipatory process.</li> <li>The guidelines should build upon their analysis of how to practically apply an ethics by design approach within the field of organoid research.</li> </ul>
	Addressing values	<ul style="list-style-type: none"> <li>Even though a fixed set of values cannot be established, identifying underlying values remains important. It was suggested that these values should be made transparent, along with an explanation of how they were determined.</li> </ul>
	Hard impacts and soft impacts	<ul style="list-style-type: none"> <li>The operational guidelines should encompass the distinction between hard and soft impacts. Even though soft impacts might not typically be the focus of ethics by design, their inclusion in the guidelines can help increase awareness among stakeholders in the field.</li> </ul>
	Sufficient implementation of anticipatory processes	<ul style="list-style-type: none"> <li>It is suggested to pay attention to how processes such as ethics by design or RAD could be further enhanced to ensure that elements of reflection, anticipation, and deliberation are fully grounded and sufficiently implemented throughout the process of application.</li> </ul>
	Example of ethics by design	<ul style="list-style-type: none"> <li>It was suggested that some examples illustrating the ethics by design approach could be added to the annex of the guidelines, along with questions that could be considered.</li> </ul>
	<b>RICOCHECK</b>	Funding eligibility
	Remuneration	<ul style="list-style-type: none"> <li>The RICOCheck should include provisions addressing the remuneration of donors.</li> </ul>
	Cadaveric donors	<ul style="list-style-type: none"> <li>The RICOCheck should address cadaveric donors.</li> </ul>
	Categories for follow-up questions	<ul style="list-style-type: none"> <li>A Participant inquired whether there had been any consideration of structuring the open follow-up questions around pre-defined categories to minimize differing interpretations.</li> </ul>
	Abbreviations	<ul style="list-style-type: none"> <li>Abbreviations should be used with care and need to be defined.</li> </ul>
	Freedom to operate	<ul style="list-style-type: none"> <li>The RICOCheck should encourage researchers and developers to actively consider their freedom to operate.</li> </ul>
	Regulation and risk determination	<ul style="list-style-type: none"> <li>Additional questions that can assist in determining risks and identifying applicable regulations in specific situations should be added.</li> </ul>

<b>Code of Conduct</b>	Compatibility with other guidelines	<ul style="list-style-type: none"> <li>The HYBRIDA Code of Conduct should ensure compatibility with existing and related guidelines.</li> </ul>
<b>Missing elements</b>	Narratology and communication practices	<ul style="list-style-type: none"> <li>If possible, the operational guidelines could assist stakeholders in the field of organoid research in constructing narratives that inform the public about organoids, and provide examples or ideas for effective communication.</li> </ul>
	Anticipation of AI in the field of organoid research	<ul style="list-style-type: none"> <li>The operational guidelines should anticipate the use of automatic tools for organoid characterisation in the future.</li> </ul>
	International difference	<ul style="list-style-type: none"> <li>The guidelines could incorporate an analysis of how ethical perceptions vary across countries, leading to different research practices and norms.</li> </ul>
	Ethical awareness through interdisciplinary dialogue	<ul style="list-style-type: none"> <li>The operational guidelines should encourage dialogue across specializations and fields among all researchers working with organoids, with the aim of raising ethical awareness.</li> </ul>
	Publication of negative results	<ul style="list-style-type: none"> <li>The operational guidelines already address the issue of not publishing negative results. To combat this publication bias, it was suggested that the guidelines include ideas for open access platforms and archives where negative results could be published.</li> </ul>
<b>Dissemination and implementation of the guidelines</b>	Dissemination Platforms	<ul style="list-style-type: none"> <li>It was suggested that reaching out to BBMRI-Eric for the dissemination of the operational guidelines, as well as coordinating with EUREC for the training of research ethics committee members in organoid-related ethics, should be considered.</li> </ul>
<b>General observations</b>	Normative claims	<ul style="list-style-type: none"> <li>The guidelines encompass both empirical and normative claims. For the normative claims, it would be beneficial to add supporting documentation and clarify the distinction between existing practices and desired practices.</li> <li>It was mentioned that the Guidelines document should be reviewed to ensure that all used sources have been referenced. Currently, some references are missing.</li> </ul>

Informed Consent		
TOPICS	ISSUES	RECOMMENDATIONS
<b>Informed consent models</b>	Consent for governance model	<ul style="list-style-type: none"> <li>• General support for the idea of a consent for governance model.</li> <li>• It is unclear how the implementation of an independent and trusted third party would differ from existing structures and bodies.</li> <li>• A concern was raised about the establishment of additional bodies or committees, particularly regarding the challenges faced by smaller countries.</li> <li>• It is important that the governance model improves existing consent practices and does not inadvertently promote less ethical routes</li> <li>• Donors' willingness to trust a third party may be influenced by their trust in science and governance structures, and this can vary across countries. Sociological advice was recommended to inform any potential implementation of the model.</li> <li>• It was suggested to consider combining the consent for governance model with dynamic consent.</li> </ul>
	Broad consent	<ul style="list-style-type: none"> <li>• Patients may be more inclined to provide broad consent, primarily driven by their urgency to find a cure for their disease.</li> <li>• Broad consent might simplify administration for biobanks, but it may also offer less protection for donors.</li> </ul>
<b>Passport</b>	Implementation of passport model	<ul style="list-style-type: none"> <li>• General support for the idea of a passport accompanying biological samples.</li> <li>• Keeping track of the metadata over time would require appropriate infrastructure.</li> </ul>
<b>Donor's Organoid Wishlist</b>	Use and terminology	<ul style="list-style-type: none"> <li>• The wishlist is seen as a valuable questionnaire accompanying the informed consent.</li> <li>• The specific designation of a 'wish' list does not support the purpose and content of such a list.</li> </ul> <p>The importance of clear and adequate written and verbal information is highlighted to make sure that donors gain exact information about their donor contribution.</p>
	Modifications and additions	<ul style="list-style-type: none"> <li>• Suggestion to include whether donors would like to be re-contacted.</li> <li>• Suggestion to include the issue of incidental findings.</li> <li>• Suggestion to include a provision to determine whether genetic modification is permitted.</li> <li>• Suggestion to include an option to consent to 'unforeseen future research'.</li> <li>• Suggestion to specify European countries vs. EU countries.</li> </ul>

		<ul style="list-style-type: none"> <li>Suggestion to define the meaning of genomic studies. Suggestion to specify the following categories: commercialisation, research structures, country selection, cerebroids and embryo models.</li> </ul>
<b>Withdrawal of consent</b>	Extent of withdrawal	<ul style="list-style-type: none"> <li>withdrawal up to the point of cell processing might be the accepted approach but suggestion to extend to the point of distribution.</li> <li>The issue of withdrawal should be addressed at both an EU and national level.</li> </ul>
	Transparent provision	<ul style="list-style-type: none"> <li>A clear and transparent provision should outline the specific limitations of the right to withdraw in the consent form.</li> <li>An option for participants to accept or decline being re-contacted should be included</li> </ul>
	Tiered withdrawal	<ul style="list-style-type: none"> <li>The practice of 'tiered withdrawals' could serve as a model for inspiration.</li> </ul>
	Minors	<ul style="list-style-type: none"> <li>More guidance should be provided about withdrawal rights for minors, including offering children additional opportunities for re-consent at the age of majority and tailoring information specifically for children</li> </ul>
	Data Protection Regulation and withdrawal	<ul style="list-style-type: none"> <li>It is not permissible to switch from consent to legitimate interests in the event of a data subject's withdrawal and insist that the data must be retained</li> </ul>

**Commercialisation, Ownership and MTAs**

<b>Commercialisation, Ownership and MTAs</b>		
<b>TOPICS</b>	<b>ISSUES</b>	<b>RECOMMENDATIONS</b>
<b>Commercialisation and existing cell lines</b>	Traceability of origin and informed consent for commercially existing cell lines	<ul style="list-style-type: none"> <li>It is regarded as a complex matter and actions with a retrospective perspective are perceived as challenging to implement.</li> <li>Companies have shown reluctance to provide informed consent forms and may instead issue a statement concerning user restrictions</li> <li>Seeking approval from a research ethics committee for the use of specific samples may be an alternative option.</li> <li>It is suggested that the EU Commission be involved as a funding body, implementing funding requirements regarding the ethical provenance necessary for the purchase of cell lines.</li> <li>It is suggested that attention be paid to potential 'reputational risks' associated with using samples that lack sufficient ethical provenance, particularly in relation to public perception and trust.</li> </ul>



<b>Ownership, patents and property rights</b>	Ownership of organoids	<ul style="list-style-type: none"> <li>• There is agreement that 'a donation is a donation', and once consent for donating is given, it should no longer be seen as one's property.</li> <li>• The legislation regarding this issue should be clear.</li> <li>• Patients and donors should be properly informed about these complex matters through informed consent procedures. Misinformation concerning donated cells should be prevented.</li> </ul>
	Patents	The issue of patenting organoids is an important topic for debate. A concern was raised that some patented methods and outcomes do not accurately reflect actual practices, and that many of these methods are not reproducible in other laboratories.
<b>Material Transfer Agreements (MTAs)</b>	Opposition between de jure and de facto understandings	<ul style="list-style-type: none"> <li>• Experts pointed to a divide between the legal and practical understanding of material transfers. While a legal experts perceived the GDPR legislation to be rather clear for EU and equivalent GDPR countries, other experts pointed to difficulties with data transfer agreements due to both national and cross-country variations in the legal GDPR interpretation.</li> <li>• A concern was also raised about the difficulty in verifying whether the original consent is acknowledged and followed when samples are reused for new projects in different labs within the same institution.</li> </ul>

Classification of Organoids for Medical Use		
TOPICS	ISSUES	RECOMMENDATIONS
<b>Potential regulatory gaps for classification</b>	Coverage of existing legislation	<ul style="list-style-type: none"> <li>• There is a consensus that no regulatory gaps exist in the classification of organoids, and there are no anticipations of any potential applications of organoids as medical products that would not fall under the existing regulations for medicinal products</li> <li>• There is a consensus on the lack of need for introducing additional requirements.</li> </ul>
	Organoid products achieving a therapeutic effect through functional integration	<ul style="list-style-type: none"> <li>• Experts concurred that these would be covered by the ATMP legislation.</li> </ul>
	Recommendations at the pan-European level	<ul style="list-style-type: none"> <li>• Particularly small jurisdictions might rely on guidance from the EU level.</li> </ul>



<b>Over-regulation</b>	Overregulation of the approval process for obtaining market authorization for new ATMPs	<ul style="list-style-type: none"> <li>Experts agreed that the area is not over-regulated and that too many regulatory burdens are not placed on the potential applicants.</li> </ul>
	Regulatory assessment	<ul style="list-style-type: none"> <li>Based on the risk-based approach and evaluated contextually on a case-by-case basis. Likely to be additionally comprehensive for organoid-based technologies due to their complex nature.</li> </ul>

<b>Sensitive Organoid Technologies</b>		
<b>TOPICS</b>	<b>ISSUES</b>	<b>RECOMMENDATIONS</b>
<b>Human stem cell-derived Embryo Models</b>	Europe-wide discussions	<ul style="list-style-type: none"> <li>The warranting of special legal and ethical protection of embryo models should be discussed at the European level.</li> </ul>
	Ethical and legal oversight	<ul style="list-style-type: none"> <li>Different embryo models requires distinct types of ethical oversight. It is recommended to follow the current ICCSR guidelines (2021) and that the aligned Guidelines categorisation remains useful for research ethics committees.</li> <li>Some procedures are deemed unsafe, e.g. the transfer of embryos models into any uterus (human or animal host).</li> </ul>
	Definitions needed	<ul style="list-style-type: none"> <li>Currently, embryo models should not be regarded as embryos, either biologically or legally.</li> <li>However, the current heterogeneous regulatory landscape creates challenges. A more precise legal definition of a human embryo is necessary to delineate its distinction from in vitro models and to help clarify the 'tipping points'.</li> <li>A clear definition of an (embryo) model is needed.</li> </ul>
	'Tipping point'	<ul style="list-style-type: none"> <li>Two complementary Turing tests are recommended as indicators to determine the reach of the tipping point: 1) if a human embryo model can 'efficiently and faithfully' form the entire embryo in vitro, and 2) the embryo model can form fertile and living animals such as pigs and non-human primates.</li> </ul>
	Cultivation	<ul style="list-style-type: none"> <li>The issue of cultivation is considered one of the most pressing questions. It is suggested to follow the recommendations of the UK and France, allowing integrated embryo models to develop until day 28. This would permit research into the period of</li> </ul>

		embryogenesis, while adhering to the gradualist approach and the principle of proportionality.
	Principle of subsidiarity	<ul style="list-style-type: none"> <li>The principle of subsidiarity could be incorporated into the operational guidelines and also be a topic for discussion at the European level.</li> </ul>
	Tone in operational guidelines	<ul style="list-style-type: none"> <li>The focus on ‘synthetic human embryos’ in the text yields an alarmist tone that does not fully represent the field in general.</li> </ul>
	Science communication	<ul style="list-style-type: none"> <li>Responsible science communication and media representation are crucial. Liaising with ESHRE for dissemination efforts is recommended.</li> </ul>
<b>Neural Organoids</b>	Nomenclature	<ul style="list-style-type: none"> <li>The term 'neural organoids' should be used as the overarching descriptor, while the use of 'cerebroids' should be avoided.</li> <li>Sentience and consciousness are terms that are applied somewhat widely and variably within the field, and thus should be precisely defined.</li> </ul>
	Guidelines inclusion	<ul style="list-style-type: none"> <li>The Operational Guidelines are correct in including the topic of neural organoids. An open-ended approach can be legitimized due to the current state of the field, which leads to less tangible ethical considerations.</li> <li>Ethical guidelines and regulations are crucial but should not impede the use of innovative methods.</li> </ul>
	Specialized ethical oversight	<ul style="list-style-type: none"> <li>The ISSCR's position, stating that no current concerns or specialized ethical oversight are warranted, is agreed upon. However, this stance should be monitored as neural organoids and assembloids become more mature and complex.</li> </ul>
	Tipping points Consciousness and sentience	<ul style="list-style-type: none"> <li>Several prerequisites are necessary, including structured organization, interaction with the environment (input-output), and a certain level of size and complexity. This can be compared to animals, which are attributed a degree of consciousness. Another potential tipping point could be sentience, but it is challenging to distinguish between 'noxious stimulus avoidance' and the experience of pain as an emotional state. The latter is seen as the primary concern</li> </ul>
	Measurement of consciousness for organoid models	<ul style="list-style-type: none"> <li>Focus is directed at ways to measure consciousness for organoid models whereas it might be more beneficial to compare to what can be measured in terms of existing brain develop requirements and prerequisites for consciousness. Drawing parallels to established understandings and alternative applied models can also provide a more robust framework for legal and ethical comparisons.</li> </ul>



# 1. Introduction to HYBRIDA

HYBRIDA is a three-year project funded by the Horizon 2020 Framework Programme which aims to develop a comprehensive ethical and regulatory framework for the field of organoid research and organoid-related technologies<sup>1</sup>.

Organoid research comes with ambitious promises of revolutionising biomedical research in the future and with it our view of the human organism and life itself. As such a train leaves the station, it is vital that ethics not only follows but is there on the train, shaping the journey as it is charted.

An organoid is an 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 using organ-specific cell types, such entities might serve as “three-dimensional culture models” mimicking the structural and functional properties of different organs, both human and non-human, such as the retina, heart, brain, intestine, kidney, pancreas, liver, inner ear, and skin.

Since Roman times, all entities have been categorised and regulated either as persons or as things (subjects or objects). Organoids, organoid research, and organoid-related technologies challenge this conceptual, epistemological, and regulatory dualism. That is, the dualistic normative framework pertaining to health and life science research is disrupted by three different kinds of uncertainty.

## 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.

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

<sup>1</sup> The description of the HYBRIDA project is reproduced from the HYBRIDA project description (HYBRIDA Consortium, 2020, pp. 2-3).



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 personalised or precision medicine, where the number of research subjects with a certain characteristic is too low for randomised controlled trials or other statistically based experiments. As precision medicine and new technologies emerge, evidence-based medicine is challenged to find new footing. Epistemological uncertainty comes in two kinds, which can be categorised as qualitative, or strict, uncertainty and 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. In order to develop ethically and socially robust ways of assessing the effects of organoid research and related technologies, there is a need to include these additional forms of uncertainty in the Health Technology Assessment.

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 will address 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. Introduction to D4.5

The main objective of work package 4 in the HYBRIDA project is to consult with and engage a broad spectrum of citizens and professional stakeholders throughout the process of developing, designing, and producing ethical and legal guidelines and frameworks concerning organoid and organoid-related technologies. The primary aim of this process has been to ensure that the documents and guidelines produced are responsive to the diverse requirements, concerns, and recommendations of citizens, stakeholders, and the research community, while remaining adaptable to scientific advancements and current and emerging ethical and legal concern.

The comprehensive ethics and regulatory framework that the HYBRIDA project aims to develop comprises four main components: 1) a set of operational guidelines for the field; 2) a Code of Responsible Conduct for researchers; 3) contributions to existing ethics and normative frameworks; and 4) if needed, a supplement to the European Code of Conduct for Research Integrity (HYBRIDA Consortium 2020, p. 3).

The engagement process has involved a three-stage approach, starting with mapping and deliberating on stakeholder concerns across different social contexts and societal groups, and ending in a final expert assessment and validation process. The overall process has been supported by a comprehensive empirical program, which included public deliberative workshops, expert co-creation workshops, expert interviews, and focus group interviews. Specifically, the first engagement activity, completed in 2021, consisted of three deliberative workshops involving the public and patients, among other stakeholders, in Denmark, Italy, and Greece. These workshops aimed to explore public attitudes towards organoids (Ravn et al., 2022; Ravn 2023). For the second stage of the engagement process, two co-creation workshops with experts and professional stakeholders, as well as 15 expert interviews, were conducted. These activities were focused on discussing and further developing the first draft of the project products (Ravn et al., 2023). This stage was completed by the end of 2022.

The focus group study, reported in this deliverable, constitutes the third and final stage of the engagement process. A total of six focus group interviews were conducted, wherein experts and professional stakeholders were consulted to help validate the latest version of the HYBRIDA products. Each focus group interview addressed different key ethical and regulatory issues through collective discussion, reflection, and idea generation. These consultations provided a structured exploration and assessment of the remaining open questions and unresolved concerns related to the latest draft versions of **the ethical and regulatory guidelines**. In addition to an introduction to the HYBRIDA project, the current report, and the focus group study's research design, the report is structured around five main empirical chapters. These chapters collectively report on the topics addressed in the six focus group discussions; i) the overall set of Operational Guidelines; ii) Informed Consent; iii) Existing Cell Lines and Ownership; iv) Classification and Regulation of Organoids for Medical Use; and v) Embryo Models and Neural Organoids.



## 3. Methodology

In this section, we outline the methodology underlying the focus group study, which constitutes the third and final stage of the HYBRIDA engagement process. Initially, we introduce the research design, followed by a description of the recruitment process and the data analysis approach of the study.

### 3.1. Research design

The focus group study seeks to assess and validate the main HYBRIDA products and contribute to their finalisation (see also the research protocol for the study, Ravn and Sørensen, 2021a). By consulting relevant experts and professional stakeholders, the study aims to “ensure that the outputs of the project meet the actual needs of relevant stakeholders and provide tangible support for researchers, research integrity bodies, research ethics committees, among others, and contribute towards the intended impacts within the field of organoid research and organoid related technologies” (Ravn and Sørensen, 2021a). More specifically, the focus group study addresses the following research questions:

- To which extent and in what way are the proposed standards in alignment with the required needs, developments and conceptualisations within the field of organoid research according to professional stakeholders? (Ravn and Sørensen, 2021).
- How should these new standards and good practices be implemented? (HYBRIDA 2020, p. 13).

The focus group method relies on data generation through group interaction and discussion (Morgan 1997). The focus group interviews create a forum for discussion, reflection, and idea generation. This approach allows us to systematically explore remaining open questions and concerns in relation to the latest draft version of the project products. It also helps to gain insight into interpretations and assessments of these products across different stakeholder groups and contextual variations (Ravn and Sørensen, 2021a).

The focus group study consisted of six focus group interviews conducted throughout September and the beginning of October 2023. Of these, three interviews took place on-site: one at Sorbonne University in Paris and two at Hotel Otillia in Copenhagen. The remaining three interviews were conducted online using Microsoft Teams to facilitate participation from across Europe. The topics for discussion and validation in the focus group study were identified in close collaboration with Work Package 5 (WP5), which is responsible for developing a set of operational guidelines and a code of responsible conduct for the field, and Work Package 6 (WP6), which is developing a regulatory framework for organoid research and organoid-based technologies. Each focus group addressed a distinct topic, although there were certain overlaps between some groups. As shown in the list below, informed consent, for example, was a topic discussed in multiple focus groups:



- Validation of operational guidelines, their relation to a Code of Conduct for the field, and ethics by design (on-site, Paris)
- Donor's wish list and informed consent (on-site, Copenhagen)
- Informed consent, withdrawal, and exchange of material (on-site, Copenhagen)
- Commercialisation, traceability of origin and donor's consent, and intellectual property rights (online)
- Classification and regulation of organoid-based technologies for medical use (online)
- Embryo models and neural organoids (online)

Each focus group interview lasted approximately one hour and thirty minutes. A moderator guide was composed for each group (see Appendix E-J) to ensure that all remaining concerns and open questions regarding the different HYBRIDA products were addressed. While the predefined questions varied between the interviews according to the topics discussed, participants in all groups were initially asked for their first impressions of the latest draft version of the specific HYBRIDA product. This was done to explore their immediate thoughts and identify any potentially overlooked issues before the finalization of the products.

All focus group interviews were conducted by members of WP4 (TR and MPS). A representative from WP5 participated in the focus group interview that discussed the 'validation of operational guidelines, their relation to a Code of Conduct for the field, and ethics by design.' Similarly, a member of WP6 was present in the group discussing the 'classification and regulation of organoid-based technologies for medical use' to assist with answering clarifying questions about the focus group material. Additionally, two participants provided written comments subsequent to the interviews.

### **3.2. Sampling, Recruitment, and Practical issues**

Each of the six focus groups consisted of five to eight participants, totalling 35 participants (one participant took part in two focus group discussions) across all groups after accounting for five cancellations. Participants were purposefully recruited based on their relevant knowledge and expertise in the areas discussed in the individual focus groups. The focus group study included representation from the research community, industry, patient organizations, biobank networks, stem cell registries, donor organizations, European agencies, research ethics committees, and research integrity offices (for a complete list of focus group participants, please see Appendix A). Of the participants, 15 were men and 20 were women, representing a total of 17 different European countries, including Austria, Belgium, the Czech Republic, Denmark, England, Finland, France, Germany, Greece, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Spain, Sweden, and Switzerland. Eight experts and stakeholders who had previously participated in the co-creation workshops and/or expert interviews during the second phase of the engagement process also took part in the focus group study. This recurrence of participants bridges the second and



third stages of engagement activities, as they are able to bring earlier deliberations and recommendations into the focus group discussions (Ravn and Sørensen, 2021a). It further enhances the transparency of the advances and adjustments made between the co-creation deliberations and the final validation and assessment process (Ravn and Sørensen, 2021b).

The recruitment process for the study relied on the vast network of the HYBRIDA consortium, referrals, and desk research (Ravn and Sørensen, 2021b). Potential participants were invited via email (see Appendix B). Upon accepting the invitation, they received a consent form (Appendix D), a letter of information about the specific interview (Appendix C), and relevant reading material to prepare for the focus group discussions. This material was sent no later than two weeks prior to their scheduled interviews. The provided material varied between groups, depending on the discussion topic. All groups discussed at least one section from the latest draft version of the operational guidelines for organoid research (Chneiweiss et al., 2023; for an earlier draft version of the set of operational guidelines, please see Chneiweiss et al. 2022). Additionally, three focus group discussions also built upon discussion papers provided by WP6 concerning the regulatory framework for the field of organoid research and organoid-based technologies. Specifically, the topics cover embryonic models and neural organoids; informed consent, withdrawal, and exchange of material and classifying and regulating organoid-based technologies for medical use (see also Lewis and Holm 2022 for a legal discussion on the issues).

All experts participated in the focus group interviews in their capacity as experts within their respective fields. As stipulated in the consent form, all experts are presented in a non-anonymous format in Appendix A to recognize their contributions and enhance transparency in terms of expertise representation. In the analysis, no quotations or text are attributed to specific experts.

For the focus group interviews in Paris and Copenhagen, a member of WP4 (MF) offered to assist participants with accommodation and travel bookings and the HYBRIDA consortium covered their expenses in relation to their participation in the focus group study. Participants in the three on-site interviews received a small token of appreciation, but no remuneration was paid for any of the focus group interviews.

### 3.3. Data Analysis

All focus group interviews were recorded. One project member subsequently transcribed the recordings verbatim, and then thematically coded the transcriptions in the software and data facilitation program NVivo 12, (MF). The coding process primarily followed a deductive strategy. The interviews were initially coded according to the main and sub-themes structuring the different moderator guides. This was accompanied by the coding strategy of initial coding (Charmaz, 2006), which allowed for emerging themes and topics to be explored and inductively derived. The findings and recommendations presented in the following chapters are based on a thematic analysis and reporting of the different ethical and legal topics discussed both within and across the six focus group interviews.



## 4. The Set of Operational Guidelines

One of the main products developed within the HYBRIDA project is a set of Operational Guidelines for the Field of Organoids and Organoid-related Technologies (Chneiweiss et al. 2023). One focus group was dedicated to discussing the guidelines at large, including a discussion on the implementation of an Ethics by Design approach and the Guidelines' interlinkage with a Code of Conduct within the field. Specifically, the discussion revolved around the following main questions:

- Does the report D.5.1 'Operational Guidelines for the Field of Organoids and Organoid-related Technologies' sufficiently cover the issues that one could expect to be covered in a set of guidelines for the field?
  - Relatedly, do the guidelines sufficiently cover issues of relevance and needs for the different stakeholders addressed (researchers, RECs, RIOs)?
  - Would some of the issues and elements discussed in D.5.1. be more relevant to include in a specific Code of Conduct document for the field?
- Third, we would like to discuss your views on the Ethics by Design description, understanding and approach as specified in D.5.1. In addition, we would like to discuss how to best implement an Ethics by Design approach within the field of organoid research?

The following sections report on expert assessments and recommendations for these cross-cutting issues and include additional and related guideline issues raised by experts across focus groups. Furthermore, this chapter also includes an expert assessment of the specific Checklist for Research Integrity Committees on Organoids, called RICOCheck. This topic was discussed in the interview concerning the classification and regulation of organoids for medical applications, particularly regarding whether additional information and questions are required in the checklist.

### 4.1. Ethics by Design

To effectively anticipate and reflect upon ethical issues related to the field of organoid research, the operational guidelines have drawn on the Ethics by Design approach, which overall relates to bringing 'ethical and societal values into the design and development of technology from the very beginning of the process' (ALLEA in Chneiweiss et al. 2023, p. 9).

Different views emerged on how the 'ethics by design' approach applies to organoids. One expert opined that in relation to emerging technologies, this approach either does not apply or applies in varying ways to biotechnologies. At the same time, this expert commented on the section in the Guidelines that discusses the meaningful use of an 'ethics by design' approach within the field of organoid technologies.



The expert agreed with the guideline argument that applying an ethics by design approach, which promotes value agreement, is challenging in the field of biotechnology due to 'tensions by definition'. The expert strongly advised building upon this analysis concerning the practical application of anticipation rather than turning to the more general philosophy of technology, as is currently done in the subsequent paragraphs. It was also noted that there is a change in the style of writing in the ethics by design annex, as it shifts from a collective perspective to an individual one. Another expert pointed out that organoid research effectively illustrates the importance of the ethics by design approach. It was noted that the application of this framework in the guidelines can foster reflection among stakeholders in the field, leading them to consider issues they might not have otherwise recognized or conceptualized. A third expert concurred with the relevance of applying an ethics by design approach within the field of organoid technologies, highlighting the value of the particular annex in demonstrating that these technologies are not 'neutral'.

A part of the ethics by design discussion focused on comparing organoid research with artificial intelligence (AI) technology from an ethics by design point of view. This comparison is mentioned in the latest draft of the Operational Guidelines, where AI is highlighted as the primary field of application for the ethics by design approach:

- It was suggested that one of the main **similarities between organoids and AI** is that researchers in both fields do not necessarily know what they are capable of. Thus, the similarity does not just lie in the technology but also in the research, which was identified as a more valuable comparison. It is mentioned that it is in terms of the research perspective that the ethics by design approach is particularly valuable.
- The latest draft of the operational guidelines mentions autonomous vehicles, which sparked some discussion. One expert questioned the **comparison between autonomous vehicles and organoids**, noting that the ethics discussion for autonomous vehicles centers around finding the 'right' ethics, whereas for organoids, it involves ethical plurality. Another expert found the comparison useful for highlighting a key difference: for autonomous vehicles, it is clearer how ethics can influence the design of the technology, while this is less apparent for organoids. In this manner, the example could serve as an educational tool to illustrate the differences among various technologies. It was also suggested that a clearer distinction should be made between 'ethics by design by environment and by user'. Although ethics in stem cell biology may relate less to the design aspect (compared to hardware, for instance), ethics are clearly connected to the environment in terms of standardization processes, guidelines, and usage. While the expert acknowledged that ethics seem to have a lesser role in the actual design, the expert also emphasized that this could be viewed as a starting point and questioned the notion that ethics cannot alter the 'biology of the cell'.
- It was suggested that some **examples illustrating the ethics by design** approach be added to the annex of the guidelines, along with questions that could be considered. Once again, autonomous



vehicles were discussed as an example. On one hand, it was argued that this would provide an easily understandable instance of ethics by design, which could then be used to contrast with organoids. On the other hand, it was suggested that equally concrete examples exist within the field of organoids, such as the study of tumoroids.

Besides the discussion and comparison with AI, a wide range of suggestions and input related to the ethics by design approach were brought up and discussed during the focus group interview:

- It was recommended to **ensure that 'ethics by design' is described consistently** throughout the entire set of operational guidelines. In the latest draft version, some inconsistencies were identified: in some sections, ethics by design is described as a continuous process, while in others, it suggests that issues should be solved from the outset. It was argued that ethics by design should be viewed as a continuous process of anticipation, considering that the future, and hence anticipation, is not static. A comparison of anticipation is made when addressing the issue of responsibility in research. This is also not done in a static fashion; responsibility is borne not only by developers but also by funders, and those who commission or sell the technology. On this basis, it was recommended to broaden some of the existing statements concerning ethics by design in the document, to resolve the identified tensions between promoting both a static and a variable approach.
- **Identifying the values underlying a technology was deemed essential.** While proposing a fixed set of values may not be feasible, ensuring their transparency and explaining how they are arrived at is emphasised as important.
- It was suggested that the operational guidelines should distinguish between '**hard impacts**', such as issues and requirements related to storing and processing organoids in biobanks, and '**soft impacts**', which include societal impact, representations and attitudes. In this regard, it is argued that a distinction is required as they require different ethical assessment processes. It is also stated that ethics by design relates to hard impacts and that it is difficult to envision how soft impacts could be addressed. Although soft impacts are difficult to predict, one expert recommended to include them in the operational guidelines through potential examples as this was seen as a valuable way to enhance researchers' awareness and encourage reflection on these aspects.
- During the discussion of ethics by design, the **RAD (Reflexive, Anticipatory, Deliberative) approach**, developed within the organoid ethics literature and applied to embryo models, was highlighted by an expert as a framework comparable to the ethics by design approach outlined in the guidelines (see, for instance, Ankeny et al., 2022). Similar to ethics by design, the RAD approach focuses on so-called 'hard impacts' and does not place much emphasis on social impacts. The expert expressed the view that these processes could be further enhanced to ensure



that elements of reflection, anticipation, and deliberation are fully grounded and sufficiently implemented throughout the process. In this context, it was suggested to apply a principle of moral complexity to align the scope and depth of the RAD processes with the complexity of the organoid entities, considering both biological and philosophical aspects. For example, it was noted that the creation of neural assembloids demands a more comprehensive RAD process compared to the creation of gut organoids.

## **4.2. Research Integrity Committee Organoid Checklist - RICOCheck**

As part of the operational guidelines, the Research Integrity Committee Organoid Checklist (RICOCheck) has been developed to assist research ethics committees and research integrity offices in assessing research projects involving the use of organoids (Chneiweiss et al., 2023). Composed as a questionnaire, the RICOCheck was discussed in one of the six focus groups, focusing on the following questions:

- Does anything need to be changed in the RICOCheck? Is there a need for more information/more questions in this checklist?

A researcher from the industry commended the level of detail in the RICOCheck, but participants also pointed to a number of additional elements and questions to be addressed in the checklist:

- In its current form, section one of the RICOCheck states that research involving **human embryonic stem cells is ineligible for EU funding**. It was suggested that this should be clarified to specify that it does not apply to products derived from embryonic stem cells, potentially through a footnote for instance.
- Some participants recommended to include **remuneration of donors** as part of the checklist with one expert specifically mentioned that in the EU it should be from non-remunerated donors when possible.
- It was suggested to address **cadaveric donors**, as the requirements related to such samples vary across countries.
- A researcher expressed uncertainty regarding the required information for the open follow-up elaborations on the closed yes-no questions. The expert inquired whether there had been consideration to structure these around **pre-defined categories**, to minimize varied interpretations.
- During the focus group interview, an expert recommended **caution with the use of acronyms**. They advised against using abbreviations without providing sufficient definitions, as the same



acronym could stand for multiple, very different concepts. Each of these concepts might be relevant to the matter at hand and could potentially lead to confusion.

- It was suggested that researchers and developers should be encouraged to consider their **freedom to operate** early on. This is to prevent them from only discovering their inability to license a product too late in the clinical trial process. While experts agreed not to use the term 'licensure' to avoid confusion, opinions differed on the preferred terminology. One expert suggested using 'patent protection,' while another favoured 'freedom to operate,' arguing that it encompasses more than just patents.
- In the discussion it was suggested to specify when **procurement** falls under the The European Union Tissues and Cells Directives (EUTCD) in relation to its intended use for human application. In this regard it was also suggested specifically that for a reviewer, it could be relevant to also gain information as to whether the purpose is for pre-clinical or clinical research, whether it is intended for human application, if there are multiple cell populations involved, and whether the cells are genetically modified since these factors play a part in determining risks. Additionally, another expert suggested including a flow diagram to illustrate the potential pathways to consider.

### 4.3. Code of Responsible Conduct for the Field of Organoids

Although primarily focusing on the set of operational guidelines for organoid research, participants in one of the focus group interviews briefly touched upon another main HYBRIDA product: a Code of Responsible Conduct for the field of Organoids and Organoid-related Technologies. This discussion was based on the following question:

Would some of the issues and elements discussed in [the operational guidelines] be more relevant to include in a specific Code of Conduct document for the field?

The latest version of the Code of Conduct was not sent to the focus group participants prior to their interview. However, printed copies were made available at the interview itself. Consequently, the relationship between the set of operational guidelines and the Code of Conduct was only briefly discussed. Two general remarks were made, echoing the co-creation workshop in Copenhagen (Ravn et al. 2023):

- One expert argued that Codes of Conduct can generally be viewed as tools for researchers to reflect on how **general ethical principles** apply more specifically to their field.
- Additionally, the expert emphasized that the HYBRIDA Code of Conduct, which is specifically aimed at organoid research and related technologies, should be **compatible with and not**

**contradict existing and related guidelines.** This was noted as a general observation rather than a call for change in the latest draft version of the Code of Conduct.

#### **4.4. Additional Issues**

In addition to the ethics by design approach, the RICOCheck, and the Code of Conduct, all of which were debated based on predefined questions, a variety of other issues, suggestions, and inputs for the operational guidelines emerged during the focus group discussions. Overall, participants across various focus groups commended the set of operational guidelines. They were praised for their clarity, and the executive summary was highlighted as an exemplary model for policy writing. Generally, the guidelines were considered useful for researchers and other stakeholders.

##### **Normative versus Empirical Claims**

In one of the focus groups, several experts noted that they found it difficult to determine whether some of the claims in the latest draft version of the operational guidelines are normative or empirical claims, mainly pertaining to the issue of informed consent practices. Thus, they recommended to make it explicit where a statement is coming from. One expert argued that it would be alright to include normative claims in the guidelines, but that it should be clearly stated when this is the case and that it should be transparent what the claim is positioned against.

##### **Suggestions for Additional Guideline Elements to be Included**

Experts and stakeholders across several focus groups highlighted various elements to include or further elaborate in the operational guidelines for organoid research:

- In one focus group, there was significant discussion about **communication practices** related to organoids. Utilizing the concept of narratology, the suggestion was made to assist stakeholders in building narratives that explain and convince people. For example, explaining why cerebral organoids are not ‘mini brains’ rather than solely relying on expert credibility to support such claims. The consensus was that including examples or ideas for effective communication in the guidelines, instead of just advising stakeholders on what not to do, would be beneficial. However, it was acknowledged that incorporating such content is challenging and uncommon in guidelines for other fields. Therefore, it was not identified as a top priority for future revisions of the operational guidelines.



- During the discussion on communication, an expert also pointed out that there is **no singular entity as ‘the general public’**. This diversity should be taken into account in communication strategies.
- Although currently conducted manually, a researcher suggested that the guidelines should anticipate the use of **automatic tools** for organoid characterization in the future. In a related discussion, another expert expressed concern that researchers might overlook potential issues, such as with the use of AI in their specific field.
- One expert expressed a wish for an **analysis of international differences** in ethical considerations. It was emphasized that just because ethical lines are drawn differently in other countries, it does not necessarily imply a lack of ethical reflection.
- An expert in ethics noted that organoid researchers often recognize ethical issues more readily in types of organoids outside their own specialty, and vice versa. Consequently, it was suggested that operational guidelines should promote **dialogue between organoid researchers across various specializations and fields**. This would help in raising awareness about these ethical considerations.
- Although the inclusion of **negative results publication** in the operational guidelines was praised, there was concern that ethical requirements alone might not be enough to effectively change publication practices. Therefore, it was suggested to also incorporate **requirements from funders** to publish all results, regardless of whether they are positive or negative. Concerns were raised by a researcher about the challenge of finding publishers for negative results. In response, it was recommended to identify and propose open access platforms and relevant archives that would accept such publications.

## Definitions and Standardisation

In one of the six focus group interviews, participants extensively discussed the issue of definitions and the prospects for standardization. While there was consensus on the importance of standardisation, experts differed in their opinions on whether and how to address this in the guidelines.

- Establishing **consensual definitions** was identified as a common challenge in new technologies, attributed to rapid changes and advances. An ethics expert requested an analysis of the dynamics complicating the consensus on definitions within the field of organoid research.
- There was significant disagreement regarding the type and level of detail needed in **definitions for standardization**. One ethics expert favoured a 'negative' definition, outlining what an organoid



is not, and linking it to issues like toxicology and precision medicine. In contrast, another expert argued for a 'positive' definition, essential for regulatory standardization, highlighting the challenges posed by vague or absent definitions in setting standards. A third expert, acknowledging the improbability of perfect definitions, considered the existing guidelines' definition of organoids functional and conducive to standardization. The expert noted that standards often evolve even without consensual definitions. Meanwhile, a fourth expert, acknowledging the difficulty in precisely defining organoids, suggested focusing on specific types of organoids instead of seeking an all-encompassing framework.

## Distinct Ethics for Organoids

Although the set of operational guidelines was commended for its usefulness to stakeholders in the organoid field and for addressing a real need, two focus groups touched upon the extent to which organoids present new and unique ethical issues. Some experts questioned the degree to which current-stage organoids differ from iPSCs, with an ethics expert suggesting that the ambiguities highlighted by organoids in the guidelines are generally present in technoscientific fields. Nevertheless, in two focus groups, experts identified several ways in which organoids may have distinct ethical considerations:

- An expert raised the question of whether one can **define a certain set of 'organoid ethics'**. The expert acknowledged that while the impact of organoids can be discussed concerning a range of topics — including animal research, biobank commercialization ethics, research ethics, and research integrity — these issues can also be addressed independently of organoids, potentially reducing the necessity for a distinct 'organoid ethics'. Nonetheless, this expert highlighted the value of 'organoid ethics' in transcending such ethical silos, offering a framework that helps stakeholders understand the interconnectedness of various ethical issues.
- Some ethics experts argued that organoids are particularly notable for their similarity. Not only do they mimic the structural and functional properties of organs, as identified in the operational guidelines, but they also possess what one expert termed '**a material similarity**'. This is underscored by literature suggesting that patients perceive organoids as patient-specific; that is, they believe an organoid made from their cells will be more effective in diagnosis and treatment. Consequently, it was suggested that organoids are associated with a sense of **belonging or bodily integrity**, potentially offering a unique aspect distinct to organoids.
- An organoid researcher highlighted the technical **differences between 2D and 3D layering**, emphasizing that 3D cultures can be grown for substantially longer periods than 2D cultures. Consequently, this means that organoids have the potential to be cultivated for much longer durations than cell lines.

### Dissemination and Implementation of the Set of Operational Guidelines

During the discussion about the operational guidelines for organoid research, experts offered suggestions on how to effectively disseminate and implement the HYBRIDA guidelines beyond the scope of the project:

- It has been agreed upon that the Operational Guidelines will be integrated into the **human Pluripotent Stem Cell Registry (hPSCreg)**. This integration will enable researchers to complete the MIAOU online form (Minimal Information about an Organoid and its Use for Researchers) and navigate through the extensive checklist, as they will be automatically directed to the relevant sections based on their responses. Furthermore, the potential use of BBMRI ERIC as an additional platform was also suggested.
- A member of a research ethics committee suggested **coordinating efforts with EUREC** to train research ethics committee members. Although not detailed in the focus group interviews, this idea aligns with discussions from the co-creation workshop in Paris (Ravn et al. 2023). During the workshop, the importance of training evaluators was emphasized, particularly because they might be less familiar with organoid research and its associated ethical issues.

### 4.5. Summary of Main Recommendations

Operational Guidelines		
TOPICS	ISSUES	RECOMMENDATIONS
<b>Ethics by Design</b>	Consistency in how ethics by design is described	<ul style="list-style-type: none"> <li>• Currently, ethics by design is described inconsistently in the guidelines. To improve clarity, it should be consistently defined throughout the document as a continuous anticipatory process.</li> <li>• The guidelines should follow up on their own analysis of how to practically apply an ethics by design approach within the field of organoid research.</li> </ul>
	Addressing values	<ul style="list-style-type: none"> <li>• Even though a fixed set of values cannot be established, identifying underlying values remains important. It was suggested that these values should be made transparent, along with an explanation of how they were determined.</li> </ul>
	Hard impacts and soft impacts	<ul style="list-style-type: none"> <li>• The operational guidelines should encompass the distinction between hard and soft impacts. Even though soft impacts might not typically be the focus of ethics by</li> </ul>



		design, their inclusion in the guidelines can help increase awareness among stakeholders in the field.
	Sufficient implementation of anticipatory processes	<ul style="list-style-type: none"> <li>It was suggested to pay attention to how processes such as ethics by design or the RAD (Reflexive, Anticipatory, Deliberative) approach could be further enhanced to ensure that elements of reflection, anticipation, and deliberation are fully grounded and sufficiently implemented throughout the process of application.</li> </ul>
	Example of ethics by design	<ul style="list-style-type: none"> <li>It was suggested that some examples illustrating the ethics by design approach could be added to the annex of the guidelines, along with questions that could be considered.</li> </ul>
<b>RICO-CHECK</b>	Funding eligibility	<ul style="list-style-type: none"> <li>The RICOCheck states that research involving human embryonic stem cells is ineligible for EU funding. However, it should be clarified that this exclusion does not apply to products derived from embryonic stem cells.</li> </ul>
	Remuneration	<ul style="list-style-type: none"> <li>The RICOCheck should include provisions addressing the remuneration of donors.</li> </ul>
	Cadaveric donors	<ul style="list-style-type: none"> <li>The RICOCheck should address cadaveric donors.</li> </ul>
	Categories for follow-up questions	<ul style="list-style-type: none"> <li>A Participant inquired whether there had been any consideration of structuring the open follow-up questions around pre-defined categories to minimize differing interpretations.</li> </ul>
	Abbreviations	<ul style="list-style-type: none"> <li>Abbreviations should be used with care and need to be defined.</li> </ul>
	Freedom to operate	<ul style="list-style-type: none"> <li>The RICOCheck should encourage researchers and developers to actively consider their freedom to operate.</li> </ul>
	Regulation and risk determination	<ul style="list-style-type: none"> <li>Additional questions that can assist in determining risks and identifying applicable regulations in specific situations should be added.</li> </ul>
<b>Code of Conduct</b>	Compatibility with other guidelines	<ul style="list-style-type: none"> <li>The HYBRIDA Code of Conduct should ensure compatibility with existing and related guidelines.</li> </ul>
<b>Missing elements</b>	Narratology and communication practices	<ul style="list-style-type: none"> <li>If possible, the operational guidelines could assist stakeholders in the field of organoid research in constructing narratives that inform the public about organoids, and provide examples or ideas for effective communication.</li> </ul>
	Anticipation of AI in the field of organoid research	<ul style="list-style-type: none"> <li>The operational guidelines should anticipate the use of automatic tools for organoid characterisation in the future.</li> </ul>



	International difference	<ul style="list-style-type: none"><li>• The guidelines could incorporate an analysis of how ethical perceptions vary across countries, leading to different research practices and norms.</li></ul>
	Ethical awareness through interdisciplinary dialogue	<ul style="list-style-type: none"><li>• The operational guidelines should encourage dialogue across specializations and fields among all researchers working with organoids, with the aim of raising ethical awareness.</li></ul>
	Publication of negative results	<ul style="list-style-type: none"><li>• The operational guidelines already address the issue of not publishing negative results. To combat this publication bias, it was suggested that the guidelines include ideas for open access platforms and archives where negative results could be published.</li></ul>
<b>Dissemination and implementation of the guidelines</b>	Dissemination Platforms	<ul style="list-style-type: none"><li>• It was suggested that reaching out to BBMRI-Eric for the dissemination of the operational guidelines, as well as coordinating with EUREC for the training of research ethics committee members in organoid-related ethics, should be considered.</li></ul>
<b>General observations</b>	Normative claims	<ul style="list-style-type: none"><li>• The guidelines encompass both empirical and normative claims. For the normative claims, it would be beneficial to add supporting documentation and clarify the distinction between existing practices and desired practices.</li><li>• It was mentioned that the Guidelines document should be reviewed to ensure that all used sources have been referenced. Currently, some references are missing.</li></ul>



## 5. Informed Consent

One focus group was dedicated to discussing how to address the issue of informed consent as well as different models of informed consent. Furthermore, the focus group focused on the idea of a Donor's Wishlist, which has been developed as part of the Operational Guidelines for the field of organoids and organoid-related technologies.

In the focus group, the following main questions were discussed:

- Should HYBRIDA propose a particular model of informed consent or continue to map the landscape of pros and cons related to the different models?
  - What are your views concerning a preferred model of consent for organoid research (e.g. dynamic consent, consent for governance model, broad consent etc.)
- What are your views on the Donor's Organoid Wishlist?
  - Is a Donor's Wishlist a good approach to safeguard the rights and wishes of donors?
  - If yes, is the current version sufficiently operational?
  - In your view, who should be in charge of follow-up procedures?
- In general, does chapter 6 on informed consent read as a complete guideline for its desired target groups and in alignment with high ethical standards?
  - Do you have suggestions for additions or revisions?

The following sections present the experts observations and recommendations on these issues and questions. The chapter concludes with a related discussion on the issue of withdrawal of consent that was discussed in the focus group on 'Informed consent, withdrawal, and exchange of material (MTAs)'.

The following main questions were sent to the focus group experts prior to the interview and discussed collectively:

How should HYBRIDA address regulatory issues concerning withdrawal of informed consent?

- In the operational guidelines (section 6.8.), the recommendation for withdrawal follows the ISSCR approach for withdrawal up to the point of cell processing. What is your view on this recommendation?
- In the discussion paper, it is recommended to determine the legal basis for withdrawal on both a national and European level. What is your view on this recommendation?

## 5.1. Informed Consent Models

### Third parties

During the discussions of informed consent, special attention was paid to the idea of a ‘consent for governance model’ (CFGM, see Boers et al, 2019) where donors would entrust consent and agreements for the reuse of their material to an independent third party representing them. Overall, the experts and stakeholders seemed to sympathise with the idea of a consent for governance model. The main part of the discussions revolved around which bodies could act as independent and entrusted third parties as well as how this governance would differ from existing structures such as biobanks and ethics committees.

- Several experts worried that adding additional governance bodies may result in **too many committees** and one pointed especially to the fact that this could be challenging to establish in smaller countries.
- It was emphasised that the governance model should **improve existing consent practices** and that it is important to make sure that it does not make less ethical routes for obtaining data, such as using already available cell lines applied for other purposes, more attractive to organoid researchers.
- **Differences in the level of existing trust in science and in existing governance structures amongst countries** was pointed out as having potential implications for donors’ willingness to entrust future consent and agreements to a third party. One expert recommended to include sociological advice on how this could be addressed and how the model could be implemented across different contexts.
- It was suggested to consider **combining the consent for governance model with dynamic consent**. Some participants saw the third parties as a potential permanent link to the donors that could facilitate opt-ins and opt-outs as well as provide information on organoid research as well as different projects which might prevent withdrawals.

In addition to discussing informed consent models, one of the focus groups also explored the concept of **broad consent**. It was argued by some participants that there likely exists a variation in consent preferences among different types of donors. For instance, patients may be more inclined to provide broad consent, primarily driven by their urgency to find a cure for their disease. This observation to some extent aligns with the results from the deliberative workshops reported by Ravn et al. (2022). An expert



noted that while broad consent might simplify administration for biobanks, it may offer less protection for the donors.

### **Passport**

The set of operational guidelines introduces the concept of a 'passport', which comprises metadata accompanying the organoid. Generally, the focus group **participants responded very positively to this idea, finding the passport concept both 'evocative' and descriptive**. However, echoing a point briefly discussed in the co-creation workshop in Paris, one expert raised a concern that the passport concept might inadvertently contribute to the humanization of organoids, thereby increasing ethical sensitivity. In contrast, another expert advocated for the usefulness of the passport, especially since organoids contain sensitive information. The experts recommended careful consideration of how to ensure that the metadata, including the donor's wish list (please refer to section 5.2. for more details), provided in the passport, is respected and adhered to by stakeholders handling and using the organoids. Furthermore, it was noted that keeping track of the metadata over time would require appropriate infrastructure.

## **5.2. The Donor's Organoid Wish List (DOW)**

There was a consensus among participants across four focus groups discussing the issue that the donor's organoid wishlist is a **valuable questionnaire** accompanying the informed consent, and it was seen as an additional means to help safeguard the rights and wishes of donors.

Participants, however, also generally agreed across three focus groups that the **term 'wishlist' does not properly serve the purpose of the checklist**, as the name fails to convey the clear status of the document. Additionally, the terminology of 'wishes' does not make it clear whether it is mandatory to follow these guidelines. One expert suggested that it would be more appropriate to refer to it as a 'requirements' list. Another expert used the term 'will list' to highlight that it is a 'binding document'.

One participant, while agreeing to the value of the wishlist, expressed concern that the checklist might **induce unnecessary fear in donors** and that they might refrain from volunteering for certain types of research due to insufficient information about the different categories and types of research listed in the checklist. The example provided is that a donor might not want to have cerebroids generated from their cells or from derived iPSCs, fearing that it sounds more 'dangerous' than it actually is. Another participant highlighted the many types of public imaginaries that the wishlist might generate. In this regard, a third participant highlighted the **importance of clear and adequate written and verbal information** to make sure that donors gain exact information about their donor contribution. In this regard, the expert mentioned that the cells cannot be perceived as independent from the donor as they constitute donor DNA. Several experts repeat this request for a dialogue approach across three focus groups. Another expert concurred with the importance of providing precise information, and stated that the wishlist will only be effective if donors properly understand what ticking the boxes entails. Otherwise, it would not



constitute informed consent. Based on knowledge about a research project concerning informed consent in the area of genomics, the expert highlighted that a range of approaches can be implemented to help secure that information concerning the content and concepts of the informed consent and the research in question is properly understood and disseminated to a diverse group of citizens and patients. For instance, accessible online tools, videos, podcasts, audio files, on-site meetings, biobank tours etc. can be initiated to help explain the research and use of donations. The expert emphasized that relying solely on a paper-based approach often fails to fully inform donors and patients, suggesting that alternative methods should also be considered.

In discussing the **follow-up procedures for implementing the donor's organoid wishlist**, one expert suggested that a registry should be responsible, while another mentioned local institutions tasked with collecting the sample. A third expert proposed implementing a procedure within the research ethics committee system. In relation to this procedure, researchers would submit a final report addressing the ethical considerations as a follow-up to their initial ethics approval.

Despite broad agreement on the value of a donor's organoid wishlist, overall, participants agreed that **the list is non-exhaustive and would benefit from modifications**. Only one expert questioned the complexity of the wishlist and the need for the amount of resources going into fulfilling the wishes. However, across three focus group discussions, experts proposed several changes and enhancements to enhance the functionality of the checklist:

- It was suggested to include whether donors would like to be **re-contacted**.
- Experts raised the issue of **unexpected findings**, suggesting its inclusion in the wishlist to ascertain donors' preferences for being contacted. It was emphasized that donors should have the choice of opting out of receiving such information. The case of hematopoietic stem cell donors, who might prefer not to know about any 'bad gene' findings, was highlighted. Additionally, an expert proposed including an option for donors to be contacted in cases of 'actionable findings,' where, for example, treatments are available. In this context, a third expert mentioned a number of relevant studies and literature focused on the terminology used for incidental findings, individuals' right to know or not know, and the appropriate timing and methods for disclosure. This information could be instrumental in informing the guidelines. Another expert mentioned that the guidelines could refer to local or national policies in this area.
- Experts from two focus groups concurred that the existing binary category of consenting to or rejecting **commercialisation** is inadequate and challenging to comprehend. Additionally, the implications regarding ownership remain unclear, as well as the specifics of what is being commercialised, such as the use of research tools, for therapeutics, etc. It is suggested that the category of commercialisation is combined with the type of research structure. In this regard, the distinctions between private laboratories, biotech companies, and industry are noted as unclear.



The separation between academic and private laboratories is also ambiguous, especially since private universities may operate their own laboratories. Additionally, there is uncertainty regarding the classification of public-private partnerships in relation to commercialisation.

- It is also mentioned that the **country selection** seem neutral at first but that it is not, and that it is difficult to understand the geographical influence in terms of legislation, data processing agreements etc. In another focus group, it is also mentioned that European countries versus **EU countries** should be specified.
- One expert also mentioned that it is not clear what it entails to **tick no to all categories**.
- One expert highlighted the need to keep the **wishlist short and clear**.
- One expert in the focus group concerning commercialisation and existing cell lines suggested to include a provision to determine whether **genetic modification is permitted** and also include an option to allow for consent to 'unforeseen future research'.
- In the focus group discussion about informed consent and withdrawal, one expert pointed out that the **term 'cerebroid'** might be difficult to comprehend. The expert suggested using 'brain' as the term for the organ to be mimicked, acknowledging the complexity and sensitivity involved in using this term. In the view of the expert, this also apply to the term embryo model as this refer to the end product. It was also suggested to define the meaning of genomic studies.

### **5.3. Withdrawal of Consent**

Within medical research ethics, informed consent and the right to withdraw remain essential elements to safeguard the autonomy, rights, and voluntariness of human research participants. Drafted in the aftermath of the Nuremberg Trials, the post-Nuremberg Ethics Code specifies the right to withdraw within the context of physical interventions. Subsequent ethical codes inherent in The Declaration of Helsinki, the CIOMS guidelines (The Council for International Organisations of Medical Sciences), and the Council of Europe Convention on Human Rights and Biomedicine introduce a broader and temporal aspect of withdrawal that goes beyond 'immediate' withdrawal and includes the right to withdraw at 'any time'. This consequently influences understandings of withdrawal for non-interventional research that, for instance, involve large data networks and human tissue collections (Melham et al., 2014).

Organoid research and organoid technologies must live up to these declarations and guidelines. However, research in the field of organoids and organoid technologies entails practical limitations to withdrawal 'at any time'. After cells have been processed and transformed (e.g., cells thawed for reprogramming), it is difficult to trace the original sample due to the exponential growth of the sample and the distribution of



samples through biobanks, for instance (Chneiweiss et al., 2023; Ravn et al., 2022). Based on this feasibility reason, researchers have pointed to the resource demands (e.g., in relation to sample monitoring, administration, and logistics) involved in tracing samples and removing data after they, for instance, have been turned into iPSC lines (Lewis and Holm, 2022; Ravn et al., 2023).

From a legal point of view, two additional aspects are of distinct relevance for organoid research:

- Regulations concerning donor withdrawals include donated tissues and cells, and it is not apparent whether donor's derived organoids are included in the rights to withdraw. Organoids grow into self-organizing structures that resemble an organ, but they are also manipulated in this process and can – at least partly – be considered biotechnological artefacts derived from the donated cells. The uncertainty as to whether organoids can be classified solely as biotechnical artefacts questions the donor's moral and legal claim to decide over their 'own' organoids for future use and consequently their right to withdraw them (Lewis and Holm, 2022).
- In relation to the future use of the donation, associated risks pertain primarily to the processing of personal data – and a potential disclosure of such information – rather than the risks of physical harm (Melham et al., 2014). In this regard, the right to withdraw also relates to GDPR (EU) and issues concerning the processing of data, data storage limitations, and the use of data for secondary research (Lewis and Holm, 2022; Melham et al., 2014). Existing guidelines and practices seem to suggest that personal data and samples will be destroyed in the case of withdrawal, but not with 'retroactive effect' for completed or ongoing studies (Melham et al., 2014; Lomax, 2013; see also discussion on 'existing cell lines', section 6.1).

In the current version of the Operational Guidelines, it is suggested to 'propose a possible withdrawal until the cells are thawed and cultured' and to include a provision for the duration of sample storage for data reuse and secondary studies (Chneiweiss et al., 2022, p. 60). In the focus group discussing 'Informed Consent, Withdrawal, and Exchange of Material, this recommendation was discussed in addition to legal determinations for addressing withdrawal at the EU level and within individual member states.

The issue of withdrawal was included as a dedicated issue for this particular focus group. Participants in the focus group concerning the 'Donors Wish list and Informed Consent' also touched upon the topic and the following reporting will draw on both discussions.

For the broader question on how to provide guidelines on the issue of withdrawal, participants raised a number of suggestions to provide as transparent and complete information as possible:

- In general, it was emphasized that there should be a **clear and transparent provision outlining the specific limitations** on the right to withdraw in the consent form. This includes information



about the probable scenario where derived cell lines may continue to be distributed despite an individual's withdrawal from the research in question (cf. retroactive effect').

- One participant suggested including an option for participants to accept or decline being re-contacted. In this regard, another participant mentioned the commonly used practice of **'tiered withdrawals'** within the biobank infrastructure to provide nuanced choices for participants about which part of the process they wish to withdraw from. For instance, a tiered approach might specify that participants only wish to withdraw from a) further communication, b) any further communication and new data collections, or c) a complete withdrawal from the study. Hence, a tiered approach could increase the level of information and nuance the element of 'irreversibility'. In this context, it was noted that the risks associated with tissue samples are related to privacy risks, not physical risks, and potential harms could be perceived as 'cultural and moral harms'. Consequently, the transformation of risks calls for a nuanced discussion about practices of withdrawal according to this participant.
- In the interview, it was suggested and agreed that more guidance be provided about **withdrawal and minors**, including offering children additional opportunities for re-consent at the age of majority. It was also mentioned that information should be specifically tailored to children if they are involved. In this context, the soon-to-be-issued materials from the Council of Europe on children's participation in research might serve as a source of inspiration. Additionally, it was noted that the Operational Guidelines mention 'consent by both parents', but an expert pointed out that this is not a requirement in all EU countries.
- On the **issue of Data Protection Regulation and withdrawal**, a legal expert highlighted several points of attention: First, the GDPR does not specify a specific period for data storage but requires 'the minimum needed to comply with what you need to comply with', in agreement with the 'concept of data minimisation'. Second, it was assessed that commercialisation issues and financial costs cannot be used as a legal basis for denying withdrawal under the 'GDPR for marketing purposes'. Third, the expert drew attention to the Article 29 Working Party (Art. 29 WP), stating that 'if the controller chooses to rely on consent for any part of the processing, they must be prepared to respect that choice and stop that part of the processing'. Based on this, it is **not permissible to switch from consent to legitimate interests** in the event of a data subject's withdrawal and insist that the data must be retained. Therefore, it is the opinion of the legal expert that one must choose between relying on consent and then accepting withdrawal regardless, or relying on legitimate interests and not accepting withdrawal. In the discussion of the ethical consequences of this another expert raised concerns that in the case of a 'use of cells for individual application' (as opposed to a population or cohort level), the legitimate interest model cannot be applied. Furthermore, the precise avenue of application is often difficult to determine from the outset. On this basis, the legal expert suggested proceeding on an 'if' basis, or **potentially adopting an 'opt-in – opt-out' approach** as suggested by the other expert.

In the current version of the Operational Guidelines, the demarcation for withdrawal is proposed to be the state of cell processing. A majority of interviewees in the expert interview study preceding the current focus group interviews also supported this suggestion (see Ravn et al. 2023). In the focus group study, this line of demarcation is not opposed but challenged by one participant:

- This expert acknowledged that withdrawal up to the point of cell processing might be the accepted approach due to feasibility issues and the significant resources invested in cell reprogramming. While this presents a valid practical and material rationale, also considering that the cells at this point are transformed into an object, it is relevant to consider the ethical perspective. From this viewpoint, it is noted that withdrawal is possible even after processing, and could be **extended up until the point of distribution**. Based on this, the group discussed experiences with withdrawals, generally recognizing that the number of actual withdrawals is very low. This observation suggests that widening the withdrawal window would probably not necessitate significant additional resources. From an ethical standpoint and considering donor rights, another participant, who is also an ethical expert, supported the idea of extending the opportunity for withdrawal as much as possible.

In the preparatory discussion paper sent to the focus group participants ahead of the discussion, it is suggested that the **issue of withdrawal should be addressed at both an EU and national level**. While no objections were raised to this proposal, based on experience, one expert encouraged the HYBRIDA consortium to **construct such a framework within the project**, as clear guidelines on withdrawal concerning informed consent standards and Material Transfer Agreements (MTAs) were seen as a valuable support to the field of stem cell and organoid research. The **request for clear guidelines** was based on the practical and logistical difficulties associated with implementing withdrawal for immortal cells that may be distributed worldwide. Additionally, it was also mentioned that biobanks may find it challenging to maintain a link to individual donors.

#### 5.4. Summary of Main Recommendations

Informed Consent		
TOPICS	ISSUES	RECOMMENDATIONS
Informed consent models	Consent for governance model	<ul style="list-style-type: none"> <li>• General support for the idea of a consent for governance model.</li> </ul>



		<ul style="list-style-type: none"> <li>• It is unclear how the implementation of an independent and trusted third party would differ from existing structures and bodies.</li> <li>• A concern was raised about the establishment of additional bodies or committees, particularly regarding the challenges faced by smaller countries.</li> <li>• It is important that the governance model improves existing consent practices and does not inadvertently promote less ethical routes</li> <li>• Donors’ willingness to trust a third party may be influenced by their trust in science and governance structures, and this can vary across countries. Sociological advice was recommended to inform any potential implementation of the model.</li> <li>• It was suggested to consider combining the consent for governance model with dynamic consent.</li> </ul>
	Broad consent	<ul style="list-style-type: none"> <li>• Patients may be more inclined to provide broad consent, primarily driven by their urgency to find a cure for their disease.</li> <li>• Broad consent might simplify administration for biobanks, but it may also offer less protection for donors.</li> </ul>
<b>Passport</b>	Implementation of passport model	<ul style="list-style-type: none"> <li>• General support for the idea of a passport accompanying biological samples.</li> <li>• Keeping track of the metadata over time would require appropriate infrastructure.</li> </ul>
<b>Donor’s Organoid Wishlist</b>	Use and terminology	<ul style="list-style-type: none"> <li>• The wishlist is seen as a valuable questionnaire accompanying the informed consent</li> <li>• The specific designation of a ‘wish’ list does not support the purpose and content of such a list.</li> <li>• The importance of clear and adequate written and verbal information is highlighted to make sure that donors gain exact information about their donor contribution.</li> </ul>
	Modifications and additions	<ul style="list-style-type: none"> <li>• Suggestion to include whether donors would like to be re-contacted.</li> <li>• Suggestion to include the issue of incidental findings.</li> <li>• Suggestion to include a provision to determine whether genetic modification is permitted.</li> <li>• Suggestion to include an option to consent to ‘unforeseen future research’.</li> <li>• Suggestion to specify European countries vs. EU countries.</li> <li>• Suggestion to define the meaning of genomic studies.</li> </ul>





		<ul style="list-style-type: none"><li>• Suggestion to specify the following categories: commercialisation, research structures, country selection, cerebroids and embryo models.</li></ul>
<b>Withdrawal of consent</b>	Extent of withdrawal	<ul style="list-style-type: none"><li>• Withdrawal up to the point of cell processing might be the accepted approach but suggestion to extend to the point of distribution.</li><li>• The issue of withdrawal should be addressed at both an EU and national level.</li></ul>
	Transparent provision	<ul style="list-style-type: none"><li>• A clear and transparent provision should outline the specific limitations of the right to withdraw in the consent form.</li><li>• An option for participants to accept or decline being re-contacted should be included</li></ul>
	Tiered withdrawal	<ul style="list-style-type: none"><li>• The practice of 'tiered withdrawals' could serve as a model for inspiration.</li></ul>
	Minors	<ul style="list-style-type: none"><li>• More guidance should be provided about withdrawal rights for minors, including offering children additional opportunities for re-consent at the age of majority and tailoring information specifically for children.</li></ul>
	Data Protection Regulation and withdrawal	<ul style="list-style-type: none"><li>• It is not permissible to switch from consent to legitimate interests in the event of a data subject's withdrawal and insist that the data must be retained.</li></ul>



## **6. Commercialisation, Ownership and Material Transfer Agreements**

Across two focus group discussions, the issues of commercialization, ownership, and material transfer agreements were explored. The discussions about the first two topics primarily focused on how to address issues related to the traceability of origins and the donor's informed consent in existing and commercially available cell lines and organoids. They also delved into how to transition from today's standard practices to more ethically sustainable practices, considering both the biological material and the associated personal data in terms of data protection measures. Furthermore, the discussions addressed questions related to intellectual property rights. Overall, two main questions were explored in relation to commercialisation, existing cell lines, and intellectual property rights. The associated issue related to informed consent is reported in section 5.

- The lack of traceability of origin and informed consent for commercially existing cell lines can cause challenges in terms of fulfilling the requirements for a valid consent for data reuse and for data processing. In your view, does chapter 6 on informed consent sufficiently address these challenges and potential solutions?
  - Do you have additional recommendations for best practice solutions?
- How should intellectual property rights be addressed in organoid research?
  - In your view, should the issue of intellectual property rights be further specified in the operational guidelines? (reference made to preparation material)

Regulatory issues related to the exchange of material and information associated with, or derived from, the analysis of the material were addressed in a second focus group. The main question discussed revolved around the following:

- How should HYBRIDA address the handling and regulation of exchange of material, for example between institutions where only one of the institutions is located in the EU/EEA.
  - In your view, is the recommendation provided in the discussant paper on exchange sufficiently clear and adequate?

### **6.1. Commercialisation and Existing Cell Lines**

It is evident from the discussion that the issue of traceability of origin and informed consent for commercially existing cell lines is a very **complex matter and that actions with a retrospective perspective are challenging to implement**. Several experts with expertise in cell lines distribution recognised the issue with older donations, for instance from the 1970ies and 1980ies where the donor is



deceased, and where the lack of consent or deficient availability of ethical provenance complicate matters. It is mentioned that companies often show reluctance to provide the informed consent template but may instead issue a statement concerning user restrictions. As an alternative, seeking approval from a research ethics committee for the use of specific samples can be a possible course of action. There is also a recognized challenge for biobanks in verifying consent for cell lines distributed globally. Consequently, they may lean towards adopting broad consent models that do not require re-consent. Lastly, the importance of retrospectively examining available informed consent forms has been highlighted by two experts, emphasizing the need to assess the nature and extent of usage on a case-by-case basis.

One expert raised concerns about the **potential 'reputational risks'** associated with using samples without sufficient ethical provenance, particularly in relation to public perception. The expert questioned whether any retrospective actions might be initiated to mitigate such risks and prevent a decline in public trust. Additionally, the expert also emphasized that shutting down research altogether is not a desirable outcome.

Another expert suggested raising awareness among companies about the value of sharing informed consent forms, including a donor's wishlist (please refer to section 5.2 for more details on the donor's wishlist). The expert proposed **involving the EU Commission as a funding body**. If the Commission were to impose certain requirements regarding ethical provenance as a part of funding research projects, it would create additional pressure on companies to sell cell lines with proper ethical provenance. In this context, a third expert suggested examining comparable cases in drug development where specific restrictions on medical access and commercial exploitation have been implemented if the research was publicly funded.

## **6.2. Ownership and property rights**

In the current version of the Operational Guidelines (Chneiweiss et al., 2023, p. 58), the issues of ownership and commercialisation of organoids are brought into question. According to existing legislation, many jurisdictions do not consider people's tissues to be their own property once these have been modified and donated. This suggests that the same principle apply to tissues created from patient-derived stem cells. Simultaneously, organoids could potentially be regarded as 'body parts' and biological tissues, akin to blood and gametes, which can be donated and, as in the US, sold for payment.

The participants, after briefly discussing the topic, agreed that **'a donation is a donation'**. Once you have consented to donating, it should no longer be seen as your property. Two experts independently likened the donation process to donating a kidney. Additionally, two participants speculated – without claiming to have knowledge of any specific research in the area – that many citizens and patients would likely waive any property rights to their donations. This perspective of citizen and patient ownership was discussed as



part of the HYBRIDA public deliberation study (please see Ravn et al., 2023a). One expert highlighted the **need for clear legislation on the issue**, while another expert emphasized the importance of **adequately informing patients and donors** about these complex matters through informed consent procedures, raising the debate about what constitutes a sufficient level of information. In this matter, a fourth expert highlighted the need for enhanced education and information regarding the use of donated cells, to prevent misinformation. This is particularly important in addressing misconceptions, such as the belief that organoids are used to create exact replicas of parts of the donor's body.

This issue also taps into the broader discussion about the normative meaning and emotional attachment that donors might associate with their organoids. It has been argued that since organoids can potentially reveal health and genetic information about their donors, this might lead to a stronger sense of attachment, concerning the donors' bodily integrity and personal identity (Boers et al., 2018; de Jongh et al., 2022; Lewis and Holm, 2022). This discussion is not unfolded in the current focus group discussion, but the issue is raised in another discussion (please see section 4.4. for a complete description). In that discussion, the distinct characteristic of 'material similarity' was attributed to organoids. This was consequently argued to create a sense of belonging or bodily integrity for donors.

As part of the discussion on ownership and property right, one expert also raised the **issue of patenting** and the importance of debating the issue more broadly. The expert mentioned that the Henrietta Lacks case prompted the important debate concerning ownership issues and while this is 'early days', the topic remains important, not least in consideration of the future structures that are likely to be created for medical applications on the basis of human stem cells. The expert also stressed that **what is most often patented is the method, as the object is difficult to patent**. The expert also problematized and raised the concern that – based on experience in the field of organoid technologies – **examples of methods and outcomes have been patented that do not correspond to what is actually being done**, and that many of these methods are not reproducible in other labs.

### 6.3. Exchange of Materials – Material Transfer Agreements (MTAs)

Material Transfer Agreements (MTAs) constitute a legal contract for the exchange of materials and benefit sharing in biomedical research. An MTA includes and regulates any rights related to 'the materials, derivatives, and associated data, including, in the case of biological samples, metadata, anonymized data, the clinical state of the donor, and other personal information' (Lewis and Holm, 2022, 51).

In one of the two expert workshops previously conducted as part of this HYBRIDA work package (see Ravn et al. 2023), organoid researchers emphasized the regulatory challenges related to data sharing across jurisdictions. They described the process as laborious, complex, and time-consuming, owing to variations in domestic laws and the fact that legal interpretations can diverge across both national and institutional contexts. On this basis, researchers called for greater standardization and harmonization of the regulatory practices related to Material Transfer Agreements (MTAs).



The exchange of biomaterials between provider and receiver is governed by a dual set of regulations, i.e. the Clinical Trials Regulation and the General Data Protection Regulation (GDPR, EU), which add to the practical complexity of these transfers, predominantly between EU/EEA and non-EU/EEA institutions and particularly in relation to the transfer of personal data (Lewis and Holm, 2022).

Researchers in the focus group interview discussing how to handle and regulate exchange of material, similarly pointed to some of the above-mentioned challenges related to the exchange of biological materials. One researcher described how their research group refrained from transferring materials to project partners in the UK and Australia because the resources required for the process did not justify the likelihood of a successful benefit sharing. Regarding GDPR-related issues, the same participant noted **difficulties with data transfer agreements** between institutions within the same country. Due to **variations in the legal interpretation of GDPR**, it took a year to resolve the legal incongruities in this particular case.

In the focus group on 'Donor's Wishlist and Informed Consent', an ethical expert mentioned a personal involvement in a project with partners both within and outside of the EU. An MTA was prepared, which also covered 'robust consent'. Despite all formal requirements being met, it was noted that controlling the use of transferred cell lines shared among multiple laboratories within the same institutions is challenging. Specifically, there are **concerns about whether the original consent is acknowledged and followed when samples are reused** for new projects. For this reason, this expert also advocated for the idea of an accompanying 'data passport' that travels with the relevant data (please refer to section 5.1).

Another participant highlighted the experiences of the European 1+ Million Genomes Initiative, demonstrating that the exchange of data is not always a straightforward endeavor. In the expert's opinion, the MTA process would benefit from the use of **unified consent forms**.

Despite such variations in the legal interpretations of the data protection regulations, a legal expert in the focus group pointed to the fact that within Europe, the **GDPR implementation should be 'pretty straightforward'** in terms of data transfers, and that this is also the case for countries such as Australia and the UK which comply with the EU data requirements. The expert adds that for non-equivalent GDPR countries without an agreement with the EU, the process are likely to be more difficult but that various GDPR tools might be used in the case of data transfers.

The focus group discussion addressed the **opposition between the de jure (legal) and de facto (practical) understanding of material transfers**. This was illustrated, among other things, by highlighting variations in legal interpretations across different countries. In this context, another expert emphasized the importance of consent associated with the sample and the necessity of including a 'data clause' in the consent forms to facilitate cross-border exchange, especially since they comprise genetic data. According to the expert's experience, countries like Belgium and Norway are seen as becoming increasingly 'strict' regarding their interpretation of the legal basis for material transfer.

## 6.4. Summary of Main Recommendations

Commercialisation, Ownership and MTAs		
TOPICS	ISSUES	RECOMMENDATIONS
<b>Commercialisation and existing cell lines</b>	Traceability of origin and informed consent for commercially existing cell lines	<ul style="list-style-type: none"> <li>• It is regarded as a complex matter and actions with a retrospective perspective are perceived as challenging to implement.</li> <li>• Companies have shown reluctance to provide informed consent forms and may instead issue a statement concerning user restrictions</li> <li>• Seeking approval from a research ethics committee for the use of specific samples may be an alternative option.</li> <li>• It is suggested that the EU Commission be involved as a funding body, implementing funding requirements regarding the ethical provenance necessary for the purchase of cell lines.</li> <li>• It is suggested that attention be paid to potential 'reputational risks' associated with using samples that lack sufficient ethical provenance, particularly in relation to public perception and trust.</li> </ul>
<b>Ownership, patents and property rights</b>	Organoid ownership	<ul style="list-style-type: none"> <li>• There is agreement that 'a donation is a donation', and once consent for donating is given, it should no longer be seen as your property.</li> <li>• The legislation regarding this issue should be clear.</li> <li>• Patients and donors should be properly informed about these complex matters through informed consent procedures. Misinformation</li> </ul>



		concerning donated cells should be prevented.
	Patents	The issue of patenting organoids is an important topic for debate. A concern was raised that some patented methods and outcomes do not accurately reflect actual practices, and that many of these methods are not reproducible in other laboratories.
<b>Material Transfer Agreements (MTAs)</b>	Opposition between de jure and de facto understandings	<ul style="list-style-type: none"><li>• Experts pointed to a divide between the legal and practical understanding of material transfers. While a legal expert perceived the GDPR legislation to be rather clear for EU and equivalent GDPR countries, other experts pointed to difficulties with data transfer agreements due to both national and Cross-country variations in the legal GDPR interpretation.</li><li>• A concern was also raised about the difficulty in verifying whether the original consent is acknowledged and followed when samples are reused for new projects in different labs within the same institution.</li></ul>



## 7. Classification and Regulation of Organoid-Based Technologies for Medical Use

One focus group discussion, comprising legal, ethical, and industry experts, deliberated on the classification and regulation of organoid-based technologies for medical use. Currently, there is no precedent for the classification and subsequent regulation of organoid-based technologies for therapies, as they remain at the preclinical stage. In this context, uncertainties might arise regarding whether to classify and regulate organoid-based technologies as medicinal products, medical devices, or as combination technologies once they are developed for medical use (Lewis and Holm, 2022).

In the focus group, the following main questions concerning how to regulate organoids for therapies were discussed:

- In your view, what are the main issues and concerns related to the current regulatory gap of classifying organoid-based technologies for medical use?
- HYBRIDA has identified an over-regulation in terms of applying for market authorization for new ATMPs making it very difficult to provide evidence for fulfilling the requirements. Do you have suggestions/recommendations for ways to address this challenge?
- To enhance the regulatory framework to be proposed in HYBRIDA, it is suggested that the European Commission has to 'offer clear guidance and legally binding provisions for the correct classification of future organoid-based technologies that achieve their primary therapeutic effect principally through functional integration' (reference made to preparation material)
  - What is your view on this recommendation?

### 7.1. Regulatory gaps and classification challenges

In relation to the main issues and concerns regarding the classification of organoid-based technologies, there was a consensus among the experts. The participants agreed that they currently do not see any regulatory gaps in the classification, nor did they anticipate any potential applications of organoids as medical products that would not fall under the existing medicinal products regulations. This applies to both models in the pre-clinical field and with therapies for human. One key argument supporting this position is that generating organoids for human application can be considered as 'substantial manipulation' of viable cells or tissues. Therefore, this process should be covered by Regulation (EC) 1394/2007 on advanced therapy medicinal products (ATMPs). This also applies to combination products that contain viable cells, as this aspect will determine their mode of classification and consequently define them as



medicinal products. It is mentioned that the application of combination products and drug device combinations for organoids is a current topic of interest for the EU Commission. Furthermore, compared to single cells, the issue of structure is crucial, and this necessitates quality control and functionality tests. This requirement is stated as another argument for **clearly situating the classification of organoid-based technologies within the medicines field and legislation if applied to humans**. Overall, experts also agreed that from a regulatory perspective, no difference exists between cell-based and organoid therapies.

It is further argued that with the current scope of the medicines legislations, there is **no need for the introduction of additional requirements** even though requirements will depend on intended use and a 'no-one-size-fits-all' model cannot be applied. However, the framework of the ATMP legislation and the 'risk-based approach' flexibly cover pre-clinical models and end products. In this regard it is stated that organoids for drug screening would fall outside of these frameworks and not involve regulatory authorities. It is also noted that cell procurement does not fall under the medicinal legislation but under The European Union Tissues and Cells Directives (EUTCD) in the case that the cells being donated are intended for human applications. In regard to the existing framework, a legal expert also emphasized that the introduction of products needs to precede the guidelines for them to be relevant. In this process, the expert called for interaction between developers and regulators to obtain scientific advice and to formulate proposals for specific requirements.

Regarding organoid products that achieve a therapeutic effect through **functional integration** (please refer to Lewis and Holm, 2022 for more details), experts concurred that these would be covered by the ATMP regulations. One expert provided the current Parkinson's trials involving tissue replacement with functional cells as an example. From a legal perspective, it was emphasized that the application method, whether as singular cells or in a '3D multicellular complex', does not affect their ATMP classification.

In the discussion about the classification and regulation of organoid technologies, participants also highlighted the following additional points:

- An expert inquired if HYBRIDA had engaged in **legal discussions about organoid technologies at the member state level** before offering recommendations at the pan-European level. The relationship and interdependence between the European Commission and national jurisdictions in regulating organoid technologies have been key points of focus in HYBRIDA. The project has analytically and empirically strived to understand the regulatory, ethical, and cultural diversity by involving a broad and diverse range of citizens, stakeholders, and experts from various countries. This approach aims to inform and enhance existing international ethical guidelines and regulatory frameworks (please also see the Methodology chapter 3). In response to the question regarding coverage at the national member state level, another expert emphasized the significance of pan-EU level discussions. The expert noted that smaller jurisdictions might lack the capacity to tackle the complex field of organoid technologies independently and would therefore rely on **guidance from the EU level**. The complex interrelations between national and European-level legislation



are emphasised by several experts in the focus group interviews. For instance, they pointed out challenges related to material transfer agreements and the establishment of oversight structures in smaller countries.

- One expert suggested tracking the **legislation on Substances of Human Origin (SoHO)** intended for human application, which was the subject of a report adopted by the European Parliament in September 2023, if this area had not been previously consulted.

## 7.2. Overregulation in regard to ATMPs

HYBRIDA has highlighted the regulatory challenges in meeting the legal requirements for obtaining market authorization for new Advanced Therapy Medicinal Products (ATMPs). These challenges include requirements related to clinical testing and the difficulties in providing and demonstrating evidence to meet the regulatory standards for marketing authorization, as outlined by Lewis and Holm (2022, p. 12). Additionally, there is a question regarding the potential over-regulation of ATMPs. **Experts agreed that the area is not over-regulated and that too many regulatory burdens are not placed on the potential applicants.** One expert mentioned that ATMPs do not differ from other medicinal products and that their safety and effectiveness are key in terms of securing the public. Another expert added that in addition to protecting the public, it is also in the interest of the scientific field to prevent any ‘adverse events’.

It was also acknowledged that regulators apply a risk-based approach in the approval of ATMPs for these types of therapies and that this relates to the level of complexity of the product. As understanding of these products grows, regulators and scientists correspondingly anticipate a more refined categorization. There was also an argument made that fulfilling regulatory requirements should be viewed not just within the legal framework but as a means to ensure the practice of good science. Furthermore, it was noted that applications for ATMPs, especially for organoid technologies characterized by their complexity, will not follow a simplistic ‘tick-box’ format. Instead, they will be assessed based on the **risk-based approach and evaluated contextually on a case-by-case basis.** Considering the complexity of developing organoids for human application, applying for market authorisation will require a level of answers and documentation that will be more comprehensive compared to other ATMPs. The justification of the product also goes beyond the issue of reproducibility – which is noted to be challenging for organoid technologies – and it is stressed that the documentation of specific data refer to the product in question and that it is **not possible to ‘cross-refer’ or claim data from other producers or sites** without having performed a direct ‘site-to-site comparison’.

Considering the complexity of developing organoids for human application, applying for market authorization will require a level of answers and documentation that is more comprehensive compared to other ATMPs. The justification of the product also goes beyond the issue of reproducibility – which is noted to be challenging for organoid technologies. It is stressed that the documentation of specific data

must refer to the product in question and that it is not possible to 'cross-refer' or claim data from other producers or sites without having performed a direct 'site-to-site comparison.

### 7.3. Summary of Main Recommendations

Classification of Organoids for Medical Use		
TOPICS	ISSUES	RECOMMENDATIONS
<b>Potential regulatory gaps for classification</b>	Coverage of existing legislation	<ul style="list-style-type: none"> <li>• There is a consensus that no regulatory gaps exist in the classification of organoids, and there are no anticipations of any potential applications of organoids as medical products that would not fall under the existing regulations for medicinal products</li> <li>• There is a consensus on the lack of need for introducing additional requirements.</li> </ul>
	Organoid products achieving a therapeutic effect through functional integration	<ul style="list-style-type: none"> <li>• Experts concurred that these would be covered by the ATMP legislation.</li> </ul>
	Recommendations at the pan-European level	<ul style="list-style-type: none"> <li>○ Particularly small jurisdictions might rely on guidance from the EU level.</li> </ul>
<b>Over-regulation</b>	Overregulation of the approval process for obtaining market authorization for new ATMPs	<ul style="list-style-type: none"> <li>○ Experts agreed that the area is not over-regulated and that too many regulatory burdens are not placed on the potential applicants.</li> </ul>
	Regulatory assessment	<ul style="list-style-type: none"> <li>○ Based on the risk-based approach and evaluated contextually on a case-by-case basis. Likely to be additionally comprehensive for organoid-based technologies due to their complex nature.</li> </ul>



## 8. Embryo Models and Neural Organoids

Within the field of organoid research, several specific organoid technologies have raised particular ethical and legal concerns due to their ontological and moral status. Among others, these include neural organoids, human embryo models, and gonadal organoids, which consequently require specific ethical reflection, discussions concerning their social acceptance, and regulation (Chneiweiss et al., 2022; Bollinger et al., 2021). The ‘sensitive’ status of these types of organoids has also been highlighted in previously conducted HYBRIDA studies, including expert workshops and expert interviews (see Ravn et al. 2023), as well as in public deliberations with citizens and patients (see Ravn et al. 2023a). Findings from these empirical studies support the notion that different types of organoids, particularly embryo models and neural organoids, pose specific implications with respect to their ethical oversight, including informed consent procedures, regulation, and scientific dissemination.

The field of organoid technology is advancing quickly, particularly in relation to in vitro embryo models, yet open questions remain about how to address ethical and regulatory issues related to these models and neural organoids. The focus group discussion dedicated to these topics also explored whether and, if so, how these organoid technologies should be incorporated into the set of operational guidelines and the regulatory framework developed for the field of organoid research. Specifically, participants in the interview were introduced to the following main questions as part of the introductory material and in the collective discussion:

- Should embryo models and/or neural organoids be included in the operational guidelines?
- Do embryo models and/or neural organoids warrant special ethical and legal concerns, including concerns regarding moral status?
- Which aims justify the use of embryo models and neural organoids? (reference made to preparation material)
- Do we need an EC-approved regulatory definition of a human embryo and an EC-approved regulatory definition of embryo models? (reference made to preparation material)

### 8.1. Human embryology and Human Stem Cell-derived Embryo Models

Human stem cell-derived embryo models are 3D structures or models created through pluripotent stem cells (hiPSCs) or embryonic stem cells (hESCs). These models can mirror aspects of the early stages of human development in vitro (embryogenesis), enhancing understanding of issues like infertility, miscarriages, placental failure, and congenital heart defects, among others. Additionally, they provide a complementary alternative to research with human embryos and animal models (Rivron et al., 2023; Hyun et al., 2020)



Compared to organoids that mimic the functional properties of organs, human embryo models replicate the developmental processes of organisms. Nonetheless, embryo models can be considered a type of organoid, similarly derived from hiPSCs. They possess the ability for self-organization and resemble the entities they model. As previously mentioned, these models can be considered a sensitive technology, and their legal and ethical implications can be discussed within the broader context of organoid technologies (Chneiweiss et al., 2022; Gaillard et al., 2022; Mollaki, 2021).

Research into early human development using human embryos can be conducted through in vitro fertilization (IVF). The internationally accepted '14-day/primitive streak rule,' established by the Warnock Committee in 1982, limits the cultivation of embryos in vitro to 14 days post-fertilization. This area of research is strictly regulated in most countries due to significant ethical concerns related to the value of human life, the attribution of moral status, and the morality of creating human embryos or 'early human life' in vitro (de Jongh, 2022, p. 15). Currently, stem cell-derived human embryo models are not classified as human embryos, and a significant distinction remains between human embryos and embryo models. For example, mouse embryo models, which are the models most similar to embryos, still do not 'form a viable organism' (Rivron et al., 2023a, p. 1; ISSCR, 2021). However, as these models evolve, several issues emerge, such as whether they can be seen as comparable to human embryos and whether they warrant special ethical and legal consideration, including their permitted days of maturation and the attribution of moral status (Blasimme and Sugarman, 2023; Hyun et al., 2020; Mollaki, 2021; Rivron et al., 2023). Additionally, previous studies in HYBRIDA have shown that the absence of clear governance structures and a lack of a clear cross-national definition of a human embryo complicate the distinction from its embryonic counterpart (Lewis et al., 2022; Ravn et al., 2023).

The researchers and ethical expert who attended the focus group interview on 'Human Embryo Models and Neural Organoids' generally agreed on the **need for discussions at a European level** about whether human stem cell-derived embryo models (SEM) warrant special legal and ethical concerns. While there was consensus that, in agreement with the ISSCR guidelines (2021), **human embryo models should not currently be regarded as embryos either biologically or legally**, the experts concurred that the lack of a clear **cross-national definition of a human embryo** complicates the distinction from its embryonic counterpart. They argued that a refined legal definition of the human embryo is needed to better clarify the '**tipping points**'—the stage at which the in vitro model and the embryo could be seen as comparable in terms of attributed moral status, thereby establishing conditions for protection. Two complementary '**Turing tests**' are suggested as a collective indicator for when the 'tipping point' has been reached; 1) if a human embryo model can 'efficiently and faithfully' form the entire embryo in vitro and 2) the embryo model can form fertile and living animals as for instance pigs and non-human primates. It is mentioned that **tests with non-human primates are very ethically complex** and that the type and number of species specified for a second Turing test should be decided within the particular jurisdiction (for more information about an ethical framework and guidelines for human embryo models see also Hyun et al. 2021; Rivron et al. 2023; ISSCR 2021).





In addition, the focus group experts problematized the current **heterogeneous regulatory landscape** for human embryology and welcomed suggestions for refining the legal definition of a human embryo – including those from the HYBRIDA consortium – as a basis for discussions within the research field and with the European Commission. While consensus at the European level was seen as recommendable, one expert advised considering the potential implications of a shared European definition, particularly whether it might counteract productive efforts and impose limitations on 'scientific advancements'.

In terms of a legal and ethical framework for human embryology and embryo models, expert attendees also raised the following issues:

- In the discussion on definitions, participants in the focus group emphasized the **need for a clear definition of what constitutes a 'model.'** One expert raised concerns that some recent papers have claimed to develop 'models,' which, according to this expert, bear no resemblance to an embryo. This discrepancy poses challenges for the field and also creates confusion in society at large. In general, there was a consensus on the importance of clearly defining what an (embryo) model is.
- One expert asserted that the most pressing current question relates to how long embryo models should be allowed to develop. Additionally, it was suggested that it would be beneficial for Europe to proceed 'more or less together' on this issue. Current and advanced discussions in France and the UK were mentioned, particularly their recommendation to allow the most complete embryo models (e.g., blastoids) to be **cultured for a duration of 28 days** (see, for instance, Agence de la biomédecine, 2023). It was argued that this time frame would permit research into the period of embryogenesis without the use of human embryos, while considering the **gradualist approach** (i.e., the moral status of the embryo increases during its development) and the **principle of proportionality** in terms of assessing 'the risk-benefit balance in relation to the objectives of the proposed research' (Agence de la biomédecine, 2023, p. 6).
- The point was raised that different embryo models, derived in various ways, necessitate **distinct types of ethical and legal oversight, in accordance with their varying levels of 'completeness.'** This completeness pertains to the presence of extraembryonic tissues from the yolk sac and placenta, and consequently, the potential to develop into a foetus or neonate. In this context, it was also noted that some procedures are deemed unsafe, such as the **prohibition of gestating human embryo models** and transferring them into any uterus (human or animal). These guidelines follow the ISSCR's 2021 guidelines, which identify two types of embryo models—Non-integrated (e.g., gastruloids) and integrated (e.g., blastoids)—and propose a three-level categorization of embryo research: 1) exempt from review by a specialized oversight process, 2) requiring review by a specialized oversight process, and 3) not allowed and currently deemed unsafe. The current version of the 'Operational Guideline' adapts this review model specifically for organoid research, including embryo models. Experts agreed that this **categorization is useful for research ethics committees in the review** and assessment of research protocols and in enhancing understandings of the 'sensitivity of experiments'.



- One participant drew attention to the **principle of subsidiarity**, which dictates that 'the means used [should] be strictly necessary to achieve the intended objectives' (Agence de la biomédecine, 2023, p. 6), and suggested that this principle could be mentioned in the guidelines. This topic was also proposed as a theme for discussion at the European level, for instance, in 'grand panels' and similar forums.
- In relation to the current version of the operational guidelines regarding human embryo models, participants generally valued the guidelines as a foundation for further discussions. However, one expert raised concerns about the **'alarmist' tone in the document** when discussing 'human synthetic embryos.' This expert feared that such a tone might not fully and realistically represent the field at large, including the many efforts within the field to continuously consider and provide ethical guidelines. These efforts for instance include the production of the ISSCR guidelines and ongoing discussions with ethical committees.
- The importance of dissemination was mentioned both in relation to the final HYBRIDA guidelines concerning organoid technologies and the importance of **responsible science communication**, among others in relation to how scientific findings are disseminated to the public and how they are represented in the media. Regarding the dissemination of guidelines, it was also suggested to **liaise with the European Society for Human Reproduction and Embryology (ESHRE)**.

## 8.2. Neural Organoids

Neural organoids model the brain and nervous system and 'are 3D neural cell structures that model certain architectural and functional features of a developing human brain. They can be cultivated in vitro out of induced pluripotent stem cells (iPSCs) derived from a human donor skin biopsy and out of human embryonic stem cells' (Haselager et al., 2020, p. 2351). Neural organoids offer novel opportunities to advance neuroscience by improving representations and models of brain function, development, and disorders. This enhances understanding of neurological diseases and neurodegenerative processes, aiding in the prevention and treatment of psychiatric, neuropsychological, and neuro-developmental disorders. To date, neural organoids have been successfully used in studies of for instance brain tumors, autism spectrum disorder (ASD), schizophrenia, Alzheimer's disease, and in determining the connection between the Zika virus and microcephaly (de Jongh, 2022; Haselager et al., 2020; The National Academies of Sciences, Engineering, and Medicine, 2021).

Notwithstanding current and prospective scientific advantages, neural organoids can be considered 'sensitive technologies' and have raised a number of ethical concerns. An increasing number of articles have discussed whether mature and advanced neural organoids could potentially develop sentience and



consciousness, respond to pain, and retain cognitive functions at some point. Consequently, there has been a discussion about whether and to what extent such potential developments necessitate their particular protection and attribution of moral status (Baertschi et al., 2020; Farahany et al., 2018; de Jongh 2022). Moreover, the sensitive nature of neural organoids has also been linked to potential public perceptions of the brain, as it is often associated with personhood and might yield particular concerns (The National Academies of Sciences, Engineering, and Medicine, 2021, p. 55; Ravn et al., 2023). This position was also observed in the public deliberations on organoid technologies conducted in HYBRIDA, where neural organoids raised concerns about their ontological, moral, and regulatory status among a majority of participants (Ravn et al., 2023a).

Despite increased attention and debate concerning these issues, a general consensus seems to characterize the field, aligning with the ISSCR position. This stance suggests that scientific developments should be ethically monitored as neural organoids and assembloids become more mature and complex. However, it asserts that no current concerns or specialized ethical oversight are warranted at this time (ISSCR, 2021, p. 10).

In the focus group discussion concerning neural organoids, it is suggested that the HYBRIDA guidelines align with the ISSCR categorisation. The ISSCR currently recommends that neural organoids be "exempt from review by a specialized oversight process" (ISSCR, 2021, p. 9). In line with these guidelines, periodic reviews are also recommended to accommodate advancements in the field. A number of additional recommendations are provided for the HYBRIDA operational guidelines regarding neural organoids,

- In regard to nomenclature, it was suggested to **apply 'neural organoid' as an overall term** as there is some consensus around this terminology within the organoid field literature. This suggestion is also in alignment with the suggested terminology provided in the former expert interview study conducted in HYBRIDA (Ravn et al. 2023). Furthermore, during the focus group interview, it was suggested not to use the term 'cerebroids,' as it is not perceived to be commonly used within the community. It was also suggested to visit existing published guidance on nomenclature. In this regard Pasca et al. (2022) for example suggest further categorizing neural organoids as either 'regionalized neural organoids' or 'unguided neural organoids,' depending on the degree of guidance in differentiating pluripotent stem cells into organoids. In this collective paper, it is also recommended to use the often applied term 'cerebral organoid' only if the organoid mainly contains cells from the cerebrum.
- The discussion around consciousness in relation to neural organoids remains complex. To ensure relevance and accuracy, it was recommended to generally **anchoring this discussion in realistic, state-of-the-art settings and expectations**. The current text in the Operational Guidelines effectively illustrates the ongoing debate surrounding neural organoids. This representation is significant, especially when considering the more abstract ethical concerns associated with neural organoids compared to those related to human embryo models. In this regard, **these less**



'**tangible ethical concerns**' was seen to justify the somewhat 'open-ended' nature of the current guideline sections addressing this topic.

- Furthermore, it was emphasized that while ethical guidelines and regulations are crucial, they should **not impede the use of innovative methods** in neural organoid research or the development of necessary therapies and that there are ethics to consider in this regard as well.
- One expert stated that the discussion on sentience and consciousness is currently focused around ways to **measure consciousness for organoid models**, and that this task remains challenging as no universally agreed definitions and measures for consciousness exist. It can then easily lead to a 'circular' argument, whereas it might be a more effective approach to compare to what can be measured in terms of existing brain develop requirements and prerequisites for consciousness - and for beings which we agree to be conscious - such as for instance degree of complexity, size, interactions with environments etc. Drawing parallels with established understandings of consciousness onset and its ethical implications could offer more tangible metrics for organoid research. In this context, the expert also recommended considering alternative applied models, along with established ethical controls and approval processes, such as those used for **animal models**. An example was here provided, illustrating that a mouse is anesthetized before being used in an experiment, whereas a fly is not. In comparison, it was noted that the size of an organoid is comparable to a cockroach's brain. Additionally, the use of **ex vivo brain samples** as a human brain surrogate was discussed. These tissue samples were viewed as more likely to exhibit consciousness due to their greater complexity, structure, and size. The expert also pointed out that **brain tumours**, despite having a higher neuron count and greater maturity level than organoids, are not often considered in discussions about the potential for consciousness.
- In discussions about **the 'tipping points' at which neural organoids might be considered conscious**, and whether this warrants specific ethical considerations and protections, an expert highlighted several prerequisites: First, a structured organization is necessary, as a randomly connected network would not be sufficient. Second, there needs to be a degree of experiential interaction with the surrounding environment, functioning in an 'input-output' manner. Lastly, a certain level of size and complexity is essential. To contextualize this, a comparison to animals, which are attributed a degree of consciousness, can be made. Another expert emphasized that the ethics do not only concern consciousness and that an additional tipping point could be that of the capacity for developing sentience and avoiding pain. In this context, the discussion about pain perception was emphasized with respect to two key aspects: a) the necessity for precise definitions of sentience and consciousness, as these terms are applied variably; and b) **the challenge in drawing the line between 'noxious stimulus avoidance' and the experience of pain as an emotional state**. The latter, which transcends sentience and is akin to a 'higher cognitive process', was seen as the primary focus of concern.

### 8.3. Summary of Main Recommendations

Sensitive Organoid Technologies		
TOPICS	ISSUES	RECOMMENDATIONS
Human stem cell-derived Embryo Models	Europe-wide discussions	<ul style="list-style-type: none"> <li>The warranting of special legal and ethical protection of embryo models should be discussed at the European level.</li> </ul>
	Ethical and legal oversight	<ul style="list-style-type: none"> <li>Different embryo models requires distinct types of ethical oversight. It is recommended to follow the current ICCSR guidelines (2021) and that the aligned Guidelines categorisation remains useful for research ethics committees.</li> <li>Some procedures are deemed unsafe, e.g. the transfer of embryos models into any uterus (human or animal host).</li> </ul>
	Definitions needed	<ul style="list-style-type: none"> <li>Currently, embryo models should not be regarded as embryos, either biologically or legally.</li> <li>However, the current heterogeneous regulatory landscape creates challenges. A more precise legal definition of a human embryo is necessary to delineate its distinction from in vitro models and to help clarify the 'tipping points'.</li> <li>A clear definition of an (embryo) model is needed.</li> </ul>
	'Tipping point'	<ul style="list-style-type: none"> <li>Two complementary Turing tests are recommended as indicators to determine the reach of the tipping point: 1) if a human embryo model can 'efficiently and faithfully' form the entire embryo in vitro, and 2) the embryo model can form fertile and living animals such as pigs and non-human primates.</li> </ul>
	Cultivation	<ul style="list-style-type: none"> <li>The issue of cultivation is considered one of the most pressing questions. It is suggested to follow the recommendations of the UK and France, allowing integrated embryo models to develop until day 28. This would permit research into the period of embryogenesis, while adhering to the gradualist approach and the principle of proportionality.</li> </ul>



	Principle of subsidiarity	<ul style="list-style-type: none"> <li>The principle of subsidiarity could be incorporated into the operational guidelines and also be a topic for discussion at the European level.</li> </ul>
	Tone in operational guidelines	<ul style="list-style-type: none"> <li>The focus on 'synthetic human embryos' in the text yields an alarmist tone that does not fully represent the field in general.</li> </ul>
	Science communication	<ul style="list-style-type: none"> <li>Responsible science communication and media representation are crucial. Liaising with ESHRE for dissemination efforts is recommended.</li> </ul>
<b>Neural Organoids</b>	Nomenclature	<ul style="list-style-type: none"> <li>The term 'neural organoids' should be used as the overarching descriptor, while the use of 'cerebroids' should be avoided.</li> <li>Sentience and consciousness are terms that are applied somewhat widely and variably within the field, and thus should be precisely defined.</li> </ul>
	Guidelines inclusion	<ul style="list-style-type: none"> <li>The Operational Guidelines are correct in including the topic of neural organoids. An open-ended approach can be legitimized due to the current state of the field, which leads to less tangible ethical considerations.</li> <li>Ethical guidelines and regulations are crucial but should not impede the use of innovative methods.</li> </ul>
	Specialized ethical oversight	<ul style="list-style-type: none"> <li>The ISSCR's position, stating that no current concerns or specialized ethical oversight are warranted, is agreed upon. However, this stance should be monitored as neural organoids and assembloids become more mature and complex.</li> </ul>
	Tipping points Consciousness and sentience	<ul style="list-style-type: none"> <li>Several prerequisites are necessary, including structured organization, interaction with the environment (input-output), and a certain level of size and complexity. This can be compared to animals, which are attributed a degree of consciousness. Another potential tipping point could be sentience, but it is challenging to distinguish between 'noxious stimulus avoidance' and the experience of pain as an emotional state. The latter is seen as the primary concern</li> </ul>
	Measurement of consciousness for organoid models	<ul style="list-style-type: none"> <li>Focus is directed at ways to measure consciousness for organoid models whereas it might be more beneficial to compare to what can be measured in terms of existing brain develop requirements and prerequisites for consciousness. Drawing parallels to established understandings and alternative applied models can also</li> </ul>





		provide a more robust framework for legal and ethical comparisons.
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# 10. Appendix

## Appendix A: List of experts

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### Alexei Grinbaum

- Research Director at CEA-Saclay/LARSIM
  - Chairman of the Steering Operational Committee on Digital Ethics at CEA-Saclay/LARSIM
  - Member of the French National Pilot Committee on Digital Ethics
  - Participated in the HYBRIDA co-creation workshop in Paris.
- 

### Alex Felice

- Professor at the Physiology and the Biochemistry Department at the University of Malta
  - Coordinator and co-founder of the EuroBioBank Network
- 

### Alfonso Martinez Arias

- ICREA Research Professor in the Department of Systems Bioengineering of the Universitat Pompeu Fabra in Barcelona
  - Group leader of the Martinez Arias Lab at the Universitat Pompeu Fabra
  - Member of The European Molecular Biology Organization
- 

### Andreas Kurtz

- Head of Biomedical Data and Bioethics at Fraunhofer Institute for Biomedical Engineering
  - PI at the BIH Center for Regenerative Therapies (BCRT) at Charité - Universitätsmedizin Berlin
  - Head of the Human Pluripotent Stem Cell Registry
  - Responsible for the EBiSC2 IT infrastructure
  - Member of the Bioethics Council at Bayer
  - Member of the working group on Basic Characterization Standards in the ISSCR Standard Initiative
- 

### Andrew Barnhart

- Postdoctoral Research Fellow at the Department of Social Ethics at University of Bonn
  - Did his PhD on ethics of organoids from the Centre for Biomedical Ethics and Law at KU Leuven
  - Participated in the HYBRIDA co-creation workshop in Paris
- 

### Antonie Fuhr

- Bioethicist at the Human Pluripotent Stem Cell Registry at the Fraunhofer Institute for Biomedical Engineering
- 

### Eimantas Peičius

- Professor of Bioethics at the Department of Bioethics at Lithuanian University of Health Sciences
  - Head of the Bioethics Centre at Lithuanian University of Health Sciences
  - Member of the Kaunas Regional Biomedical Research Ethics Committee
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	<ul style="list-style-type: none"><li>▪ Member of the Lithuanian Bioethics Committee Bioethics Board</li></ul>
<b>Eirik Joakim Tranvåg</b>	<ul style="list-style-type: none"><li>▪ Senior advisor at the Norwegian Biotechnology Advisory Board in Norway</li><li>▪ Did his PhD on priority setting for new and expensive cancer drugs</li></ul>
<b>Elena Martínez Fraiz</b>	<ul style="list-style-type: none"><li>▪ Group Leader of the Biomimetic Systems for Cell Engineering group at the Institute for Bioengineering of Catalonia</li></ul>
<b>Erdina Ene</b>	<ul style="list-style-type: none"><li>▪ Legal expert at BBMRI-ERIC with expertise on privacy and compliance issues, who supports the BBMRI-ERIC ELSI team on legal matters.</li></ul>
<b>Helle Bruunsgaard</b>	<ul style="list-style-type: none"><li>▪ Senior Consultant at the Department of Clinical Immunology at Rigshospitalet</li><li>▪ Medical Manager of Transplantation Immunology Section/HLA laboratory and Danish Stem Cell Donors East at the Department of Clinical Immunology at Rigshospitalet</li><li>▪ Clinical Research Associate Professor of Clinical Immunology at the Department of Clinical Medicine at University of Copenhagen</li></ul>
<b>Hjördis Czesnick</b>	<ul style="list-style-type: none"><li>▪ Research Integrity Advisor and Head of Office of the German Research Ombudsman</li><li>▪ Member of the European Network of Research Integrity Offices (ENRIO)</li><li>▪ Participated in the HYBRIDA co-creation workshop in Copenhagen</li></ul>
<b>Ilona G. Reischl</b>	<ul style="list-style-type: none"><li>▪ Chair of the Committee for Advanced Therapies (CAT) at the European Medicines Agency</li><li>▪ Assessor at the Austrian medicines and Medical Devices Agency (AGES MEA/Austrian Agency for Health and Food Safety)</li></ul>
<b>Jacqueline Barry</b>	<ul style="list-style-type: none"><li>▪ Chief Clinical Officer at Cell and Gene Therapy Catapult</li><li>▪ Member of the ISSCR Manufacturing, Clinical Translation and Regulatory Committee</li><li>▪ Coordinator of the UK Advanced Therapy Treatment Centre Network</li><li>▪ Deputy Chair of the International Scientific Advisory Board for the Pluripotent Stem Cells and Engineered Cells at the UK Regenerative Medicine Platform</li></ul>
<b>Krista Varantola</b>	<ul style="list-style-type: none"><li>▪ Members of the ALLEA Permanent Working Group on Science and Ethics</li><li>▪ Chair of ALLEA's Code of Conduct Drafting Group</li><li>▪ Former Rector and Chancellor of the University of Tampere</li></ul>

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- Participated in the HYBRIDA co-creation workshop in Copenhagen.

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**Kristian Tryggvason**

- Founder and CEO of Alder Therapeutics
- Founder and board member at BioLamina
- Former co-chair and member of the ISSCR Manufacturing, Clinical Translation and Regulatory Committee

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**Lars Ursin**

- Associate Professor of Bioethics at the Norwegian University of Science and Technology
- Member of the National Committee for Medical and Health Research Ethics in Norway (NEM)

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**Laurent David**

- Associate Professor of Cellular biology and Director of iPSC Core Facility, INSERM, Université de Nantes
- Action Vice Chair, The European Network for Stem Cell Core Facilities (CorEuStem)
- Treasurer and co-founder of The French Society for Stem Cell Research (FSSCR)
- Member of Stem Cell COREdinates
- Participated in the HYBRIDA co-creation workshop in Paris and in the HYBRIDA expert interview study.

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**Madeline Lancaster**

- Group leader at the Medical Research Council Laboratory of Molecular Biology at University of Cambridge
- Co-chair of the stem cell-derived model systems working group in the ISSCR standards initiative for pluripotent stem cell research

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**Magdalena Skowronska**

- Scientist at Roche Cell and Organoid Banking.

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**Margherita Daverio**

- Assistant Professor at LUMSA University
- Part of the I-Consent project

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**Martine de Vries**

- Full professor and head of department of Medical Ethics and Health Law at the Leiden University Medical Centre
- Member of the Committee on Ethics and Law Health of the Health Council of the Netherlands.
- Member of the Central Committee on Research involving Human Subjects.
- Chair of the Netherlands Centre for Ethics and Health
- Principal investigator within reNEW's PREPARE theme

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**Michael Morrison**

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	<ul style="list-style-type: none"><li>▪ Senior Researcher in Sociology with the Centre for Health, Law and Emerging Technologies (HeLEX) and Associate Fellow at the Institute for Science, Innovation and Society at the University of Oxford</li></ul>
<b>Mie Seest Dam</b>	<ul style="list-style-type: none"><li>▪ Assistant Professor at the Section of Health Services Research at University of Copenhagen</li></ul>
<b>Nick Meade</b>	<ul style="list-style-type: none"><li>▪ Director of Policy at the Genetic Alliance UK</li><li>▪ Participated in the HYBRIDA co-creation workshop in Copenhagen.</li></ul>
<b>Nicolas Rivron</b>	<ul style="list-style-type: none"><li>▪ Group Leader of Laboratory for Blastoid Development at the Institute of Molecular Biotechnology at the Austrian Academy of Science</li><li>▪ Working group member of ISSCR Guidelines Update Task Force</li></ul>
<b>Nils Pfaff</b>	<ul style="list-style-type: none"><li>▪ Director, R&amp;D Strategy and Portfolio at Bayer Pharmaceuticals.</li><li>▪ Member of the ISSCR Manufacturing, Clinical Translation and Regulatory Committee</li></ul>
<b>Pia Jensen</b>	<ul style="list-style-type: none"><li>▪ Lab manager at the Protein Research group at the University of Southern Denmark</li></ul>
<b>Renata Veselská</b>	<ul style="list-style-type: none"><li>▪ Professor of Molecular Biology and Genetics, and Professor of Bioethics at Masaryk University</li><li>▪ Member of the European Group on Ethics in Science and New Technologies</li></ul>
<b>Signe Mežinska</b>	<ul style="list-style-type: none"><li>▪ Associate Professor in Bioethics at the University of Latvia</li><li>▪ Chairperson of the Research Ethics Committee for Life Sciences and Medicine at the University of Latvia</li><li>▪ Member of the Central Medical Ethics Committee of Latvia</li><li>▪ Former member of UNESCO's International Bioethics Committee</li><li>▪ Participated in the HYBRIDA co-creation workshop in Paris</li></ul>
<b>Therése Kallur</b>	<ul style="list-style-type: none"><li>▪ Chief Scientific Officer and Vice President Business Development at BioLamonia</li></ul>
<b>Tine Friis</b>	<ul style="list-style-type: none"><li>▪ Postdoc at Medical Museion at the Department of Public Health at University of Copenhagen</li><li>▪ Affiliated with the Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW)</li></ul>

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- Vasiliki Mollaki**
- Scientific Officer, Hellenic National Commission for Bioethics and Techno-ethics
  - Visiting Professor of Biotechnology and Law, International Hellenic University
  - External Ethics Expert to the European Commission
  - Participated in the HYBRIDA expert interview study.
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- Xavier Guchet**
- Professor of philosophy and ethics of technology at the University of Technology of Compiègne
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- Yasemin J. Erden**
- Associate Professor in Philosophy, Ethics Epistemology of AI at Twenty University
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*The participant overview was compiled in November-December 2023*

## Appendix B: Collective Invitation E-mail

**Subject:** Invitation to participate in focus group on organoid research in connection with the HYBRIDA project



Dear x,

As part of the EU funded project HYBRIDA (Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies, 2021-24), we are conducting a focus group study with leading experts and stakeholders.

A key objective in HYBRIDA is to develop a comprehensive regulatory and ethics framework for organoid research and organoid-related technologies that can support the research community and other stakeholders such as research ethics committees, research integrity offices and biobanks in ethical matters and implications concerning organoid research, e.g. through developing a set of operational guidelines for the field and a Code of Responsible Conduct for organoid researchers.

(Focus Group 1, red.) Based on your expertise, we would like to invite you to participate in a focus group interview. The interview will focus on donors and models of informed consent, and will take place on **Friday 22<sup>nd</sup> September 2023 from 14:00 to 15:30 in Copenhagen** (venue TBA). For this focus group, participants representing [...] are invited to discuss HYBRIDA's pre-final ideas for a donor's wish list and informed consent related to the field of organoid research.

(Focus Group 2, red.) Based on your expertise, we would like to invite you to participate in a focus group interview. The interview will focus on how to address questions related to (lack of) traceability, informed consent etc. in existing and commercially available cell-lines as well as intellectual property rights within the field of organoid research. It will take place **online on Tuesday 3<sup>rd</sup> October 2023 from 15:00 to 16:30 CEST**. For this focus group [...] are invited to discuss and advise on how to address this issue within the HYBRIDA products.



(Focus Group 3, red.) Based on your expertise, we would like to invite you to participate in a focus group interview. The interview will focus on ethical and regulatory issues related to embryonic models and neural organoids. It will take place **online on Friday 15<sup>th</sup> September 2023 from 15:00 to 16:30 CEST**. For this focus group, participants representing [...] are invited to discuss HYBRIDA's pre-final ideas on how to address this ethical and regulatory issue.

(Focus Group 4, red.) Based on your expertise, we would like to invite you to participate in a focus group interview. The interview will focus on the relation between the operational guidelines and the Code of Conduct, as well as on the implementation of an ethics-by-design approach. It will take place on **Friday 8<sup>th</sup> September 2023 from 14:00 to 15:30 in Paris** (venue TBA). For this focus group, participants representing [...] are invited to assess and help validate the latest version of the products.

(Focus Group 5, red.) Based on your expertise, we would like to invite you to participate in a focus group interview. The interview will focus on how to classify and regulate organoid-based technologies for medical use. It will take place **online on Friday 6<sup>th</sup> October 2023 from 15:00 to 16:30 CEST**. For this focus group, participants representing [...] are invited to discuss HYBRIDA's proposal on how to address this regulatory issue.

(Focus Group 6, red.) Based on your expertise, we would like to invite you to participate in a focus group interview. The interview will focus on the regulatory issues related to informed consent, withdrawal, and exchange of material, and will take place on **Friday 29<sup>th</sup> September 2023 from 14:00 to 15:30 in Copenhagen** (venue TBA). For this focus group, participants representing [...] are invited to discuss HYBRIDA's proposal on how to address these issues.

Considering your vast expertise within the field, we would greatly value your participation. If you are available to participate in the focus group, we would be very grateful if you would let us know within the next week. We will reimburse your travel costs and will be happy to assist with travel bookings. HYBRIDA will also cover needed accommodation. If you wish to participate, we will send you a detailed letter of information regarding the focus group.

In case you have any questions concerning the project and/or details of the focus group, please contact me, Mads P. Sørensen ([mps@ps.au.dk](mailto:mps@ps.au.dk)), or Tine Ravn ([tr@ps.au.dk](mailto:tr@ps.au.dk)).

Kind regards,



**HYBRIDA**

Mette Falkenberg, Research assistant, Danish Centre for Studies in Research and Research Policy, Aarhus University

On behalf of

Senior researcher Tine Ravn and Senior researcher Mads P. Sørensen, Danish Centre for Studies in Research and Research Policy, Aarhus University



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101006012.



## Appendix C: Collective Letter of Information

# Letter of information to Experts about the HYBRIDA Project and the Focus Group study

## The HYBRIDA Project

The HYBRIDA project is a 3-year project (2021-2024), funded by the European Commission's Horizon 2020 framework programme (grant no. 101006012). HYBRIDA aims to create a regulatory framework for organoid-based research and resulting technologies with a particular focus on ethical questions.

## Creating an Ethical Framework for Organoid Research

Since Roman law, all entities have been categorized and regulated either as persons or as things (subjects or objects). However, organoids have brought disruption to the dualistic normative framework related to health and life science research. Since it is not clear whether it, as an entity, should be categorised as a subject or an object, three uncertainties must be overcome: conceptual (ontological), epistemological/methodological, and regulatory:

First, conceptual uncertainty (ontological uncertainty): How should one conceive of entities that cannot be categorised 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 personalised or precision medicine, where the number of research subjects with a certain characteristic is too low for randomised controlled trials or other statistically based experiments. As precision medicine and new technologies emerge, evidence-based medicine is challenged to find a new footing. Epistemological uncertainty comes in two kinds, which can be categorised as qualitative, or strict, uncertainty and 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.

Third, regulatory uncertainty: This uncertainty emerges because parts of regulatory frameworks concerning the rights and duties of persons have been merged with elements of regulation dealing with the stewardship of objects or things. These forms of uncertainty are of particular importance.

The HYBRIDA project will address 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.

The main aim of HYBRIDA is to build a comprehensive ethical dimension for organoid-based research and resulting technologies. This comprehensive ethical and regulatory framework will be composed of the following:

- Operational guidelines for the field
- A code of responsible conduct (CoC) for researchers (in academia and industry)
- Contributions to existing ethics and normative frameworks
- If needed, a supplement to the European Code of Conduct for Research Integrity (ECoC).

More details on the project can also be found here: <https://hybrida-project.eu/>.

## The Aim of the Focus Group Study

To ensure that the outcomes of the HYBRIDA project address actual needs and support stakeholders within the field of organoid research and organoid related technologies, the project applies a three-stage engagement process in which experts and stakeholders are involved. The focus group study constitutes the third and final stage of the engagement process. In a total of six focus group interviews, experts and professional stakeholders are consulted to help validate the latest version of the HYBRIDA products. Each focus group interview addresses different key ethical and regulatory issues through collective discussion, reflection, and idea generation, and the consultations will provide a structured exploration and assessment of remaining open questions and unresolved concerns related to the latest draft versions of the project products.

### **[Focus Group 1, red.] The Questions that We are going to Discuss in Your Focus Group**

This focus group will discuss how to address the issue of informed consent as well as different models of informed consent. Furthermore, it will focus on the idea of a Donor's Wishlist, which has been developed within the HYBRIDA project as part of the Operational Guidelines (D.5.1 'Operational guidelines for the field of organoids and organoid-related technologies'). This focus group will have representation from [...].

In the focus group, we will discuss the following main questions:

- Should HYBRIDA propose a particular model of informed consent or continue to map the landscape of pros and cons related to the different models?



- What are your views concerning a preferred model of consent for organoid research (e.g. dynamic consent, consent for governance model, broad consent etc.)
  - What are your views on the Donor's Wishlist?
- Is a Donor's Wishlist a good approach to safeguard the rights and wishes of donors?
- If yes, is the current version sufficiently operational?
- In your view, who should be in charge of follow-up procedures?
  
- In general, does chapter 6 on informed consent read as a complete guideline for its desired target groups and in alignment with high ethical standards?
- Do you have suggestions for additions or revisions?

### **[Focus Group 2, red.] The Questions that We are going to Discuss in Your Focus Group**

This focus group will focus on how to address issues related to traceability of origins and donor's informed consent in existing and commercially available cell-lines and organoids, and it will discuss how to transition from today's standard practice into a more ethically sustainable practice in terms of both the biological material and the associated personal data in relation to data protection measures. Furthermore, the discussion will address questions related to intellectual property rights. In this focus group, [...] will be represented.

In the focus group, we will discuss the following questions:

- The lack of traceability of origin and informed consent for commercially existing cell lines can cause challenges in terms of fulfilling the requirements for a valid consent for data reuse and for data processing. In your view, does chapter 6 on informed consent sufficiently address these challenges and potential solutions?
- Do you have additional recommendations for best practice solutions?
  
- In general, how should we manage the transition towards more regulated and informed consent within organoid research?
- In your view, does chapter 6 on informed consent provide sufficient guidance for such a transition?
  
- How should intellectual property rights be addressed in organoid research?
- In your view, should the issue of intellectual property rights be further specified in the operational guidelines? (please see section 7.3)

### **[Focus Group 3, red.] The Questions that We are going to Discuss in Your Focus Group**

This focus group will focus on ethical and regulatory issues related to embryonic models and neural organoids. It will discuss whether and, if so, how these should be addressed in the set of operational



guidelines for the field of organoid research developed within the HYBRIDA project. Furthermore, the focus group will discuss a regulatory framework for research on embryonic models and neural organoids. Representatives from [...] will participate in this focus group.

In the focus group, we will discuss the following questions:

- Should embryo models and/or neural organoids be included in the operational guidelines?
- Do embryo models and/or neural organoids warrant special ethical and legal concerns, including concerns regarding moral status?
- Which aims justify the use of embryo models and neural organoids? (please see attached section 3.3)
- Do we need an EC-approved regulatory definition of a human embryo and an EC-approved regulatory definition of embryo models? (please see attached discussion paper)

#### **[Focus Group 4, red.] The Questions that We are going to Discuss in Your Focus Group**

This focus group will primarily focus on a validation of the set of operational guidelines (D.5.1.) produced in HYBRIDA and discuss their relation to a Code of Conduct within the field. Furthermore, the focus group discussion will address the implementation of an Ethics by Design approach. [...] will participate in this focus group.

In the focus group, we will discuss the following questions:

- 1) Does the report D.5.1 ‘Operational guidelines for the field of organoids and organoid-related technologies’ sufficiently cover the issues that one could expect to be covered in a set of guidelines for the field?  
Relatedly, do the guidelines sufficiently cover issues of relevance and needs for the different stakeholders addressed (researchers, RECs, RIOs)?
- 2) Would some of the issues and elements discussed in D.5.1. be more relevant to include in a specific Code of Conduct document for the field?
- 3) Third, we would like to discuss your views on the Ethics by Design description, understanding and approach as specified in D.5.1. In addition, we would like to discuss how to best implement an Ethics by Design approach within the field of organoid research?

#### **[Focus Group 5, red.] The Questions that We are going to Discuss in Your Focus Group**

In this focus group we will discuss the classification and regulation of organoid-based technologies for medical use. There is currently no precedent for how to classify and subsequently regulate organoid-based technologies, as they are still at the preclinical stage. Uncertainties pertain to whether to classify and regulate organoid-based technologies as medicinal products, medical devices, or as combination



technologies once they are developed for medical use. To address this issue, [...] will be represented in this focus group interview.

In the focus group, we will discuss the following questions:

- Overall, we will discuss how to regulate organoids for therapies
- In your view, what are the main issues and concerns related to the current regulatory gap of classifying organoid-based technologies for medical use?
- HYBRIDA has identified an over-regulation in terms of applying for market authorization for new ATMPs making it very difficult to provide evidence for fulfilling the requirements. Do you have suggestions/recommendations for ways to address this challenge?
- To enhance the regulatory framework to be proposed in HYBRIDA, it is suggested that the European Commission has to 'offer clear guidance and legally binding provisions for the correct classification of future organoid-based technologies that achieve their primary therapeutic effect principally through functional integration' (discussion paper p.3)
- What is your view on this recommendation?
- The RICOCheck (see materials). Related to the discussion of the two first issues, does anything then need to be changed in the RICOCheck? Is there a need for more information/more questions in this checklist?

### **[Focus Group 6, red.] The Questions that We are going to Discuss in Your Focus Group**

In this focus group, we will discuss how to address withdrawal of consent within the regulatory framework as well as in the Operational Guidelines for organoid research and organoid based technologies. Furthermore, the focus group discussions will address regulatory issues related to the exchange of material and information associated with or derived from the analysis of the material. [...] will participate in this focus group.

In the focus group, we will discuss the following main questions:

- How should HYBRIDA address regulatory issues concerning withdrawal of informed consent?
- In the operational guidelines (section 6.8.), the recommendation for withdrawal follows the ISSCR approach for withdrawal up to the point of cell processing. What is your view on this recommendation?
- In the discussion paper, it is recommended to determine the legal basis for withdrawal on both a national and European level. What is your view on this recommendation?



- How should HYBRIDA address the handling and regulation of exchange of material, for example between institutions where only one of the institutions is located in the EU/EEA.
- In your view, is the recommendation provided in the discussant paper on exchange sufficiently clear and adequate?
  
- In general, does chapter 6 on informed consent read as a complete guideline for its desired target groups and in alignment with high ethical standards and data protection measures?
- Do you have suggestions for additions or revisions?

### **[Focus Group 1, red.] Materials and Preparation**

Materials provided for this focus group discussion include:

- A consent form
- A document containing selected sections from the latest draft version of the set of Operational Guidelines (D.5.1 ‘Operational guidelines for the field of organoids and organoid-related technologies’, Chneiweiss et al., 2023)
- Section 1.2: Executive Summary (pp. 7-13)
- Chapter 6: Organoids and informed consent (pp. 34-50)

In order to enable the focus group discussion, we kindly ask you to read the material in preparation for the focus group interview.

### **[Focus Group 2, red.] Materials and Preparation**

Materials provided for this focus group discussion include:

- A consent form
- A document containing selected sections from the latest draft version of the set of Operational Guidelines (D.5.1 ‘Operational guidelines for the field of organoids and organoid-related technologies’, Chneiweiss et al., 2023)
- Section 1.2: Executive summary of HYBRIDA’s operational guidelines (pp. 7-13)
- Chapter 6: Organoids and informed consent (pp. 34-50)
- Section 7.3: Organoids as marketable commodities: the commercial status and ownership of the cells/tissues (p. 58)

In order to enable the focus group discussion, we kindly ask you to read the material in preparation for the focus group interview.

### **[Focus Group 3, red.] Materials and Preparation**

Materials provided for this focus group discussion include:

- A consent form
- A document containing selected sections from the latest draft version of the set of Operational Guidelines (D.5.1 ‘Operational guidelines for the field of organoids and organoid-related technologies’)
- Section 1.2: Executive Summary (pp. 7-13)
- Section 3.3: Organoids and Specific Ethical Issues (p. 26)
- Chapter 7: Open Ethical Questions (pp. 51-58) And a draft regulatory proposal concerning embryonic models:
- Organoids and the Regulation of In Vitro Embryonic Research (pp. 1-2)

In order to enable the focus group discussion, we kindly ask you to read the material in preparation for the focus group interview.

### **[Focus Group 4, red.] Materials and Preparation**

Materials provided for this focus group discussion include:

- A consent form
- The latest draft version of the set of Operational Guidelines (D.5.1 ‘Operational guidelines for the field of organoids and organoid-related technologies’)

In preparation for the focus group, we kindly ask you to pay special attention to the Executive Summary, Annex 3 (section 11.3), and Annex 4 (section 11.4) of the report D.5.1 ‘Operational guidelines for the field of organoids and organoid-related technologies’ and, if possible, to skim the remaining text in order to enable the focus group discussion. We do not expect you to read the full report closely.

### **[Focus Group 5, red.] Materials and Preparation**

Materials provided for this focus group discussion include:

- A consent form
- A document containing selected sections from the latest draft version of the set of Operational Guidelines (D.5.1 ‘Operational guidelines for the field of organoids and organoid-related technologies’, Chneiweiss et al., 2023):
  - Section 1.2: Executive summary of HYBRIDA’s operational guidelines (pp. 7-13)
  - Chapter 5: RICOCheck for International Review Boards (Research Ethics Committee, Research Integrity Committee) (pp. 31-33)
  - Section 11.10: Annex 10: RICOCheck full questionnaire (pp. 115-123)



As well as a brief discussion paper regarding a regulatory proposal on the classification and regulating of organoid-based technologies for medical use (Lewis et al., 2023):

- o Classifying and Regulating Organoid-Based Technologies for Medical Use (pp. 1-3)

In order to enable the focus group discussion, we kindly ask you to read the material in preparation for the focus group interview.

### **[Focus Group 6, red.] Materials and Preparation**

Materials provided for this focus group discussion include:

- A consent form
- A document containing selected sections from the latest draft version of the set of Operational Guidelines (D.5.1 'Operational guidelines for the field of organoids and organoid-related technologies', Chneiweiss et al., 2023)
  - o Section 1.2: Executive Summary of HYBRIDA's operational guidelines (pp. 7-13)
  - o Chapter 6: Organoids and informed consent (pp. 34-50)

And a discussion paper concerning informed consent, withdrawal and exchange of material (Lewis et al., 2023):

- o Informed Consent, Withdrawal, and Exchange of Material (pp. 1-3)

In order to enable the focus group discussion, we kindly ask you to read the material in preparation for the focus group interview.

### **[Focus Group 1, red.] Date and Venue**

The focus group interview will take place on Friday 22nd September from 14:00-15:30 PM in Copenhagen at Hotel Ottilia.

The address is: Hotel Ottilia, Bryggernes Plads 7, 1799 København V, Denmark. Taxa and bus arrival at Pasteursvej 4, 1799 København V.

### **[Focus Group 2, red.] Date and Venue**

The focus group interview will take place online on Tuesday 3rd October from 15:00-16:30 CEST using Microsoft Teams. It is possible to access the programme through the internet browser. Thus, it is not necessary to download the Microsoft Teams programme.

Please find the link for the meeting below. We have also sent out a separate calendar invitation for easy access.

Link: [...]

### **[Focus Group 3, red.] Date and Venue**

The focus group interview will take place online on 15th September from 15:00-16:30 CEST using Microsoft Teams. It is possible to access the programme through the internet browser. Thus, it is not necessary to download the Microsoft Teams programme.

Please find the link for the meeting below. We have also sent out a separate calendar invitation for easy access.

Link: [...]

### **[Focus Group 4, red.] Date and Venue**

The focus group interview will take place on 8th September from 14:00-15:30 PM in Paris at Sorbonne University.

The address is: Room B120, 1st floor, Cassan Building, Sorbonne Université, Campus Pierre et Marie Curie, 7 Quai Saint Bernard 75005, Paris, France.

### **[Focus Group 5, red.] Date and Venue**

The focus group interview will take place online on Friday 6th October from 15:00-16:30 CEST using Microsoft Teams. It is possible to access the programme through the internet browser. Thus, it is not necessary to download the Microsoft Teams programme.

Please find the link for the meeting below. We have also sent out a separate calendar invitation for easy access.

Link: [...]

### **[Focus Group 6, red.] Date and Venue**

The focus group interview will take place on Friday 29th September from 14:00-15:30 PM in Copenhagen at Hotel Ottilia.

The address is: Hotel Ottilia, Brygernes Plads 7, 1799 København V, Denmark. Taxa and bus arrival at Pasteursvej 4, 1799 København V.

## Travel and Accommodation

HYBRIDA will be able to reimburse travel expenses to and from the focus group and cover expenses for accommodation. Research Assistant at Aarhus University Mette Falkenberg (mefa@ps.au.dk) will be happy to assist with any travel arrangements and bookings needed. If participants prefer to book their own travelling, Mette will subsequently assist with the reimbursement. Please remember to document expenses. As the project is publicly funded, we kindly ask to choose the most economic travel connections (within reason) and we encourage participants to book via Aarhus University or on their own as soon as possible.

We very much look forward to the focus group interview. If you have any questions concerning the project and/or the details of the focus group study, please contact Tine Ravn, Senior Researcher at Aarhus University, [tr@ps.au.dk](mailto:tr@ps.au.dk), Mobile: [phone number omitted] .

Kind regards,

Senior Researcher, PhD Tine Ravn, Danish Centre for Studies in Research and Research Policy, Aarhus University; Senior Researcher, PhD Mads P. Sørensen, Danish Centre for Studies in Research and Research Policy, Aarhus University; M.D. Dr. and Research Director Hervé Chneiweiss, French National Institute for Health and Medical Research (INSERM); Dr. Ioana Andreescu, French National Institute for Health and Medical Research (INSERM); Prof. Søren Holm, Centre for Social Ethics and Policy (CSEP), Manchester University; Dr. Jonathan Lewis, Centre for Social Ethics and Policy (CSEP), Manchester University; and Dr. Heidi Beate Bentzen, Centre for Medical Ethics, University of Oslo.



## **Appendix D: Consent Form**

# Consent Form

### **Informed consent form for interviewees in HYBRIDA’s focus group study, September/October 2023**

#### **Short introduction to organoids and the HYBRIDA project**

The key objective of HYBRIDA is to develop a comprehensive regulatory and ethical framework for organoid research and related technologies that can support the research community and other stakeholders such as research ethics committees, research integrity offices and biobanks in ethical matters concerning organoid research. For this purpose, HYBRIDA will produce: (a) Operational guidelines for the field, (b) a code of responsible conduct (CoC) for researchers (in academia and industry), (c) a set of contributions to existing ethics and normative frameworks and, if needed, (d) a supplement to the European Code of Conduct for Research Integrity (ECoC).

#### **The aim of the focus group study**

To help ensure that the products produced in HYBRIDA are aligned with current ethical needs and requirements and can respond to potential developments in the field of organoid research, a comprehensive citizen and stakeholder engagement process has been initiated as part of the HYBRIDA project. To date, three cross-country public deliberations on attitudes and expectations towards organoid research have been conducted. Furthermore, two co-creation expert workshops together with individual expert interviews have been carried out to further help the project develop a regulatory framework for organoid research.

The focus group interview, in which you are going to take part, is one of six focus groups carried out to validate the core products developed in the HYBRIDA project. The results of the interviews will thus inform a final round of adjustments and improvements of the regulatory and ethical guidelines and recommendations produced.

#### **Funding**

The project is funded by the European Union’s HORIZON 2020 Research and Innovation programme under Grant Agreement no. 101006012.

### Use of data and dissemination of findings

Personal data collection, storage and use of the data collected during the focus group study will be in alignment with the European Union's General Data Protection Regulation (GDPR) and Aarhus University's privacy policy: <https://international.au.dk/about/profile/privacy-policy/browse> If you consent to take part in the focus group interview – by signing this document – information, incl. personal information, provided during the interview will be processed based on Article 6(1)(e) of the General Data Protection Regulation and section 10(1) of the Danish Data Protection Act.

As a basis for analysing the comments and recommendations provided by participants, the focus group interview will be recorded. The findings from the focus group will be analysed by researchers in HYBRIDA and reported as part of the project deliverables to the EU Commission. Participants attend the focus group in their position as experts within their field. All names will be listed in an appendix in the report in order to acknowledge all expert contributions and increase transparency in terms of expertise representation. However, interviewees will be pseudonymised in the text and no quotes or text will be assigned to named participants. Recordings, notes and interview transcripts will only be accessible to members of the project team and handled with confidentiality.

### Risk and inconveniences

We do not expect any potentially critical ethical implications of the focus group study with regard to human dignity and integrity, or privacy of persons.

### Supervision

Research coordinator, senior researcher Mads P. Sørensen ([mps@ps.au.dk](mailto:mps@ps.au.dk)) welcomes any questions about this study.

### Consent

Participation is voluntary and participants are free to withdraw from the study at any time and without giving any reason for withdrawing by contacting Mads P. Sørensen ([mps@ps.au.dk](mailto:mps@ps.au.dk)).

By signing the consent form, you indicate that you agree with all the statements below:

- I have read the information provided about the study. I have had the opportunity to ask questions and my questions have been sufficiently answered. I have had enough time to decide whether I would like to participate.
- I am aware that participation in the study is voluntary. I also know that I can decide at any moment to not participate or to withdraw from the study. I do not have to provide any reasons for not participating or terminating enrolment in the study.
- I accept that I participate as an expert and that my name will be mentioned in an appendix in the research report, but that I otherwise will be pseudonymised.
- I give consent to the recording of the interview.



- I want to participate in the focus group study.

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Date and Participant's signature

---

Name in Block letters

14/8-23 *Mads P. Sørensen*

Date and Project contact's signature

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Mads P. Sørensen

Name in Block letters

## Appendix E: Moderator Guide Focus Group 1

### Focus group 1. Donor's Wish list and Informed Consent. Moderator guide

#### Consent form (5 minutes)

#### Introduction (10 minutes)

*Welcome*

*Short introduction to the focus group – HYBRIDA project, aim, returning experts, issue of anonymity*

- Three stage approach
- This focus group will discuss how to address the issue of informed consent as well as different models of informed consent. Furthermore, it will focus on the idea of a Donor's Wishlist, which has been developed within the HYBRIDA project as part of the Operational Guidelines (D.5.1 'Operational guidelines for the field of organoids and organoid-related technologies').
- *Introduction of participants*

#### Opening questions (10-15 minutes)

1. Before we delve into the specific topics related to informed consent, do you have any immediate responses and feedback to the materials, you have received?
  - Probes: immediate impressions, questions or concerns?

#### First topic (30-35 minutes):

##### Completion of Operational Guidelines in terms of informed consent

1. Based on your work and position – what do you regard to be the most important issues to take into account in informed consent processes related to stem cells and organoids?

Probe: particular donor concerns, challenges, biobank infrastructure, withdrawal, re-consent etc.

2. In general, does chapter 6 on informed consent read as a complete and useful guideline for its desired target groups and in alignment with relevant ethical standards?

Probe: Sufficient content, structure, and guidance? Sufficient operational and supportive? Sufficient standardized procedures?

Probe: Do you have suggestions for additions or revisions?

3. Should HYBRIDA propose a particular model of informed consent or continue to map the landscape of pros and cons related to the different models?

Probe: implications for implementation? Biobank infrastructure?

Probe: What are your views concerning a preferred model of consent for organoid research (e.g. dynamic consent, consent for governance model, broad consent etc.)

4. The guidelines attempts to specify the role of biobanks regardless of the specific type of consent by suggesting different steps, biobanks could take to safeguard the best interest of the donors (section 6.2., e.g. anonymized passport etc.) What is your view on these recommendations? (foster ethical practices, biobank standardizations etc.

*Short break (10 minutes)*

### **Second topic (20-25 minutes):**

#### **Donor's Wishlist**

5. What is your view on the Donor's Wishlist?

Probe: Is a Donor's Wishlist a good approach to safeguard the rights and wishes of donors?

Probe: If yes, is the current version sufficiently operational?

6. In your view, who should be in charge of follow-up procedures? (biobanks?)

#### **Recommendations and additional topics (5 minutes)**

The end of the project and a phase of finalizing the guidelines

8) Based on our discussion today, do you have any last suggestions or advices for us on how to finalize the operational guidelines in terms of informed consent in ways that could enhance their use and impact within the research community?

Probes: any other closing comments?

#### **Rounding off/debriefing (5 minutes)**

- Thank you for your participation.
- What will happen now: transcripts, analysis, report to the EC (we'll send the report to you)
- End with a short evaluation
- Gifts

## **Appendix F: Moderator Guide Focus Group 2**

### **Focus group 2. Commercialization, informed consent and intellectual property rights**

**Consent form (5 minutes)**

**Introduction (10 minutes)**

*Welcome*

*Short introduction to the focus group – HYBRIDA project, aim, returning experts, issue of anonymity*

- Three stage approach
- This focus group will focus on how to address issues related to traceability of origins and donor's informed consent in existing and commercially available cell-lines and organoids, and it will discuss how to transition from today's standard practice into a more ethically sustainable practice in terms of both the biological material and the associated personal data in relation to data protection measures. Furthermore, the discussion will address questions related to intellectual property rights.
- *Introduction of participants*

**Opening questions (10-15 minutes)**

1. Before we delve into the specific topics, do you have any immediate responses and feedback to the materials, you have received?
  - Probes: immediate impressions, questions or concerns?

**First topic (40-45 minutes):**

**Completion of Operational Guidelines in terms of informed consent and traceability**

1. Based on your work and position – what do you regard to be the most important issues to take into account in informed consent processes related to stem cells and organoids?

(e.g. Particular donor concerns in terms of traceability, industry challenges, biobank infrastructure, withdrawal, re-consent in terms of data protection etc.)



2. The lack of traceability of origin and informed consent for commercially existing cell lines can cause challenges in terms of fulfilling the requirements for a valid consent for data reuse and for data processing.

What do you see as the main challenges in this regard? (immortality of cell lines, transfer of samples/MTAs etc.)

3. In your view, does chapter 6 on informed consent sufficiently address these challenges and potential solutions?

Probe: Do you have additional recommendations for best practice solutions?

4. In your view, how should we manage the transition towards more regulated and informed consent within organoid research? (e.g. withdrawal regulation, what do we do with existing cell lines; should we still use them or try to move towards new cell lines?)
5. In your view, does chapter 6 on informed consent provide sufficient guidance for such a transition?
6. In chapter 6 on consent, HYBRIDA suggest to implement the practice of a 'passport' that could accompany the distribution of samples. What is your view on such a passport model? (increase data protection, transparency etc.)
7. The chapter on informed consent also describe a researcher choice between either anonymization or pseudonymisation (p.36) – in terms of data protections measures and GDPR requirements, do you regard this line of guidance to be sufficiently clear for researchers?

**Second topic (20 minutes):**

**Intellectual property rights**

8. How should intellectual property rights be addressed in organoid research and in the consent form? (is it sufficient what is there right now?)
9. In your view, should the issue of intellectual property rights be further specified in the operational guidelines? (please see section 7.3)

**(Ownership, organoids as commercial objects, section 7.3?)**

### **Recommendations and additional topics (5 minutes)**

The end of the project and a phase of finalizing the guidelines

10) Based on our discussion today, do you have any last suggestions or advices for us on how to finalize the operational guidelines and regulatory framework - in terms of informed consent issues and exchange of materials - in ways that could enhance their use and impact within the research community?

- Probes: any other closing comments?

### **Rounding off/debriefing (5 minutes)**

- Thank you for your participation.
- What will happen now: transcripts, analysis, report to the EC (we'll send the report to you)

## **Appendix G: Moderator Guide Focus Group 3**

### **Focus group 3. Embryo Models and Neural Organoids. Moderator guide. Online.**

**Consent form (Oral consent, 5 minutes)**

**Introduction (5 minutes)**

*Welcome*

*Short introduction to the focus group – HYBRIDA project, aim, returning experts, issue of anonymity*

- Three stage approach
- This focus group will focus on ethical and regulatory issues related to embryo models and neural organoids. It will discuss whether and, if so, how these should be addressed in the set of operational guidelines for the field of organoid research developed within the HYBRIDA project. Furthermore, the focus group will discuss a regulatory framework for research on embryonic models and neural organoids
- Reference of participants in the report – no individual quotes

*Introduction of participants*

**Opening questions (10-15 minutes)**

1. Before we delve into the specific topics related to embryonic models and neural organoids, do you have any immediate responses and feedback to the materials, you have received?

- Probes: immediate impressions, questions or concerns?

**First topic (30-35 minutes):**

## The status of embryo models and neural organoids in the Operational Guidelines

2. In your view, do embryo models and/or neural organoids currently warrant any special ethical and legal concerns, that we need to take into account in the project, in general? (e.g. concerning moral status?) and/or do you foresee any such challenges in the near future?

Probes: Concerns that need to be reflected in the guidelines and/or regulatory framework?

3. In your view, should the operational guidelines for organoid technologies address embryo models and/or neural organoids as distinct types of organoids in regard to their status and regulation?

4. In the current version, embryo models and neural organoids are primarily addressed in a chapter on 'open ethical questions', identifying current and prospective ethical issues rather than providing clear guidelines. What is your view on addressing embryo models/neural organoids in such a way in a set of guidelines for the organoid research field?

Probe: In your view, do the guidelines sufficiently support researchers within your fields of research?

Probe: In your view, which terminology is the most appropriate to use in the guidelines (currently embryonic models, cerebroids)

5. In addition to the open question chapter, section 3.3. translates the three ISSCR review categories into the field of organoid research, for instance specifying lines of research that should be prohibited. What is your view on this suggested classification?

Probe: In your view, is the classification aligned with the justified aims of using embryo models and neural organoids?

Probe: What would be an example of embryonic or neural organoid research in category 3/i.e. that should be prohibited?

(6. Do you have any recommendations on how to support the practical implementation of the operational guidelines within your field?)

*Short break – if needed (5 minutes)*

**Second topic (20 minutes):**

**Regulatory issues related to embryonic models and neural organoids**

In addition to the set of operational guidelines for the organoid field, the project also produces a regulatory framework identifying gaps in terms of over- and under regulation. Legislation regarding embryo models has increasingly become a topic of concern in this regard.

7. In the discussion paper, our partners from Manchester University suggest that we need an EC-approved regulatory definition of a human embryo and an EC-approved regulatory definition of embryo models. What is your view on this recommendation?

8. Are there any open legal or regulatory questions that need to be answered in relation to neural organoids?

**Recommendations and additional topics (5 minutes)**

The end of the project and a phase of finalizing the guidelines

10) Based on our discussion today, do you have any last suggestions or advices for us on how to finalize the operational guidelines in ways that could enhance their use and impact within the research community?

- Probes: any other closing comments?

**Rounding off/debriefing (5 minutes)**

- Thank you for your participation.
- What will happen now: transcripts, analysis, report to the EC (we'll send the report to you – as well as the final guideline documents)

## Appendix H: Moderator Guide Focus Group 4

### Focus group 4. Peer Review Group. Moderator guide

Consent form (5 minutes)

Introduction (5 minutes)

*Welcome*

*Short introduction to the focus group – HYBRIDA project, aim, returning experts, issue of anonymity*

- Three stage approach
- This focus group will primarily focus on a validation of the set of operational guidelines (D.5.1.) produced in HYBRIDA and discuss their relation to a Code of Conduct within the field. Furthermore, the focus group discussion will address the implementation of an Ethics by Design approach

*Introduction of participants*

Opening questions (10 minutes)

1. Before we delve into the specific topics related to the operational guidelines, do you have any immediate responses and feedback to the materials, you have received?
  - Probes: immediate impressions, questions or concerns?

First topic (25 minutes):

#### Completion of the Operational Guidelines

2. In your view, does the report D.5.1 ‘Operational guidelines for the field of organoids and organoid-related technologies’ sufficiently cover the issues that one could expect to be covered in a set of guidelines for the field?
  - Probes: Sufficient content, structure, and guidance? Sufficient operational and supportive? Sufficient standardized procedures?
3. Relatedly, do the guidelines sufficiently cover issues of relevance and needs for the different stakeholders addressed (researchers, RECs, RIOs, donors)?
4. How would you assess the accessibility and usability of the guidelines?
  - Probes: design, lengths, amount and type of information



(information on online survey assess to the checklists – MIAOU, EChOES, RICOcheck, DOW)

5. Do you have any recommendations on how to support the practical implementation of the different guidelines and checklists?

Probes: types of collaborations, online solutions etc.?

### **Second topic (15 minutes):**

#### **Code of conduct**

Introduction to the CoC (build around ALLEA topics) – objectives and potential overlap of topics

- 6) In your view, would some of the issues and elements discussed in D.5.1. be more relevant to include in a specific Code of Conduct document for the field to avoid overlap and to streamline the operational guidelines?

7. Currently, the guidelines and Code of conduct (ORF-ECoc) exist as two different document, however with the ECoC clearly referring to the operational guidelines. Do you see a need to interlink the two documents further to promote responsible research within the field?

Probes: why and how can this be done?

*Short break (10 minutes)*

### **Third topic (20 minutes):**

#### **Ethics by design approach**

- 8) What is your views on the Ethics by Design approach that is applied in the operational guidelines?

- 9) In your opinion, how to best implement an Ethics by Design approach within the field of organoid research?

### Recommendations and additional topics (5 minutes)

The end of the project and a phase of finalizing the guidelines

- 10) Based on our discussion today, do you have any last suggestions or advices for us on how to finalize the operational guidelines in ways that could enhance their use and impact within the research community?
- Probes: any other closing comments?

### Rounding off/debriefing (5 minutes)

- Thank you for your participation.
- What will happen now: transcripts, analysis, report to the EC (we'll send the report to you)
- End with a short evaluation
- Gifts

## **Appendix I: Moderator Guide Focus Group 5**

### **Focus group 5. Classification and regulation of organoid-based technologies for medical use.**

**Consent form (5 minutes)**

**Introduction (10 minutes)**

*Welcome*

*Short introduction to the focus group – HYBRIDA project, aim, returning experts, issue of anonymity*

- Three stage approach
- In this focus group we will discuss the classification and regulation of organoid-based technologies for medical use. There is currently no precedent for how to classify and subsequently regulate organoid-based technologies, as they are still at the preclinical stage. Therefore, uncertainties pertain to whether to classify and regulate organoid-based technologies as medicinal products, medical devices, or as combination technologies once they are developed for medical use.
- *Introduction of participants*

#### **Opening questions (10-15 minutes)**

1. Before we delve into the specific topics, do you have any immediate responses and feedback to the materials, you have received?
  - Probes: immediate impressions, questions or concerns?

#### **First topic (40-45 minutes):**

##### **Regulatory gaps and classification challenges in terms of organoid-based technologies for medical use**

(Overall, we will discuss how to regulate organoids for therapies)

1. In your view, what do you identify as the main issues and concerns related to the current legislative landscape of regulating organoid-based technologies for medical use? ('overregulation', determine the category under which the product falls under either medical device regulations or medicinal products directive/regulations)

Probe: What do you identify as the main challenges?



2. Based on your work and position – what do you regard to be the most important issues to take into account in classification processes related organoid technologies?

(e.g. unclear definitions - heterogeneous nature of ATMPs (Advanced Therapy Medical Products), The EMA (European Medicines Agency), lack of standardization and legislation)

Probe: How to handle borderline cases (“i.e., where it is not clear whether a technology falls under the medical device regulations or the medicinal products directive/regulations)

Probe: How to handle combination technologies “that incorporate elements of both medicinal products and medical devices”

3. In the discussion paper forwarded to you, Jonathan includes the example of a transplantation of a brain organoid into large injury cavities in a patient’s visual cortex, questioning how we should classify this organoid technology – do you have a suggestion on how to solve this classification challenge?
4. In your view, how can HYBRIDA sufficiently address these challenges and potential solutions in the regulatory framework produced?
5. HYBRIDA has identified an over-regulation in terms of applying for market authorization for new ATMPs making it very difficult to provide sufficient evidence for fulfilling the requirements.

Do you have suggestions/recommendations for ways to address this challenge?

6. To enhance the regulatory framework to be proposed in HYBRIDA, it is suggested that the European Commission has to ‘offer clear guidance and legally binding provisions for the correct classification of future organoid-based technologies that achieve their primary therapeutic effect principally through functional integration’ (discussion paper p.3)

What is your view on this recommendation?

### **Second topic (20 minutes):**

#### **RICOCHECK**

7. As preparation for today’s discussion, you have also read the “The Research Integrity Committee Organoid Checklist” (the so-called RICOCheck). What is your overall impression of this Checklist?



(is it helpful, is it addressing the right issues, is anything missing?)

8. Based on our discussions of regulatory and classification issues, do you think that the RICOCheck needs to be modified to provide additional information for review board members (RECs and RIOs)? (e.g. data confidentiality, 'privacy-by-design', public engagement)

Probe: Do you have additional recommendations for best practice solutions?

### **Recommendations and additional topics (5 minutes)**

The end of the project and a phase of finalizing the guidelines

9. Based on our discussion today, do you have any last suggestions or advices for us on how to finalize the operational guidelines and regulatory framework - in terms of regulatory and classification issues - in ways that could enhance their use and impact within the research community?
  - Probes: any other closing comments?

### **Rounding off/debriefing (5 minutes)**

- Thank you for your participation.
- What will happen now: transcripts, analysis, report to the EC (we'll send the report to you)

## **Appendix J: Moderator Guide Focus Group 6**

### **Focus group 6. Informed Consent, Withdrawal, and Exchange of Material. Moderator guide**

**Consent form (5 minutes)**

**Introduction (10 minutes)**

*Welcome*

- *Short introduction to the focus group – HYBRIDA project, aim, returning experts, issue of anonymity*
- *Three stage approach*
- *In this focus group, we will discuss how to address withdrawal of consent within the regulatory framework as well as in the Operational Guidelines for organoid research and organoid based technologies. Furthermore, the focus group discussions will address regulatory issues related to the exchange of material and information associated with or derived from the analysis of the material*
- *Introduction of participants*

**Opening questions (10-15 minutes)**

1. *Before we delve into the specific topics, do you have any immediate responses and feedback to the materials, you have received?*
  - *Probes: immediate impressions, questions or concerns?*

**First topic (20 minutes):**

**Completion of Operational Guidelines in terms of informed consent**

1. *Based on your work and position – what do you regard to be the most important issues to take into account in informed consent processes related to stem cells and organoids?*

*Probe: particular donor concerns, challenges, biobank infrastructure, withdrawal, re-consent etc.*

2. *In general, does chapter 6 on informed consent read as a complete and useful guideline for its desired target groups and in alignment with relevant ethical standards and data protection measures?*

*Probe: Sufficient content, structure, and guidance? Sufficient operational and supportive? Sufficient standardized procedures?*

**Second topic (20 minutes):**

**Withdrawal of consent**

(Regulations guiding donor withdrawals only extend to cells and tissues – not clear whether regulation include organoids derived from donor cells)

5. In your views, how should HYBRIDA address regulatory issues concerning withdrawal of informed consent?
  
6. In the operational guidelines (section 6.8.), the recommendation for withdrawal follows the ISSCR approach for withdrawal up to the point of cell processing. What is your view on this recommendation?
  
7. In the discussion paper, it is recommended to determine the legal basis for withdrawal on both a national and European level. What is your view on this recommendation?

*Short break (10 minutes)*

**Third topic (20 minutes):**

**Exchange of materials (MTAs)**

(Short intro to topic)

8. How should HYBRIDA address the handling and regulation of exchange of material, for example between institutions where only one of the institutions is located in the EU/EEA.
  
9. In your view, is the recommendation provided in the discussant paper on exchange sufficiently clear and adequate?

**Recommendations and additional topics (5 minutes)**

The end of the project and a phase of finalizing the guidelines

8) Based on our discussion today, do you have any last suggestions or advices for us on how to finalize the operational guidelines and regulatory framework - in terms of informed consent issues and exchange of materials - in ways that could enhance their use and impact within the research community?

- Probes: any other closing comments?



**Rounding off/debriefing (5 minutes)**

- Thank you for your participation.
- What will happen now: transcripts, analysis, report to the EC (we'll send the report to you)
- End with a short evaluation
- Gifts

