HYBRIDA

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D4.4: Report on the expert interviews and co-creation workshops

HYBRIDA

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

Report Factsheet:

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ABSTRACT:	The report presents the empirical findings from the second stage of engagement in the HYBRIDA project, covering expert co-creation and consultation. Two co-creation expert workshops were conducted in Paris, May 2022, and in Copenhagen, June 2022, involving a total of 27 external experts and 11 internal HYBRIDA members. The aim of the workshops was to identify ethical and legal challenges in alignment with the required needs, developments, and conceptualisations within the field of organoid research and to co-produce potential solutions to further develop the four HYBRIDA products, including 'Operational Guidelines for the Field of Organoids and Organoid-related Technologies' and a 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies'. Following the two expert workshops, an expert interview study with 15 experts within the field was conducted in November and December 2022. The main aim was to further explore ethical and legal issues pertaining to organoid research, and enquire into emerging and persisting open question within HYBRIDA, e.g. concerning informed consent, sensitive organoid technologies, and science communication.
Keyword List:	Expert co-creation workshops, expert interviews, organoid technologies, informed consent procedures, legal and ethical aspects

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Executive Summary

WP Aim and Research Design

HYBRIDA applies a three-stage engagement process (1. exploration of public attitudes, 2. co-creation/consultation, and 3. validation) involving the scientific community, the public, and other key stakeholders in deliberative, co-creation, and consultation activities throughout the process of developing, producing, and validating the following practice-relevant products: a) operational guidelines for the field of organoid research, b) a code of responsible conduct for researchers, c) enhancement of existing ethics and normative frameworks, and d) a supplement, if needed, to the European Code of Conduct (ECoC).

The report presents the empirical findings from the second stage of engagement, covering expert co-creation and consultation. Two co-creation expert workshops were conducted in Paris, May 2022, and in Copenhagen, June 2022, involving a total of 27 external experts and 11 internal HYBRIDA members, representing the following stakeholder groups: research communities (incl. industry), research ethics committees (RECs), research integrity offices (RIOs), policy makers, legal experts, patient organisations, and biobanks.

The aim of the workshops was to identify ethical and legal challenges in alignment with the required needs, developments, and conceptualisations within the field of organoid research and to co-produce potential solutions to further develop the four HYBRIDA products.

The first workshop focused on the first version of 'D5.1 Operational Guidelines for the Field of Organoids' (Chneiweiss et al., 2022), including sections on 'Organoids and Informed Consent', 'Minimal Information About an Organoid and its Use' (MIAOU), and an 'Evaluation Checklist for Organoid Ethical Studies' (EChOES).

The second workshop covered the first version of a 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies' (Chneiweiss et al., 2022a), including a potential supplement to the European Code of Conduct (ALLEA, 2017). Issues of informed consent and potential legal issues and gaps were also among topics discussed in the workshop.

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Following the two co-creation workshops, an expert interview study with 15 experts within the field was conducted in November and December 2022. The main aim was to further explore ethical and legal issues pertaining to organoid research and organoid-related technologies, and enquire into emerging and persisting open question within HYBRIDA, e.g. concerning informed consent, sensitive organoid technologies, and science communication.

Operational Guidelines: 'Minimal Information About an Organoid and its Use' (MIAOU)

Participants in the first co-creation workshop found the MIAOU, which aims to provide a minimum information checklist on organoid production for researchers, to be a very useful tool for critical reflection and promotion of awareness concerning key ethical challenges. Suggestions were made to keep the MIAOU concise and operational, containing a minimum set of standards, additionally specifying the provenance of the biomaterial and the types of organoids produced. It was furthermore suggested to refrain from referring to organoid metadata as a "passport" or "identity sheet" to avoid any humanisation. Participants highlighted clear and transparent science communication as an important token of responsible conduct of research (RCR) and as an important topic to include in the operational guidelines. The need for a precise organoid nomenclature was underlined.

Operational Guidelines: 'Evaluation Checklist for Organoid Ethical Studies' (EChOES)

The EChOES comprises a set of guidelines for scientific evaluation and one for ethical review. The first co-creation workshop focused on the latter, recommending a clear focus on issues specifically relevant to organoid research and organoid-related technologies, specifying the composition of evaluator target groups and related content with specific and tangible questions (e.g. agreement with the Helsinki Declaration, legal basis, data sources etc.). Participants suggested to keep the list short and to avoid redundant bureaucracy. The following topics were suggested for inclusion:

i. Risk-benefit assessment (e.g. control patients)
ii. Insurance and payment
iii. Assessment of whether the research adheres to current legal and national frameworks
iv. Commercialisation issues
v. Public communication

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vi. Categorised organoid usage

The Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies

The second co-creation workshop – covering the main objective of translating general research integrity principles into specific guidelines relevant to organoid research – found the notion of a targeted Code of Conduct for organoid research to be a valuable addition to the European Code of Conduct for Research Integrity.

Based on the first draft version of the Code, suggestions were made to:

i. align the applied terminology with current legal frameworks (e.g. in relation to data protection).
ii. to include illustrative examples of e.g. practices of questionable research practices (QRPs) within the field.
iii. to elaborate on the role of different stakeholders such as RIOs, publishers, and funders to promote responsible research and reinforce an implementation of the Code.

In order to facilitate continued adherence to and awareness of the Code of Conduct, the workshop explored potential incentives, also proposing an international 'seal of approval' for scientific journals promoting the CoC.

A Supplement to the European Code of Conduct for Research Integrity

Participants in the second workshop recognised the value of fashioning a supplement to the European Code of Conduct with organoid field-specific clarifications. The HYBRIDA Code of Responsible Conduct was considered an example of such a supplement. Particular attention and recommendations were provided on expanding on the section on 'Safeguards' (ALLEA, 2017, p. 6);

i. In terms of the handling of research subjects, attention should be directed at animal research and towards organoids that may warrant particular consideration and protection.
ii. The issue of ethics dumping could be addressed in the supplement, referring to the Global Code of Conduct for Research in Resource-Poor Settings.

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iii. Attention towards socio-demographic diversity in research protocols was highlighted in relation to translational organoid research and drug screening (e.g. variation in risk factors across ethnicities).

iv. Attention should be directed towards management of expectations and the avoidance of therapeutic misconception.

Regulatory Issues and Gaps Concerning Organoid Technologies

Experts in the second co-creation workshop identified two main regulatory issues for the field:

i. The challenges pertaining to cross-country data sharing was raised as a regulatory issue in regard to variation in domestic laws. The preparation of Material Transfer Agreements (MTAs) between different parties was perceived as a complex, time-consuming endeavour that may also be subject to varying legal interpretations across countries and institutions. Workshop participants regarded a harmonisation of regulatory practices as a desirable, albeit not easily realisable, improvement to the state of organoid research.

ii. Cerebral organoids and embryoids were seen as organoid types warranting special legal concern. Speaking to the latter, experts pointed to a legal gap and lack of clarification between human embryos and advanced embryo models.

Main Ethical and Legal Issues within Organoid Research

Experts in the interview study generally identified informed donor consent procedures and research related to embryonic models as key current ethical and legal issues within organoid research. Across the interviews, neural organoids were also mentioned as an area of ethical concern to a certain extent, in addition to the issue of responsible science communication. Other ethical and legal topics raised included a) gonadal organoids (e.g. concerns in relation to human reproduction and human cloning), b) chimeras and animal research (e.g. concerns regarding animal welfare and cerebral organoids), c) organoid complexes and assembloids (e.g. concerns related to their in-vitro handling, cerebral organoids, gamete organoids, and organs-on-chip), and d) access to health care (e.g. concerns about health inequalities and lack of access to treatments).

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Embryonic Models

Experts in the interview study found the quickly advancing field of embryonic models to warrant particular attention, with some explicitly pointing to the potential negative consequences of research into 'synthetic mouse embryos' (e.g. in relation to aspects such as commercialisation and informed consent, misleading terminology and public unease). The need for conceptual and legal clarity was raised in relation to the distinction between human embryos and advanced embryonic models. A specified 'governance framework' was suggested to outline the functioning and use of embryonic models, clarify a potential application of the 14-day limit within this research, and align ethical review and informed consent processes to the purpose of the research.

Cerebral/Neural Organoids

The position of the interviewed experts on cerebral organoids was generally aligned with the 'ISSCR guidelines for Stem Cell Research and Clinical Translation', asserting that the current stage of research into neural organoids does not currently warrant special ethical or legal concerns, but that continued ethical awareness is called for, as research on neural organoids advances (International Society for Stem Cell Research, 2021, p.10). Nonetheless, experts did see neural organoids as more sensitive in nature compared to other types of organoids, not least in terms of the concern they may raise within the public perception. In addition, experts identified the creation of chimeras through neural organoid transplantation as a particular issue of concern.

Cross-Cutting Issue: Informed Consent

In general, the external participants across the expert co-creation and consultation processes (n = 41) find informed consent to be a salient ethical and legal issue within organoid research. The variation in perspectives and positions on preferred consent models speaks to the complexity involved in balancing the provision of specific donor information with the open-ended character of organoid research, underpinning more profound and longstanding debates concerning the implementation of a *genuine* informed consent.

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i. Proper information and involvement of donors and patients

- Participants emphasise the need to provide patients and/or donors with clear, understandable, and sufficient information to enable them to make informed and autonomous decisions while ensuring that the consent is truly voluntary.
- Granting of decision-making power to patients/donors and greater involvement of different stakeholders through open and disclosing consent processes are suggested as means to increase trust, potentially minimise the need for reconsent, and reduce the risk of withdrawals.
- The type of information included in informed consent particularly tailored to organoid research could include information regarding the process of obtaining tissue and source material from the donor; organoid features and functions; the process in which the organoids are involved, activities post study completion; potential commercialisation; and sharing of open data.

ii. 'Open-endedness' and future use

- The 'open-endedness' of biomaterial donated for organoid research constitutes a consideration that relates to the difficulties of specifying future uses and risks. The open-ended nature of organoids might cause unease and concern among donors. Some experts suggest to consider potential time restrictions on the use of donations.
- Protection of donors and patients through proper, responsible, and adequate consent processes are highlighted together with a concurrent need not to 'block any progress' that would also be in the interests of patients and society at large.

iii. Contextual dimensions: Not 'one-size-fits-all policy'

- The contextual dimension is highlighted as relating to the need to take different contextual factors into consideration (e.g. cultural and religious aspects) and in regard to the specific use of the donation and type of organoids made. Standard consent may suffice in some instances,

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whereas more ethically sensitive organoids such as cerebral organoids, gonad organoids, embryo models, and assembloids may call for 'special consideration' due to their ethical nature and 'moral' positioning within public understandings.

- Informed consent is highly case-specific and it is not feasible, nor potentially desirable, to create a one-size-fits-all model for a consent form within organoid research. It is suggested that variation could be accommodated through bespoke 'decision-tree' models of informed consent tailored to the 'the nature of the research'.

iv. Data protection and anonymisation

- Challenges related to data handling, data storage, privacy protection, and traceability are emphasised. Consequences and risks of data protection measures should be transparently stated in the consent form, including aspects related to distribution and commercialisation.

v. Issues of withdrawal

- Withdrawal of consent was perceived as an important aspect to consider for organoid research.
- The difficulties of tracking down samples, e.g. after the derivation of iPS cells, was emphasised.
- The withdrawal clause should be very clear and transparent in terms of uses and limitations.

vi. Models of informed consent

- Expert opinions reflected different views on the best model of informed consent within organoid research, highlighting a number of advantages and disadvantages of the following models: broad consent, dynamic consent, specific consent, and entrusted third party.
- The pros and cons pertaining to each models mirror a broader academic debate concerning the de facto implementation of a genuine informed consent within the field and the argument that one model does not necessarily fit all purposes.
- A number of experts preferred a broad consent model to accommodate the open-ended character of organoid research and potential future clinical applications, while also pointing to the unfeasibility and resource demanding aspects of re-contact processes. The disadvantages of the broad consent model were, however, voiced by a larger group of experts, emphasising the preferences for re-approach options and that broad consent does not provide sufficient information nor allow

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donors to enact permissive control of the specific use/re-use of their samples, potentially discouraging donor participation and undermining trust within the field.

Cross-Cutting Issue: Science Communication and Scientific Dissemination

The importance of sound and transparent public science communication, accurate science representation, and clear management of expectations comprised a recurrent, underlined theme mentioned by experts across the two co-creation workshops and in the interview study. Responsible science communication within organoid research was perceived as both a researcher obligation and a way to foster public trust and support. Stakeholders, such as communication offices, journal editors, science journalists, funding agencies, and politicians, were also held to play an important role in counteracting sensational science representation.

The expert interview study found that a certain degree of hype can be identified within organoid research, particularly within the field of neural organoids and embryonic models. Agreement existed to the fact that while some hype may be a prerequisite for increased awareness and funding streams, overstated and unmet expectations may easily result in a number of negative consequences such as public mistrust, field restrictions, marketing of untested treatments, among others. Attempting to actively regulate hype surrounding organoids was not perceived to be a fruitful nor realistic strategy for addressing hype. Rather, experts pointed to guidelines such as the ISSCR guidelines (2021) as a beneficial strategy. In addition, it was recommended to a) promote dedicated training and education initiatives to science communicators, b) reinforce public outreach activities, c) increase science community coordination internally, e.g. through networks, collaborations, and social media strategies, and d) agree on and apply a precise nomenclature in order to avoid creating scientific misconceptions and misrepresentations. Terms such as ‘mini-brains’, ‘brain organoids’, and ‘synthetic embryos’ should be avoided.

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Table 1. Summary of Main Issues and Recommendations in the Second Stage of Engagement

HYBRIDA PRODUCTS		
PRODUCT	**ISSUES**	**RECOMMENDATIONS**
Operational Guidelines		
MIAOU	Type and scope of information to be provided in a set of 'Minimal Information About an Organoid and its Use'	• Should contain a minimum set of standards and specify the provenance of biomaterial and organoid types produced • Should stimulate ethical reflections • Avoidance of humanised metadata designations such as 'identity sheet' or 'passport' • Attention to and implementation of a precise organoid nomenclature • Science communication issues important to include in guidelines
EChOES	Key topics and sub-topics to be included in an evaluation checklist for ethical review	• Should be tailored to organoid research and organoid-related technologies, including a specification of target group composition and tangible questions • Issues to be included could be risk-benefit assessment; insurance and payment; assessment of adherence to current legal and national frameworks; commercialisation issues; public communication; and categorised organoid usage
Informed Consent	Important aspects to consider in informed consent processes, e.g. tailored to organoid research and preferred models of consent	• Salient ethical and legal issue within organoid research • Proper information and actual involvement of patients/donors are highlighted as significant • Information to be included could be the process of obtaining tissue and source material from the donor; organoid features and functions; the process in which the organoids are involved, activities post study completion; potential commercialisation; and sharing of open data • Time restrictions on use could potentially be included • Issues related to data protection, anonymisation, withdrawal, and commercialisation should be clearly stated

		• Contextual factors should be taken into account in terms of organoid uses and types • Avoidance of a 'one-size-fits all' policy • Not one model of consent preferred. Pros and cons associated with different models. Concerns raised regarding the broad consent model in particular
Code of Responsible Conduct (CoC)	Extent to which the Code of Responsible Conduct is in alignment with the required needs, developments, and conceptualisations within the field of organoid research and the field of research integrity/research ethics.	• Alignment between applied terminology and existing legal frameworks should be implemented (e.g. in relation to data protection) • QRP exemplifications could be included for illustration • Specification of stakeholder roles should be included (e.g. RIOs, publishers, and funders) • Attention should be given towards incentives for user compliance
Supplement to ECoC	Assessment of the need for a supplement to the European Code of Conduct (ECoC).	• The HYBRIDA Code of Conduct considered to be a supplement • The ECoC section on 'safeguards' could be further developed for organoid research, e.g. in relation to animal research, ethics dumping, variation in risk factors and expectation management
ETHICAL/LEGAL ISSUES		
TOPICS	**ISSUES**	**RECOMMENDATIONS**
Regulatory gaps	Particular regulatory gaps specified in the 2nd expert workshop	• Cross-country data sharing challenging due to variation in domestic laws. Material Transfer Agreements (MTAs) may be subject to varying legal interpretations. Greater harmonisation would be desirable • Cerebral organoids and embryoids warrant special legal concern. Legal gap identified between human embryos and advanced embryo models
Embryonic models	Particular ethical/legal issues pertaining to embryonic models	• Warrant particular attention • Need for conceptual and legal clarity as to the distinction between human embryos and advanced embryo models

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Cerebral/Neural organoids	Particular ethical/legal issues pertaining to cerebral organoids	• Currently warrant no special ethical nor legal concerns but continuous awareness is needed • Neural organoids as more sensitive in nature compared to other types of organoids, not least in terms of the concern they may raise amongst the public • Creation of chimeras a special issue of concern
Additional key legal/ethical issues	Legal/ethical issues within organoid research emerging in expert interview study	• Gonadal organoids; chimeras and animal research; organoid complexes and assembloids; and access to health care
Science communication and hype	Particular ethical issues pertaining to science communication and dissemination. Scope and managing of hype	• Sound and transparent public science communication key to foster trust and support • Some hype identified. Could be managed through guidelines; dedicated training and education of science communicators; public outreach activities; and increased science community coordination. • Precise nomenclature should be applied to avoid misconceptions and misrepresentations

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1. Introduction

1.1. Introduction to HYBRIDA

HYBRIDA aims to develop a comprehensive regulatory framework for organoid research and organoid-related technologies. Funded by the Horizon 2020 Framework Programme, the project runs for three years, ending primo 2024.[1]

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.

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 statis-

[1] The description is reproduced from the HYBRIDA project description (HYBRIDA Consortium, 2020, pp. 2-3).

tically 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.

1.2. Introduction to WP4 and the Co-creation Workshops and Expert Interviews

To support the research community and other stakeholders in addressing ethical and legal challenges related to organoid research and organoid-related technologies, HYBRIDA aims to develop a comprehensive regulatory framework consisting of four main products: a) a set of operational guidelines for the field of organoid research, b) a code of responsible conduct for researchers, c) enhancement of existing ethics and normative frameworks, and d) a supplement, if needed, to the European Code of Conduct (HYBRIDA Consortium, 2020, p. 3).

In addition to the three types of uncertainties described in section 1.1., it is important to “take into account the knowledge and experiences of a broad range of relevant stakeholders and the civil society,

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to understand not only the current status and challenges of organoid research, but also the hopes, concerns, expectations and visions for the future of organoid research which are of importance for assessing new organoid technologies and of key ethical importance" (Ravn and Sørensen, 2021, p. 6). Work package (WP) 4 facilitates the involvement of experts and stakeholders through three stages of engagement activities. First stage of the engagement process explored public attitudes towards organoids. It consisted of three deliberative workshops conducted across Greece, Italy, and Denmark, and was completed in November 2021 (please see Ravn et al., 2022 for further details and results). The second stage, which was finalised by the end of 2022, aimed to further develop a first draft of the project products by engaging experts and professional stakeholders in two co-creative workshops and a series of expert interviews for consultation. The third and final stage of the engagement process will consist of six focus groups with experts and stakeholders to assess and validate a second version of the products (Ravn and Sørensen, 2021, pp. 5-6).

This deliverable reports on the key findings from the second stage of the engagement process. Chapter 2 details the co-creation and expert interview methodology. Chapter 3 outlines the findings from the first co-creation workshop held in Paris in May 2022, while Chapter 4 presents the findings from the second workshop conducted in Copenhagen, June 2022. Finally, the main results from the expert interview study conducted in November and December 2022 are outlined in Chapter 5.

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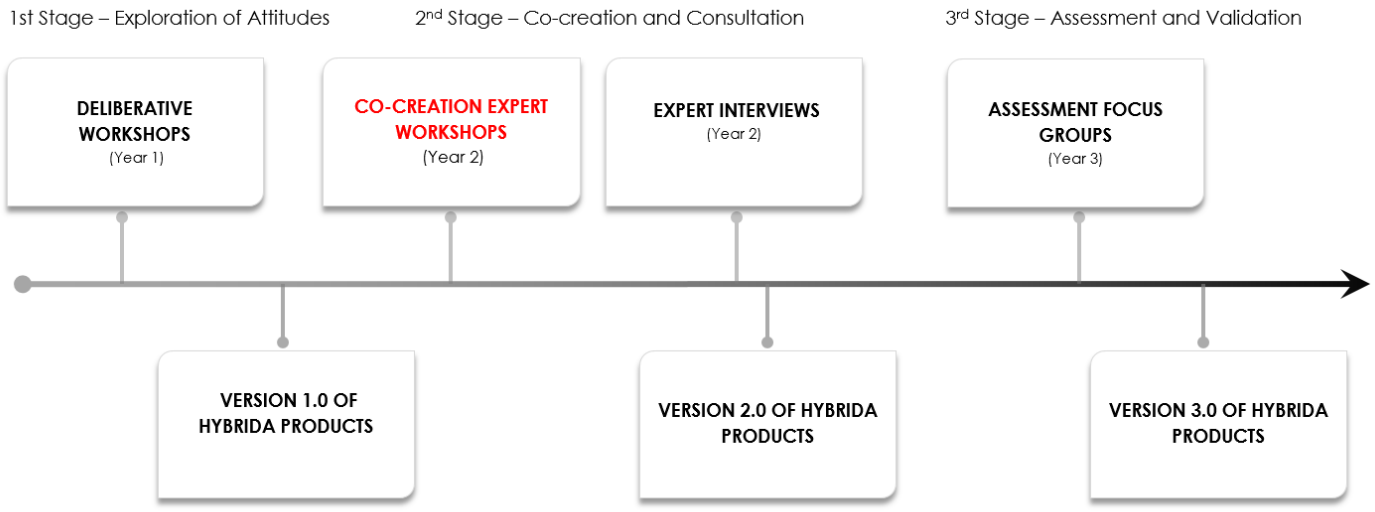
2. Methodology

In this chapter, we outline the methodology underlying the second stage of the engagement process, covering the particular research designs, the sample and recruitment processes, and the data coding and analyses of the co-creation workshops and expert interviews, respectively. Analyses and findings from the activities follow in Chapter 3, 4, and 5.

2.1. Methodology: Co-creation Workshops

The first part of the second stage of the engagement process consisted of two co-creation workshops (Figure 1). By engaging relevant stakeholders and experts, the workshops aimed to identify ethical and regulatory gaps related to the field of organoid research, as well as to strengthen and further develop the first versions of the 'Operational Guidelines for the Field of Organoids and Organoid-related Technologies' (Chneiweiss et al., 2022) and the 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies' (Chneiweiss et al., 2022a) drafted by WP5. Inputs from the co-creation workshops as well as persisting project gaps or ambiguities subsequently informed the following expert interview study (Chapter 5).

Figure 1. Overview of successive engagement activities and studies according to stage and timeline



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2.1.1.Research Design

WP4 facilitated two co-creation workshops, one held at Sorbonne University in Paris 19th May 2022 and another at Hotel Ottilia in Copenhagen 23rd June 2022. Both workshops were designed to address the overall objective of identifying:

1) *What standards of conduct and good practices should be followed to be in line with the enhanced ethics and regulatory frameworks*? (HYBRIDA Consortium, 2020, p. 13).

Furthermore, the workshops asked the following research question:

2) To which extent and in what way are the proposed standards (1st version of HYBRIDA products) in alignment with the required needs, developments, and conceptualisations, within the field of organoid research according to key professional stakeholders within the field? (Ravn and Sørensen, 2021, p. 21).

Co-creation is a participatory bottom-up method created to foster user involvement in innovation processes, collectively addressing and finding empirically grounded and need-based solutions to identified challenges (Lee et al., 2018; Vandael et al., 2018; Dijk-de Vries et al., 2020, see also research protocol, Ravn and Sørensen, 2021 for details on the method).

By inviting different experts and stakeholders to jointly develop the HYBRIDA products and identify ethical and regulatory issues and gaps related to organoid research and related technologies, the aim is to help ensure that 'the practice-guiding products builds on solid, holistic, and interdisciplinary assessments and recommendations from key stakeholders' (Ravn and Sørensen, 2021, p. 24).

In the two co-creation workshops, a total of 27 external experts participated (Appendix A) together with 11 members of the HYBRIDA consortium, representing WP4, WP5, and WP6. Both workshops took place over a long afternoon and lasted four and a half hours. They were both structured as a two-phase co-creation and deliberation with each phase entailing small-group and plenary discussions. In each of these rounds, participants were divided into three groups to discuss different themes. Each session was concluded by a round of summaries relayed by rapporteurs who had been appointed by each group, and a short plenum discussion to allow for further insights, nuances, and suggestions. A detailed overview of the agenda of the two workshops can be found in Appendix B and C.

In line with the bottom-up approach of the co-creation methodology, the discussions were guided by different pre-defined themes and open questions. The guiding questions varied across the workshops, as

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did the HYBRIDA products in focus (the themes are presented in more detail below). For the Paris workshop, the themes were selected in collaboration with WP5 to support the development of the 'Operational guidelines for the field of organoid research'. For the Copenhagen workshop, the themes were selected based on input from both WP5 and 6, to also support the creation of all products in HYBRIDA, including the analysis of gaps in the regulatory framework for organoids and organoid research, which is part of the work in WP6. Relevant stakeholder representation in terms of perspectives and expertise was ensured when assembling the groups for discussions.

In Paris, all experts first discussed and provided suggestions for improvements of the preliminary version of the 'Operational guidelines for organoid research' that had been drafted by WP5 (Chneiweiss et al., 2022) and distributed to all participants prior to the workshop. Two groups discussed the chapter on 'Minimal Information About an Organoid and its Use' (MIAOU), while a third group discussed informed consent procedures. Table 2 lists the questions guiding the first round of discussion in the workshop in Paris:

Table 2. 1st Co-creation Workshop. Questions for the First Round of Discussions. Regarding the MIAOU and Informed Consent

MIAOU
Main question 1. Please discuss to which extent the 'MIAOU' (section 4) is in alignment with the required needs, developments, and conceptualisations within the field of organoid research.
Supporting questions 1a. Is the minimal set of information provided sufficient for researchers? - Sufficient content, structure, and guidance (metatext)? - Sufficiently operational and supportive?
Informed donor consent
Main question

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1. Please discuss to which extent the consent form (section 6) is in alignment with the required needs, developments, and conceptualisations within the field of organoid research.
Supporting questions 1a. Is sufficient information provided (content, structure, and guidance (metatext))? 1b. Is it sufficiently operational and supportive? 1c. Is the 'Consent for Governance model' the best model? Is it sufficiently operationalised?

During the second round of the discussion in the workshop in Paris, all three groups discussed and prioritised the most important challenges related to organoid research needed to be addressed in an 'Evaluation Checklist for Organoid Ethical Studies'(EChOES) and translated these into concrete suggestions for topics that could be included in the checklist. As opposed to the first round of discussion, no material had been sent to the participants in advance. However, a first draft of the evaluator checklist was handed out at the workshop for consultation.

Table 3. 1st Co-Creation Workshop. Questions for the Second Round of Discussions. Regarding an 'Evaluation Checklist for Organoid Ethical Studies' (EChOES)

Evaluation checklist
Main questions 1. Please discuss and prioritise the most important challenges related to organoid research that need to be addressed in an evaluator checklist. 2. Please translate these challenges into concrete suggestions for topics and sub-topics that should be included in the checklist.
Supporting questions 1a. Should the checklist include particular stakeholder sections? 1b. To which extent should the checklist focus on yet unrecognised ethical challenges?

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In the second workshop in Copenhagen, all participants discussed the first version of a 'Code of Responsible Conduct for the Field of Organoid Research', which had also been drafted by WP5 and distributed to all participants in advance.

Table 4. 2nd Co-Creation Workshop. Questions for the First Round of Discussions. Regarding a Code of Responsible Conduct'

Code of Responsible Conduct
Main question 1. Please discuss to which extent the Code of Responsible Conduct is in alignment with the required needs, developments, and conceptualisations within the field of organoid research and the field of research integrity/research ethics.
Supporting questions 1a. If needed, how can a Code of Responsible Conduct be tailored to the field of organoid research? 1b. Does the first draft version of the Code of Responsible Conduct sufficiently address its intended stakeholders (scientists, research organizations, industries, regulatory instances, and states)?

Despite the different workshops' emphases, the theme of informed consent was part of the guiding questions across both workshops. Based on the first workshop, it was agreed that further elaboration and additional inputs on how to best structure informed consent within the field of organoid research were needed. Thus, for the second round of discussions in Copenhagen, one group discussed informed consent based on the same version of the operational guidelines as was used for the workshop in Paris. The material was handed out at the workshop. Another group addressed the potential need for a supplement to the European Code of Conduct, while a third group discussed potential legal challenges and gaps related to the field of organoid research. Findings from the two co-creation workshops are presented in Chapter 3 and Chapter 4.

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Table 5. 2nd Co-Creation Workshop. Questions for the Second Round of Discussions. Regarding Informed Consent, a Supplement to the European Code of Conduct, and Legal Issues and Gaps

Informed Donor Consent
Main question 1. Please discuss to which extent the consent guidance is in alignment with the required needs, developments, and conceptualisations within the field of organoid research.
Supporting questions 1a. Can a genuine 'informed' consent be obtained? 1b. Is the 'Consent for Governance model' the preferred model to implement?
Supplement to the European Code of Conduct
Main questions 1. Please assess the need for a supplement to the European Code of Conduct (ECoC). 2. Please discuss and provide recommendations for how such a supplement could look like (e.g., topics/sub-topics, change of existing formulations etc.).
Legal Issues and Gaps
Main questions 1. On the basis of your knowledge and research, can you identify existing legal gaps for the derivation, use and/or storage of organoids? 2. As organoids become more complex and developed, could you envision particular areas in need for additional regulation? Potential focus areas: Informed consent, withdrawal of consent, property rights and user rights, the use and storage of organoids as an institutional practice, patentability and ownership, classification (moral status), and differentiation between organoid types.

Following each co-creative workshop, participants were asked for oral as well as written feedback in order to help WP5 and 6 to develop the HYBRIDA products further. Five participants provided additional comments in writing after the workshop.

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2.1.2.Sampling, Recruitment and Practical issues

Experts and stakeholders were purposefully sampled for the two workshops based on their areas of expertise. Fifteen external experts participated in the workshop in Paris alongside nine members of the HYBRIDA consortium form WP4 and WP5. Their expertise covered a wide range of areas; five researchers within the fields of ethics and organoid research; four members of Research Ethics Committees (RECs) and Institutional Review Boards (IRBs); two members of Research Integrity Offices (RIOs); one policy maker; one representative from a patient organisation; and two representatives of biobanks (please see Appendix A for a detailed description of participants). With two late cancellations due to illness, a total of 12 external experts participated in the second co-creation workshop (Appendix A) in addition to seven members of the HYBRIDA project. The external experts for the workshop in Copenhagen counted six researchers predominantly from the field of organoid research, three members of RECs or IRBs, two members of RIOs, and one representative from a patient organisation (please see Appendix A for further details). The sample of stakeholders in each workshop was gender balanced. Hosting the workshops in different countries also made it possible to attract experts from across Europe, ensuring that many different countries were represented (France, England, Croatia, Italy, Belgium, Norway, the Netherlands, Germany, Denmark, Finland, Ireland, Austria, and Latvia).

Once they had accepted the invitation to participate (Appendix D; Appendix E), the experts received two rounds of material via e-mail. Following the initial agreement to participate, the experts received a preliminary agenda and a detailed information letter (Appendix F; Appendix G). Two weeks before the workshop was due to take place, the participants received another e-mail containing practical information, including contact details, a reminder of the information letter, the final agenda (Appendix B; Appendix C), an informed consent form to sign (Appendix H; Appendix I), as well as the first version of the relevant HYBRIDA product that was going to the be discussed in further detail at the workshop. For the first workshop, the participants received a draft version of the operational guidelines for organoid research (Chneiweiss et al., 2022), while the participants in the second workshop received a first draft of the code of responsible conduct for organoid research (Chneiweiss et al., 2022a). All participants returned a signed copy of the consent form either via e-mail prior to the workshop or at the workshop, where hard copies of the form were handed out.

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Prior to the workshops, members of WP4 were in contact with all participants to assist with booking of transportation and accommodation. The project covered participants' travel expenses and accommodation. The workshop in Copenhagen was hosted at a hotel where all participants in need of accommodation were booked in by the Aarhus University (AU) partner. For the Paris workshop, which took place at Sorbonne University, some participants booked their own accommodation. Participants were not remunerated further for participating in the workshops. However, all participants were invited for a dinner after the respective workshop and received a small gift as an appreciation of their time and contribution.

2.1.3. Data Analysis

The co-creation workshops, including the individual group discussions, were audio-recorded. The analysis of the co-creation workshops is based on full recordings of both workshops and extensive and detailed summary reports that were produced for each of the workshops by a WP4 member (MF). The first round of analysis was structured by the themes reflected in the set of guiding questions, while a second round of analysis exploratively examined additional themes and subthemes that organically emerged from the co-creative process.

Insights and suggestions from the second stage of the engagement process will inform the further development of the project through reporting and more directly via the participation of WP5 and WP6 representatives in the workshops. WP5 and WP6 have also had access to the recordings, extensive summaries, and transcripts for the further developments of the HYBRIDA products.

2.2. Methodology: Expert Interviews

In addition to the two co-creation workshops described above, an interview study was conducted with 15 experts. The main objective of the co-creation workshops was to involve different stakeholders in an up-stream innovation process, identify ethical and regulatory challenges in organoid research and co-create potential solutions to enhance the initial set of operational guidelines, regulatory mapping and Code of Conduct produced. The expert interviews aimed to clarify and further explore open questions

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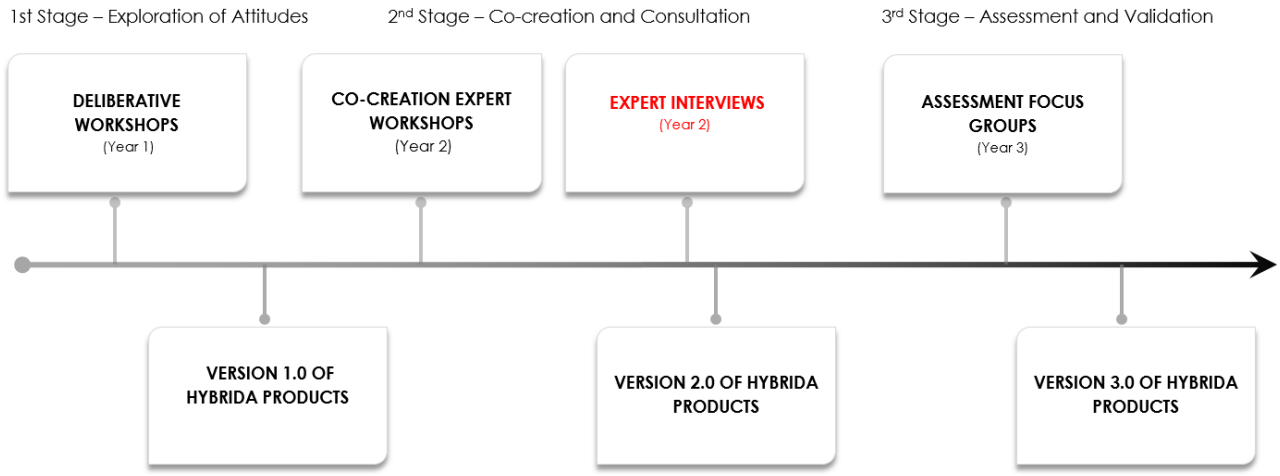
from the workshops and development process of HYBRIDA's products. Figure 2 shows how the expert interviews fit into and support the overall engagement process in HYBRIDA.

Figure 2. Overview of successive engagement activities and studies according to stage and timeline



The workshops and expert interviews are independent but also connected activities. They build upon and inform each other and together help advance our understanding of the needed ethical and regulatory framework for organoid research and organoid-related technologies. It is therefore essential that they involve a range of stakeholders from the research community and civil society (for details on the empirical framework, please see the study research protocols, Ravn and Sørensen, 2021, 2021a). The expert interview study also seeks to answer the main objective in HYBRIDA concerning 'what standards of conduct and good practices should be followed to be in line with the enhanced ethics and regulatory frameworks?' (HYBRIDA Consortium, 2020, p. 13). Whereas the co-creation workshops enquire into the proposed products and standards developed, the expert interviews more openly explore the field-specific question, 'what are the main ethical and legal issues concerning organoid technologies?' Subsequently, it probes a set of more narrowly defined themes concerning informed consent, sensitive technologies, and scientific communication through which new questions have emerged or ambiguous ones endured.

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2.2.1. Research Design

The expert interview can be defined as 'a qualitative interview based on a topical guide, focusing on the knowledge of the expert, which is broadly characterised as specific knowledge in a certain field of action' (Mauser and Nagel in Döringer, 2021, p. 265). Expert interviews give insights into unique expert information, knowledge (e.g. contextual, interpretative ('know-why'), and technical/process oriented ('know-how')). Expert interviews are often conducted with the purpose of a) exploring an uncharted field of study, b) collecting 'contextual' information complementing other data sources, or c) creating an empirical foundation for generating theory (Bogner and Menz, 2009). While the study design remains explorative in its approach to enquiring into ethical and legal issues concerning organoid technologies, it aligns primarily with the 'systematising interview' in its efforts to provide additional and contextual information on expert views, practices, opinions, and recommendations with the objective to complement existing work and data sources within HYBRIDA.

For this study, 15 expert interviews were conducted with different types of experts within the field. They were conducted as semi-structured interviews, i.e. they had a relatively comprehensive and structured set of themes and questions but remained open to emerging issues and flexible to tailoring the main interview guide to specific sets of expertise. One member of the WP team (TR) conducted the interviews online via Microsoft Teams. The majority of interviews lasted between 30 and 45 minutes; the shortest lasted approximately 25 minutes; the longest around one hour and ten minutes. Two of the interviewees requested to see the interview questions prior to the interview, and they received the list of main topics and main questions (not additional probes) at least two workdays before their respective interviews (see Appendix J for Interview guide).

The construction of the interview guide was commenced on 7th October 2022 with a joint meeting with project partners from INSERM (WP5), Manchester University (WP6), Oslo University (WP2), and AU (WP4) to discuss design, recruitment of experts, the status of remaining questions, topics, and needs for additional expert knowledge. After additional bilateral exchanges, the AU partners sent a version of the interview guide to all partners for review and comments. The final version encompasses five main themes in addition to an intro, research background, and debriefing:

1. Prospects and advantages of organoid research and related technologies

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2. Prominent ethical and legal issues – field-specific
3. Informed consent procedures and ethical oversight
4. Sensitive technologies
5. Expectations and scientific dissemination

(For a detailed overview, please see Interview guide, Appendix J).

In alignment with the stages of the engagement process in HYBRIDA, the expert interviews were designed with the primary purpose of further informing the ongoing work on the operational guidelines for organoid research, the Code of Responsible Conduct in WP5 and the proposal for addressing legal gaps within organoid research in WP6. In addition, ongoing work on organoid technologies and personalised disease models in WP2 comprised intersecting thematic foci and data interest, and a question concerning promising clinical application was added to the main theme of technological advantages. Likewise, a question concerning regulation of hype was included in the theme of scientific communication. A specific question on the challenges of precision medicine for evidence medicine was also included, but only in the few instances where the question would be of relevance to the expert in question.

2.2.2. Sampling and Recruitment Procedures

As described per grant agreement, the expert interviews were scoped to include seven HYBRIDA advisory board members and eight external experts. Four out of seven advisory board members accepted the invitation to participate in an interview, and the remaining interview sample covers 11 external experts (for a complete list of interviewed experts, please see Appendix A).

Advisory board members are familiar with the HYBRIDA project at large, have particular insights into the processual steps and expected project outcomes, and are prominent experts within the field of organoid research, bioethics, and technology assessment.

The remaining external experts were recruited through a purposeful sampling strategy with focus on ‘selecting information-rich cases for in-depth study’ (Patton, 2015, p. 265), based on a specific purpose grounded in substantial criteria while securing efficiency and validity (Palinkas et al., 2015, p. 534).

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Potential experts were invited to participate because of their vast field-specific expert knowledge on organoid technologies and/or stem cell technologies from a bioethical, legal, or medical vantage point.

All external experts have a background within medicine (for details on expertise, affiliation, involvement in ethical committees, legislative processes etc., please see Appendix A) but are specialised in different kinds of organoid technologies, ethical or legal issues concerning informed consent, emerging technologies etc. of high relevance to the research question and research themes. In addition to a collective and diverse set of expertise within organoid research or related technologies, gender and geographical diversity among members of the sampling pool was prioritised, the latter adding an international dimension to the expert sample as it included experts from Australia, Israel, the US as well as the EU.

Experts were recruited based on a varied recruitment strategy, primarily applying project partner co-nominations, referrals, and experts identified through the project. Two experts were approached due to their great interest in participating in the co-creation workshop in Copenhagen, but both were unfortunately unable to attend the event.

Potential experts received an invitation by e-mail detailing the purpose of the HYBRIDA project and the expert interview. The invitation to advisory board members contained a bit more contextual information concerning the process and status of HYBRIDA activities tailored to the interviewee's familiarity with the project. Invitation letters to advisory board members and external experts can be found in Appendix K and Appendix L, respectively. The recruitment process was run by one WP4 team member (MF), and the process was carefully registered in an Excel sheet specifying contact details, status of invitations, reminder e-mail, timeline etc. Twelve interviews were conducted during November 2022; the remaining three primo December 2022. Following the interviews, the experts received a 'thank you' e-mail from the interviewer (TR) with the following reports attached:

- The current version of the 'D. 5.1. Operational guidelines for the field of organoids and organoid-related technologies'
- 'D.6.1. Regulating organoid and organoid-related activities: An analysis of the regulatory gaps and areas of over-regulation'
- 'D4.3. Public attitudes, understandings and perspectives on organoid research - findings from a series of deliberative workshops'

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All experts were interested in the existing HYBRIDA reports. This report will also be sent to the experts in due course.

Each interviewee received and returned an informed consent form prior to the interview. In the few cases where this was not the case, an oral confirmation was provided at the beginning of the interview, and the consent was returned after the interview. The consent form is provided in Appendix M. The consent form includes specifications of the study purpose, funding, and use of data (i.e. GDPR, privacy policy, data processing, and data storage), a section on potential risks and inconveniences (no foreseen risks are expected in relation to the interviewees' participation in the study), and information about recordings and anonymity. In regard to the latter, experts are interviewed in their professional capacity as esteemed academic researchers with crucial and profound knowledge about organoid research and/or organoid-related technologies. Due to their professional representation and for reasons of transparency, participating external experts appear in a non-anonymous format like the advisory board members and are openly listed in Appendix A. As stated in section 2.2.3, across-case observations and perspectives are analysed, and no individual statements are conveyed. Information concerning the approach to anonymity was also a part of every introduction to the interview to ensure agreement and allow for potential clarifying questions.

2.2.3. Data Coding and Analysis

All interviews were recorded through Microsoft Teams, and translation software (Microsoft Streams and NVivo facilities) were used to auto-generate transcriptions. Two student assistants subsequently checked for accuracy and provided verbatim transcriptions of each interview based on common guidelines for transcription. All transcriptions were finally checked again and uncertainties cleared for the sake of reliability and validity by one of the WP team members (MF). Transcriptions were then imported to the software and data facilitation programme NVivo 12 and thematically coded by one team member (TR) according to the main- and sub-themes stated in the interview guide. This fairly structured and pre-constructed focused set of codes was accompanied by an exploratively oriented coding strategy through the process of initial coding (Charmaz, 2006), where an exploration of emerging themes resulted in an additional set of more inductively derived codes. The thematic analysis presented in chapter 5 focuses primarily on main and recurring themes and sub-themes and reports on the key across-case findings

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representing main convergent and divergent views and central lines of argumentation in regard to ethical and legal issues concerning organoid technologies.

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3. Findings from the 1st Co-Creation Workshop concerning Operational guidelines

In this chapter, we present the results from the co-creation workshop on the 'Operational guidelines for organoid technologies' that was held in Paris, May 2022. The chapter revolves around the three central topics of discussion at the workshop, which are included as separate thematic sections in the operational guidelines. First, we present our findings related to 'Minimum Information About an Organoid and Its Use' (MIAOU), which provides a minimum information checklist on organoid production for researchers. In the second section, we outline the main discussions and recommendations on 'Organoids and Informed Consent' procedures. In the third and final section, we present the findings on the 'Evaluation Checklist for Organoid Ethical Studies' (EChOES), which aims to establish an ethical checklist for scientific evaluation and one for research integrity bodies and research ethics committees.

As a conceptual basis, in this report we apply the following definition of an organoid; 'a three-dimensional structure derived from (pluripotent) stem cells, progenitor, and/or differentiated cells that self-organise through cell-cell and cell-matrix interactions to recapitulate aspects of the native tissue architecture and function *in vitro*' (HPB Organoid Consortium, 2021, p. 817). A large number of organoid types can potentially be created corresponding to the different tissues and organs in the body. To date, researchers have been able to produce organoids that resemble, for instance, the brain, kidney, pancreas, retina, lung, intestine, stomach, and liver.

3.1. Minimum Information About an Organoid and Its Use (MIAOU)

The findings in this section draw upon the two group discussions on the MIAOU. From the co-creation workshop, it seemed evident that the invited experts welcomed and found the initiative to create opera-

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tional guidelines relevant for the field of organoid research. Throughout the workshop, the experts focused on co-creating recommendations for improvements and additions to the guidelines, which will be the main focus of the current chapter.

3.1.1. A Tool to Stimulate Reflection

In both discussant groups, the authors of the draft version explained the objectives of the MIAOU and its intention to create a tool to enhance and ensure trust between organoid researchers. The participants acknowledged its usefulness. One pointed specifically to its value for reproducibility, but they also encouraged a debate about the status of the guidelines, and whether it should move beyond mere technical descriptions. A majority of the external experts perceived the MIAOU as a tool to stimulate ethical reflection amongst organoid researchers. They argued that it should focus more on raising awareness of potential ethical challenges related to the field of organoid research. This is underlined by the agreement across the two groups that some of the ethical questions later discussed for the Evaluation Checklist should already be considered for the MIAOU. In order to promote ethical thinking amongst organoid researchers, different structural suggestions were presented and discussed.

- One suggestion was to instigate the MIAOU by an information sheet of core ethical dilemmas in order to prime organoid researchers to think ethically before assessing the questions in the MIAOU. It was emphasised that the ethical dilemmas should be specifically related to the field of organoid research. To achieve this, participants suggested drawing on the different types of uncertainties related to organoids that are addressed within the HYBRIDA project.
- A second suggestion was to provide examples of best practices for researchers with little experience in reflecting on ethical issues related to organoid research. The reasoning was to make the checklist more intelligible for researchers by providing a greater basis for interpretation and individual case adaptation.
- A third suggestion was to reformulate the phrase ‘Please specify’ for some of the questions to promote ethical reflection. Participants expressed concern that it would be possible for organoid researchers to answer the list of technical yes and no questions and to elaborate on their answers without considering potentially related ethical issues.

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Further discussion revolved around whether a separate list of ethical questions additional to the MIAOU could be created and tailored to different research situations. However, it was argued that some technical issues and ethical questions remain inseparable. An example is the possibility of withdrawing consent, where one participant pointed to the intertwined issues of data management (storage, data deletion etc.), technical processes, ethical dilemmas, and the design of the informed consent, asserting that the MIAOU should be able to address interlinked issues and procedures. However, no consensus was reached on whether to divide the technical and ethical questions into two separate lists.

3.1.2. Additions and Elaborations

The experts suggested additional issues to be addressed to align the MIAOU with the needs and developments within the field of organoid research, following the encouragement that the MIAOU should stimulate and invite ethical reflection. First, it was suggested to add supplementary questions on the source material used to make organoids as well as their teleology. For the former, it was argued that it may pose different ethical issues depending on whether an organoid is made from 'bodily cells or of embryonic cells'. For the latter, the participants suggested to elaborate on and include the different types of organoids that research may aim to create, in addition to the distinction between the different uses of organoids, e.g., for basic research, preclinical or clinical use. Thus, a specification of whether organoid research aims at creating gastruloids, cerebral organoids etc. was argued to be useful, as different types of organoids may pose different ethical challenges.

Second, public communication and scientific dissemination were seen as a very important aspect of a responsible conduct of research (RCR) within organoid research. The experts suggested addressing this topic in the guidelines to help ensure that organoid researchers communicate their research in a 'fair and transparent way'. It was argued that reflective questions would need to illuminate and clarify what is meant by fair and transparent, as this is not necessarily a given. Even though participants found it challenging to compile a complete list of instructions to communicate fairly and transparently, one concrete suggestion was to address language specifications and nomenclature such as the use of metaphors or designations. Although it was not explicated in the workshop, this can be seen to refer to the conceptual uncertainty of organoids, which was also expressed by publics and patients, among others, in the three deliberative workshops conducted in stage 1 of the engagement process. An example is the use of the

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term ‘mini-brain’ (Ravn et al., 2022; for details on the conceptual aspects of organoids, see also Gaillard et al., 2022).

This uncertainty was also touched upon in relation to the way that the MIAOU itself is phrased. A workshop participant raised the concern that it might humanise organoids if the metadata of an organoid is referred to as a passport or an identity sheet, as both formulations are normally associated with persons. The participant discouraged use of these wordings. Overall, it was emphasised that researchers should aim to prevent hype around organoid research.

Following from the many suggestions for further inputs and elaborations, some participants expressed a worry that the minimum standards would develop into maximum standards. They emphasised that the document should address the most important issues that are specific to the field of organoid research and be kept as concise as possible to make sure that organoid researchers actually consult and use it.

3.1.3. Summary

In sum, many experts pointed to a need to stimulate ethical reflection amongst researchers within the field of organoid research and pointed to the MIAOU as a first place to introduce ethically stimulating questions. It was pointed out that the MIAOU should focus on selected topics to keep focus on the minimum information needed, including questions on public communication and the source material as well as the teleology of the organoid. The questions should be specific to organoid research and the document as concise and short as possible.

3.2. Informed Consent

Throughout the workshop, informed consent was a recurring issue discussed across the different groups. The findings presented in this section are based primarily on inputs from the group discussion specifically on informed consent, but it also includes arguments from plenum and additional group discussions.

Informed consent is a means to safeguard ‘individuals’ and patients’ rights to autonomy and self-determination’ from both an ethical and a legal point of view at where their consent to participate is based on

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an informed and voluntary basis (Mollaki, 2021, p. 4; Sugarman et al., 2019). From a practical angle, 'informed consent provides an opportunity for patients to obtain the information they need about risks, benefits, and alternatives before they decide whether to proceed with an intervention' (Sugarman et al., 2019, p. 1651).

3.2.1. How to Inform Consent

Overall, the discussion on informed consent revealed problems in pinpointing what aspects are unique to the field of organoid research and how they should be structured compared to consent forms in other areas of medical research. Thus, part of the discussion on informed consent related to general principles and how consent can be genuinely informed. It was argued that only the individual donors signing the form can determine whether the provided information is sufficient for their consent to be informed. This argument rests upon the fundamental principle that informed consent should not be about indemnifying researchers but about ensuring autonomy and safeguarding of research participants, making sure they are comfortable, and about creating trust.

The participants presented different suggestions on how to make sure that sufficient information is provided and on how to create trust between donors and organoid researchers. Information regarding the following aspects were suggested as potential topics to consider in a consent form tailored to organoid research:

i. Process of obtaining tissue and source material from the donor
ii. Organoid features and functions
iii. The process in which the organoids are involved
iv. Activities post study completion
v. Potential commercialisation
vi. Sharing of open data

Experts agreed that the rapidly evolving field of organoid research calls for a continuous update of information for consent. Without further elaboration, withdrawal of consent was also highlighted as an

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important aspect to consider for organoid research. One participant highlighted the possibility of providing on-site and face-to-face information about the consent form. Another participant suggested having a study nurse inform and collect consent. It was argued that someone who seems closer to the patient or donor might present less of a barrier and make it easier to ask 'stupid questions'.

3.2.2. Contextualising Informed Consent

According to the experts, the multifaceted and diverse nature of organoid research should be mirrored in the consent forms in agreement with the numerous types of organoids made and their vast variety of uses. Some participants pointed out that informed consent is highly case-specific and that it would be impossible to create a one-size-fits-all model for a consent form for organoid research. In other words, participants highlighted the importance of contextualising the informed consent for organoid research. The experts agreed that a good way to accommodate this variety would be to structure the consent form as a decision tree or as a set of building blocks, starting with 'the nature of the research'. For illustration, the idea of a decision tree was compared to the structure of a questionnaire which progresses according to the answers provided. By creating different blocks that are 'exchangeable' and 'universally applicable', it was argued that it would be possible to add or remove parts to create a consent form that is tailored to a specific research project.

3.2.3. Stakeholder Involvement

One particularity of organoid research that was pointed out during the co-creation workshop was the feeling of being personally involved when donating cells. Following this, experts recommended involving stakeholders in the planning of research projects to increase trust and to incorporate mechanisms for participant engagement in biobank governance structures. Emphasis was placed on *actual* stakeholder involvement to avoid the problem of on-paper participation. Importance was also ascribed to making consent forms not only 'legally sound' but also intelligible and understandable to donors and aligning the consent situation with the reality of patients and donors. From a patient perspective, the close interlinkage between involvement and increasing trust was underlined. Hence, participation and transparency

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help foster trust in a research project or biobank and are perceived to increase the willingness of patients and the general public to participate in research, as well as to reduce the risk of dropouts.

As a part of the discussion on informed consent, a different angle on the structure and governance of biobanks was brought up. It was questioned whether the business model of a biobank, i.e., whether it is for-profit or non-profit, matters to the purpose of consent. A counterargument was that variation across biobanks can be perceived from a positive perspective, as it can allow donors to select a biobank they trust.

3.2.4. Summary

In sum, the theme of trust permeated the discussion on informed consent. The experts pointed to two suggestions for the process of informed consent within organoid research. First, it was argued to involve stakeholders from the beginning of a project and/or in biobank governance structures as it increases trust, levels of participation, and minimises the risk of withdrawal. Second, experts recommended structuring consent forms for organoid research like a decision tree or as building blocks to accommodate great variation within the field in terms of organoid types and usages.

3.3. Evaluator Checklist

The findings in this section are mainly based on the final part of the co-creation workshop where all three groups discussed the EChOES. The draft version of the list was not sent in advance but was handed out prior to the discussions. In some groups, it was used as a steppingstone for discussion, while others did not use it for consultation.

3.3.1. Purpose of the Evaluation Checklist for Organoid Ethical Studies (EChOES)

A part of the discussion on the EChOES revolved around the checklist as a tool to promote organoid-specific ethical awareness amongst evaluators and correspondingly help researchers to develop their

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ethical thinking. Some participants pointed to the phrasing of checklist questions, i.e., that they are specific (e.g., particular compliance with the Declaration of Helsinki) and tangible (e.g., as to specific data sources and legal bases). It was suggested to use the checklist as a way to educate evaluators about the ethics relevant for organoid research, e.g., by including samples of completed checklists to assist evaluators who are not experts on organoids.

Across the groups, it was discussed which evaluators the checklist should be designed for and to what extent it makes sense to compile one checklist for all evaluators or individual lists for different evaluators. One suggestion was to compile all information for a research project to minimise researcher workload and leave it to evaluators to select relevant information. It was questioned whether this would result in too long a document. The main argument for dividing by evaluator type was a potential difference in reviewer attention and different requests for answers. An expert pointed out that evaluators might evaluate the same principle differently, e.g., open science might be valued by funders as it promotes reproducibility, while others might evaluate that it potentially compromises privacy of research participants. Regardless, it was recommended to explicate the targeted evaluator(s) and related content.

3.3.2. What Should Be Included in the Evaluation Checklist?

It was clear from the discussions that the checklist needs to focus on what is specific to organoid research and organoid-related technologies. The experts provided various inputs for what could be included in an evaluator checklist, with a predominant focus on the content relevant for evaluations by RECs. Some experts pointed to the risk-benefit assessment of organoid research as the main question to be assessed by evaluators, for instance the challenge of control patients.

Additional topics suggested to be addressed in the evaluator checklist were:

vii. Insurance and payment
viii. Assessment of whether the research adheres to current legal and national frameworks
ix. Commercialisation issues
x. Public communication
xi. Categorised organoid usage

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The wish not to add too much additional bureaucracy and red tape to research was also emphasised, and it was advised to keep the checklist short, for example to one page of ten questions on ethics that a reviewer would need to see answered by the researcher.

At the workshop, different checklists for different reviewers were handed out, including a European checklist and one for the institutional RECs. For the European checklist, some experts suggested that certain types of organoids such as cerebral organoids, blastoids and chimeras should automatically trigger an ethical assessment. It was further recommended by an expert to include potential future organoid-related technologies as the field is rapidly evolving.

3.3.3. Summary

The checklist was seen as an educational tool for evaluators and should serve to stimulate ethical reflections amongst organoid researchers in extension of the MIAOU. Experts suggested a range of topics to be included in the Evaluation Checklist, and it was emphasised that the checklist needs to address organoid particularities to be a valid and relevant tool and to avoid redundancy.

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4. Findings from the 2nd Co-creation Workshop concerning a Code of Conduct

In this chapter, we present the findings from the expert co-creation workshop on the 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies' that took place in Copenhagen, June 2022. The chapter is divided into four sections that discuss the main themes in the following order: informed consent; the need for a supplement to the European Code of Conduct; the HYBRIDA Code of Responsible Conduct; and regulatory issues and gaps related to the field of organoid research.

4.1. Informed Consent

As in the first workshop, informed consent was one of the main themes. The findings presented in this section predominantly draw upon suggestions from the group discussing informed consent, but it also includes additional inputs from the other groups.

4.1.1. Informing on Duration and Cost of Organoid Research

From a research perspective, time and resources were identified as some of the challenges with implications for informed consent in organoid research. Organoids take long to produce, and they may be used in research for many years. To accommodate this challenge, the workshop participants pointed to two ways to strengthen the section on informed consent in the second version of the operational guidelines.

First, the duration that material is stored and used for research is usually specified in the consent form. However, cell lines may be used in organoid research for years beyond the project for which the source material was initially collected, making it difficult to predict in the initial consent form how long cell

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lines will be used. Therefore, an expert advised explicitly to inform research participants in the consent form if and why the exact duration cannot be determined in advance.

Second, experts stressed that research participants who donate tissues or cells for organoid research should have the right to withdraw from a project. However, a researcher pointed out that retraction of consent can have negative consequences. Withdrawing consent would prevent continuous use of cell lines and possibly delay scientific advancement, as it is costly and time-consuming to develop new organoids for research. Thus, the experts suggested informing research participants about potential consequences and implications of withdrawal as part of the consent process.

4.1.2. Models of Consent and the Issue of Trust

It was evident from the discussions that the experts had different views on which model for informed consent would be most appropriate for organoid research. Some researchers seemed to take a more pragmatic stance on the issue. One argued that dynamic consent is inconvenient, as the same cell lines are reused in research over time, and requiring continuous (re)consent from donors would be highly time-consuming. Another researcher suggested a broader consent model which would allow organoid researchers to use anonymised cell lines for different types of research as long as it does not move into the field of application or commercialisation.

Other experts, including members of RECs and legal experts, seemed to agree that broad consent is not without challenges. First, it was argued that future proofing of consent might be difficult due to the rapid advancements within the field. Second, it was suggested that broad consent might discourage potential donors from participating in research as they would no know exactly what their cells will be used for, and re-using donated cells for new strands of research without reconsent might undermine trust in the field. The latter point was made with reference to the Henrietta Lacks (HeLa) case. Several experts emphasised the importance of preventing a repetition of this scenario and of ensuring trust within the field. The experts seemed to agree that a communication task remains in acknowledging what happened and explaining why it will not reoccur. Communication with ethnic minorities was emphasised and, crucially, explaining why their participation is highly valuable to organoid research and how they are protected, to avoid HeLa scenarios in the future.

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A potential approach to ensuring trust among donors is participant and stakeholder involvement. It was suggested that the involvement of stakeholders throughout the application process and when drafting the informed consent form would help increase trust, potentially minimise the need for reconsent, and the risk of withdrawals.

4.1.3. Incidental Findings

A final theme that was touched upon in relation to informed consent was whether to share incidental findings with research participants. The experts who were specifically asked to discuss informed consent seemed to agree that sharing incidental findings with research participants is not always a good idea. Informing patients that they do not respond well to a drug or donors that they suffer from a disease may reduce their quality of life. They argued that such information should only be shared if the accidentally discovered disease is curable. Furthermore, if it is decided to share incidental findings with a research participant, it should be explained to them that organoid models do not necessarily mimic adult tissue. Finally, some experts briefly argued that participants should be able to refuse being informed of incidental findings but not to self-select among potential findings.

4.1.4. Summary

In general, experts agreed that informed consent plays an important role in ensuring trust within the field of organoid research. The discussions on informed consent also reflect the balancing between individuals' autonomy and the societal benefits of organoid research. It was suggested that incidental findings should only be shared with participants in certain circumstances. The workshop participants did not reach agreement about which model of consent to recommend for organoid research.

4.2. The Need for a Supplement to the European Code of Conduct

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This section addresses whether the emerging field of organoid research necessitates a supplement to the European Code of Conduct. The findings mainly draw upon the deliberation specifically focusing on this question as well as contributions from one group discussion on the 'Code of Responsible Conduct for the Field of Organoid Research'.

4.2.1. A HYBRIDA Supplement to the European Code of Conduct

In general, a supplement to the European Code of Conduct was endorsed, and the experts viewed the draft version of the HYBRIDA Code of Responsible Conduct for organoid research as a preliminary supplement. The general principles stated in the European Code of Conduct for Research Integrity (ALLEA, 2017) were regarded to serve as 'a mindset' on how to conduct research responsibly more generally, encouraging research communities and stakeholders to reflect upon how these values apply to their research in practice, thereby supplementing the ALLEA principles with field-specific clarifications. It was thus argued that the HYBRIDA Code of Conduct should illustrate how the ALLEA principles translate to the field of organoid research.

One expert suggested that the HYBRIDA Code of Responsible Conduct might follow a structure similar to the European Code of Conduct with focus on areas in which organoid research calls for supplementary clarification. Special attention was drawn to the section on Safeguards (ALLEA, 2017, p. 6), as it was argued that these practices in many ways are specific to the emerging field of organoid technologies. Several experts directly or indirectly provided suggestions on how safeguards could be translated to the field of organoid research:

- *Researchers comply with codes and regulations relevant to their discipline*
  The experts discussed whether it would be a good idea to include references to additional guidelines and material with relevance for the field of organoid research, such as the ISSCR Guidelines, in the 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies'. On the one hand, it was clear from the discussion that many of the participating experts, including organoid researchers, would find such references highly informative and useful. On the other hand, one expert expressed concern that references to external material would imply endorsement of its

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content, which may later be altered. Another expert emphasised that the references should be added in the HYBRIDA Code of Conduct only and not to the European Code of Conduct.

- *Researchers handle research subjects, be they human, animal, cultural, biological, environmental, or physical, with respect and care, and in accordance with legal and ethical provisions*

  It was argued that respect towards research entities such as animals ought to be included in the 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies'. It was further suggested to reflect upon whether certain types of organoids warrant a particular kind of respect.
- *Researchers have due regard for the health, safety, and welfare of the community, of collaborators and others connected with their research*

  It was suggested that ethics dumping could be a potential issue within the field of organoid research, and that it may be addressed under this safeguard with reference to the Global Code of Conduct for Research in Resource-Poor Settings. Following the discussion on the potential endorsement problem of referencing external resources, it was emphasised that this document has already been endorsed by the Commission.
- *Research protocols take account of, and are sensitive to, relevant differences in age, gender, culture, religion, ethnic origin, and social class*

  Experts pointed to the importance of this safeguard when using organoids for testing drugs, as it was argued that a drug may work differently or encompass different risk factors across ethnicities etc.
- *Researchers recognise and manage potential harms and risks relating to their research*

  Although not mentioned in relation to this safeguard, management of expectations was argued to be of great importance when conducting organoid research to prevent mental harm to patients living with a currently incurable disease by giving them false hopes (please see section 4.3.3. for elaboration).

The 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies' may supplement the European Code of Conduct by illustrating and explicating how the ALLEA principles and practices apply to the field.

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4.2.2. A potential Source of Inspiration for ALLEA

Although the discussions predominantly focused on the 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies' as a supplement to the European Code of Conduct, it was also suggested that ALLEA might find inspiration in the HYBRIDA project during its next revision of the European Code of Conduct in which it consults different stakeholders.

Furthermore, harassment of researchers on social media across fields, not least within organoid research, is a fairly recent phenomenon which one expert pointed out is not currently addressed in the European Code of Conduct. In its revision process, it was thus suggested that ALLEA could consider institutions' responsibility to protect their researchers from this and handle such instances.

4.2.3. Summary

To summarise, the workshop experts seemed to agree that the 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies' is a welcome supplement to the European Code of Conduct, translating general principles into field-specific guidelines.

4.3. A Code of Responsible Conduct for Organoid Research

Experts argued that in order to constitute a supplement to the European Code of Conduct and align with the needs and developments within the field of organoid research, the HYBRIDA Code of Responsible Conduct for organoid research should focus and elaborate on what is specifically relevant for organoid research. Based on inputs and suggestions from the first round of discussions, the following presents expert recommendations on how to strengthen the HYBRIDA Code of Conduct.

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4.3.1. A Clear and Explanatory Code

Concern was expressed that some terminology in the first version of the 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies' 'resonates legally' but does not refer to an actual legal framework. One term in need of clarification is the term 'data ownership'. From a legal perspective, it is not clear what this means exactly, and as opposed to the term 'data controller', 'data ownership' is not a legal concept. Another example that was mentioned is the term 'accountability', which was argued to hold a dual meaning: a reference to the ALLEA European Code of Conduct, which highlights the importance of accountability for responsible research (ALLEA, 2017), or, in the context of data, a reference to the GDPR regulation, in which accountability constitutes a legal concept. The group generally agreed that a table of definitions should be developed and included in the Code of Conduct to avoid confusion.

Another way to clarify the Code of Conduct could be to include concrete and illustrative examples, for instance in relation to questionable research practices (QRPs), which were argued to be insufficiently specified in the first version. One example of a questionable research practice in organoid research that was mentioned is selecting and working with a very limited number of biological replicates showing the most promising results and thereby omitting variability.

Experts argued that the 'Code of Responsible Conduct for the Field of Organoids and Organoid-related Technologies' should include a paragraph concerning revision and review specifications. As the emerging field of organoid research is advancing rapidly, an expert recommended that the Code of Conduct should be revised and updated frequently.

4.3.2. The Role of Different Stakeholders

Another theme in the discussions was inclusion of additional stakeholders in the HYBRIDA Code of Responsible Conduct for organoid research.

One expert suggested elaborating on the role of RIOs as meditators in authorship conflicts. It was argued that although they do not only mediate authorship conflicts amongst organoid researchers, it is of particular importance to this field.

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Experts also pointed to funders and publishers as important stakeholders to include. First, it was argued that they were relevant actors in terms of the reproducibility challenge within the field. The problem was seen to be compiled of different issues such as presentation of selected data, not publishing negative results, and an absence of retractions in cases where protocols are not reproducible. Organoid researchers argued that there is a constant pressure to publish results in order to signal success and thus ensure the next grant. This was argued to have vital implications for both the quality of science and ethical training of the next generation of organoid researchers. In terms of quality of research, it was argued that the pressure might lead researchers to present selective data and not publish negative results, thereby making it difficult to reproduce study protocols. In terms of lack of ethical supervision of younger researchers, the experts argued that being a good supervisor is not recognised equally to publishing scientific papers. Thus, the publication and funding pressure risks leading senior researchers to focus on technical training alone, so they have more time to write grant applications.

Second, publishers were mentioned as a potentially relevant stakeholder group in the implementation of the HYBRIDA Code of Conduct. Some experts underlined the importance of reflecting upon how to ensure that the code is implemented in practice. This could include considerations about target groups as well as how to reach researchers who only use organoids for a small part of a large clinical trial or have moved into the field of organoid research from a different field. The experts argued that due to the pressure to publish, there needs to be even stronger incentives to comply with the Code. One suggestion was to create a type of 'seal of approval' for journals that would signal that they comply with the relevant standards within the field and could provide an incentive across countries to abide by these standards in order to get published.

4.3.3. Science Communication

One of the groups agreed that organoid technologies are not only innovative and pioneering but also hold a potential to become controversial in the same way as other new technologies, such as genome editing or mitochondrial replacement therapy. To counter this, emphasis was placed on the importance of responsible communication with the general public as well as patients. In this regard, management of expectations was considered to be essential, not least when communicating with patients. As opposed to the general public, patients living with unmet health needs might have a vested interest in organoid

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research and thus have high hopes for potential therapies. It is important not to overpromise or exaggerate the potential of the research and instead explain the research that is being conducted, its objectives, and its limitations. It was argued to be equally important to communicate uncertainties and risks related to the particular research. The many interviews given by scientific experts during the Covid-19 pandemic were used as an illustrative example of such scientific communication. Furthermore, it was argued that researchers should communicate in a way that does not add fuel to hysteria around the field of organoid research. Should this happen, it is crucial that researchers defend against it. One expert also argued that researchers and institutions share the responsibility to communicate transparently and responsibly.

4.3.4. Summary

Experts recommended including illustrative examples and a table of definitions to clarify the terminology in the HYBRIDA Code of Responsible Conduct for organoid research. They also suggested expanding the list of stakeholders to funders and publishers in the next version of the code. Science communication was highlighted as an important area that should be addressed in the Code of Conduct.

4.4. Regulatory Issues and Gaps

Based on inputs from two successive group discussions, one of which focused specifically on the regulatory framework around organoids, this sub-section presents the results on potential legal gaps and issues within the field of organoid research.

4.4.1. Current Regulatory Issues

Apart from the derivation of cells for organoid research, which was considered to be well regulated, it was clear from the workshop that the experts in general found regulation of organoids and their use to be limited. Experts identified two main regulatory issues for the field of organoid research: sharing

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material for research across countries and institutions; and concerns regarding specific types of organoids.

First, a researcher pointed to the difficulties related to sharing material across countries. It was argued that material transfer agreements (MTAs) are very time-consuming due to differences in national and institutional regulations, the risk being that once the MTA has been settled, the transfer of material is no longer relevant. It was further discussed whether it would be possible to map different legislations to get an overview or to harmonise EU legislation within this area. The experts found that the latter would be very helpful for researchers but difficult to achieve.

Second, experts discussed whether certain types of organoids call for additional regulation. Although one expert generally considered organoids to be covered by the existing regulatory system, there was consensual recognition amongst the experts that cerebral organoids may cause concern due to uncertainty whether they possess some degree of consciousness. It was also discussed whether embryoids are currently underspecified and underregulated. A discussion which illustrates an interrelation between ontological uncertainty and regulatory uncertainty addressed by HYBRIDA. The ontological uncertainty relates to a lack of clarification on whether embryoids classify as human embryos. Depending on the ontological position on whether embryoids are classified as embryos or not, they may fall under existing embryo regulation such as the 14-day rule. Some experts encouraged a legal definition or consensus within the scientific community on how they should be defined. Other experts argued that definitions and regulations of embryos differ across countries and that it may not be possible to develop uniform guidelines and regulations for embryoids across countries.

4.4.2. A Potential Future Gap

In the context of advances in organoid research and new emerging technologies, some experts identified assembloids, which are not currently regulated, as a potential future regulatory gap. Brain assembloids were identified as in particular need of regulation. One expert argued that such an assembloid would have no experiences or memories and maintained that it would merely be a model; other experts reasoned that we have to ask whether it can be said to be conscious and which moral status it has. Exactly how this could be regulated was not clear from the discussions.

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4.4.3. Summary

Experts seemed to agree that regulation of organoid technologies is currently limited. It was discussed whether this requires further regulations at present. Some experts argued that certain types of organoids may need to be classified and regulated accordingly. MTAs were mentioned as an area in which alignment of regulation would be beneficial to researchers. In the future, the development of assembloids could be an area that requires regulation.

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5. Findings from the Expert Interview Study concerning main Ethical and Legal Issues in Organoid Research

The following sections report on the main findings from the interview study with experts in organoid research, bioethics, and/or stem cell technologies. The interviews explore ethical and legal issues pertaining to the field of organoids from different expert perspectives, as well as more narrowly defined topics such as informed consent procedures and ethically sensitive technologies for which open questions remain to be examined (for details, see method description, section 2.2).

5.1. Prospects and Advantages of Organoid Technologies

When asked about the main advantages of organoid technologies, several experts highlight their feature of being 'three-dimensional culture models' as a benefit, as they are closer in mimicking the structural and functional properties of the human organ than two-dimensional systems. Despite stated limitations and being 'imperfect systems', experts generally see them as providing 'powerful models' for studying the complex normal and pathological functioning of organs and human developmental biology through human biological material. They are highlighted as improving our understanding of the biology of pancreatic cancers, genetic disorders, and other types of cancer through disease modelling, and as models for drug development, test, and screening, for instance for personalised medicine. Several experts mention that for clinical applications, organoids have successfully been used to predict a specific drug treatment response for cystic fibrosis (CF) patients.

Other advantages mentioned are the increasing replacement of animal models and animal testing by organoid models and the benefits of biobanking from which samples can be used to study 'complex diseases'. For further and future advances, the possibilities with assembloids and regenerative medicine are also brought up in the interviews. Furthermore, organ-on-chip models are mentioned as a promising tool for future diagnostics. For future and very distant advantages, transplantation of bioartificial organs (or part of organs) for translational research is mentioned as a more long-term goal of organoid research.

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5.2. Main Ethical and Legal Issues within Organoid Research

At the beginning of the interview, experts are asked in an open fashion what they see as the main ethical and legal issues concerning organoids from the perspective of their own work and field of expertise. While the answers are context-dependent on areas of research and hence the sample of experts, informed consent including proper information and engagement, data sharing, data protection, and anonymity; research related to embryonic models; and to some extent neural organoids are recurrent ethically charged themes mentioned across the interviews. Some experts mention science communication aspects explicitly, e.g. responsible and properly informed communication with the public and patients and dialogue, as areas of ethical concern. These main themes are all addressed separately in the sections below. Additional areas are mentioned as ethical and legal issues to be taken into consideration for organoid research and organoid-related technologies:

- *Gonadal organoids*: One expert mentions the ethical and legal aspects of gonadal organoids as issues not given enough attention considering the pace of advancement. iPSCs can be used to generate testis and ovarian organoids and potentially in vitro gametes such as sperm and eggs for the purpose of research in infertility issues, and/or clinical and therapeutic purposes could be imagined within the field of reproduction to be used for in vitro fertilization (IVF). The fact that iPSCs from a male donor/patient in theory could be used to produce ovarian tissue and vice versa is seen to potentially challenge established ways of reproduction and creating concerns about reproductive human cloning (see also Mollaki, 2021, p. 7; Gaillard et al., 2022).
- *Chimeras and animal research*: The development of chimeras, 'defined as organisms composed of cells from two or more species' (de Jongh et al., 2022, p. 14), concerns for instance cases where human-derived organoids are transplanted into animals. In relation to cerebral organoids, the ethical issues of a humanisation of animals and animal welfare, in general, are raised as particular concerns (see de Jongh et al., 2022 for a detailed literature review of the ethical implications concerning chimeras).
- *Organoid complexes and assembloids:* The assembling of different organoids may raise ethical issues, as sensitive matters are seen to increase with the proportional reassembling of 'the biological

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processes of humans'. Relatedly, particular aspects concerning both ethical and legal aspects are seen according to their in-vitro handling; the use of the original biological materials, the length of maturation, and their complexity, which relates to the creation of potential assembloids (see also Munsie et al., 2017). Ethical issues concerning cerebral organoids and gamete organoids are highlighted as important. In relation to the cerebral organoids, *organs-on-chip (OOC)* are mentioned as raising ethical issues when combined into assembloids.

- *Access to health care:* One expert points to the ethical aspects related to general healthcare inequality issues and access, emphasising that advances in emerging technologies, including organoid technologies, should result in treatments for patients. This argument resonates well with the argument and recommendation brought forward in the three deliberative workshops with public and patients, among other stakeholders, where participants advocated for organoid research promoting health equality and being broadly accessible (see Ravn et al., 2022).

5.2.1. Personalised Medicine and Evidence Medicine

Within precision medicine/personalised medicine, a 'precision paradox' has been emphasised as an inherent facet. Whereas the objective is to create personal treatments, the number of patients with the same condition might be low, challenging the application of randomised control trials and other statistical methods, potentially resulting in increased uncertainty and imprecision, as ordinary standards within evidence medicine may be difficult to uphold (Vogt, 2022). An interesting question is whether precision medicine implies a change in evidence standards. As described in section 2.2.1., this question is included as an additional probe tailored to some experts, and the following summarises the responses from three experts.

For organoid research, it is mentioned that randomised trials might be set up at some point, for instance randomising participants by applying a 'chip model versus not'. Second, while it is stated that the issue on randomisation remains complex, and unproven therapies should be avoided and patients protected, there is also a need to balance (negative) effects, as personalised medicine allows small patient groups, who for instance do not have 'the most frequent mutations', to take part in new treatments otherwise not accessible. Third, it is indicated that the area is strictly regulated, and one expert suggests that closer collaboration among researchers and regulators should be initiated to develop and align new approaches

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and regulatory processes with a new research reality within precision medicine vis-à-vis organoid technology.

5.3. Sensitive Technologies

The HYBRIDA project has shown that some types of organoids might raise particular ethical and legal concerns due to their moral status, for instance cerebral organoids/neural organoids and embryoid models. These two areas of inquiry were included as distinct themes in the expert interview guide (please see appendix J for a precise wording of probes).

5.3.1. Embryonic Models

The HYBRIDA consortium is increasingly preoccupied with embryonic models, not least due to recent research into 'synthetic mouse embryos' by Jacob Hanna and Magdalena Zernicka-Goetz which has caused concern within the scientific community, amongst other reasons due to the commercialisation plans to generate 'human synthetic embryos' (Chneiweiss et al., 2022, p. 64). Within WP5, a working group has been formed to look further into embryonic models.

Embryonic models or embryoids are 3D structures or entities that can mirror aspects of the early stages of human development (embryogenesis) in vitro to improve our understanding of issues such as infertility, birth defects, and miscarriages. Embryonic models such as gastruloids or blastoids can be seen as sub-organoid types, as both embryonic models and other types of organoids can be derived from pluripotent stem cells with the ability to self-organise. However, whereas organoids can mimic the functional properties of organs, embryonic models replicate the development of organisms. Due to their commonalities, their ethical and legal implications are nevertheless often discussed collectively within the framework of organoid research (de Jong et al., 2022; Chneiweiss et al., 2022; Gaillard et al., 2022; Mollaki, 2021).

According to the recently issued ISSCR guidelines, two types of embryo models can be defined: 'non-integrated stem cell-based embryo models' such as gastruloids, which can 'experimentally recapitulate some, but not all aspects of the peri-implantation embryo' and 'these stem cell-based embryo models

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do not have any reasonable expectations of specifying additional cell types that would result in formation of an integrated embryo model'. In turn, the 'integrated stem-cell based embryo models contain the relevant embryonic and extra-embryonic structures and could potentially achieve the complexity where they might realistically manifest the ability to undergo further integrated development if cultured for additional time *in vitro*'. Blastoids constitute such an integrated model (International Society for Stem Cell Research, 2021, p. 64). As the integrated model potentially can be developed into a foetus, it is specified that these models should only be used for research and not reproductive purposes, and that a specialised review should be in place. The ethical and legal implications are hence seen as different, but both models raise the question to 'what extent do these entities mimic real embryos? (Gaillard et al., 2022, p. 21). Relatedly, maturation also constitutes a main issue. The restrictions of the '14-day/primitive streak rule' apply to human embryos cultivated in vitro but not to embryo models (International Society for Stem Cell Research, 2021, p. 64; Gaillard et al., 2022, p. 34). A key matter in this regard is the classification and the moral status of embryonic models, whether they can be seen as comparable to embryos, and consequently how this should be reflected in legal and ethical measures (Chneiweiss et al., 2022).

In the expert interview study, several experts explicitly mention that the field is 'emerging quickly', and that it should warrant particular attention when asked about the legal and ethical issues of organoid technologies. Some experts directly speak about the work on 'synthetic mouse embryos', disagreeing with the applied terminology for several reasons; one states that they are embryoids, not embryos, and should not be presented as such. Other experts also point to its misleading denotation and connotation but emphasise the potential negative consequences and uneasiness it can cause in the general public. Such misrepresentative labelling could tie in with the already ethically charged debate about creating human embryos for research and add to potential discomfort and uncertainties, including the question of whether it at some point could be done with humans too. Another expert highlights the commercialisation aspect and its implications for informed consent processes as the ethical issue causing primary concern.

Many of the interviewed international experts draw attention to the very diverse sets of regulations across countries, including ongoing or recently implemented changes in the production of national regulations within the field, causing distinctions in regulatory needs and applications. One explicitly mentions the benefits of harmonised regulation at the EU level but finds its actual implementation difficult to envision. Another expert mentions 'The Convention on Human Rights and Biomedicine' (the Oviedo

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Convention) as a shared framework for the ratified countries, stipulating that human embryos cannot be created for research purposes (Council of Europe, 2022).

It has been indicated that the lack of a cross-national legal, biological, and ethical definition of a 'human embryo' complicates the attribution of moral status to its embryonic counterparts (de Jongh et al., 2022, p. 15; Lewis and Holm, 2022). Several experts support the idea of a shared definition of a human embryo, while one expert voices concern that this might imply a setback in achieved regulatory changes. Another expert argues that a definition of a human embryo would clarify the distinction between human embryos and human embryoids, benefitting research on the latter by clearly outlining their functioning and use, also helping to clarify the potential application of the 14-day limit within embryoids research or other potential required standards. Another expert points to the regulatory and ethical need for an 'appropriate governance framework', taking into consideration that they are models, adapting and aligning proper review processes, ethical oversight mechanisms, and responsible informed consent processes to the purpose of the research.

5.3.2.Cerebral Organoids

Within the research literature on organoid research, an increasing number of articles are engaging in discussions as to whether cerebral organoids should be granted special legal or ethical concern.

Cerebral organoids '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).

While they show great promise for studying the brain and for developing therapies for neurological and psychiatric disorders, have helped screen for useful drugs and determined the connection between the Zika virus and microcephaly, among other progressions, to their constitution as neural entities entails particular ethical concerns; predominantly the potential of mature cerebral organoids to develop sentience, respond to pain, retain cognitive functions, or acquire consciousness has caused concern and questions whether such states may lead to the attribution of moral status and consequently particular protection (Baertschi et al., 2020; Farahany et al., 2018; Haselager et al., 2020; Mollaki, 2021).

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Experts participating in the expert interview study mention that cerebral organoids are promising research tools and models to increase scientific understandings of neurological diseases and neurodegenerative processes, amongst other areas. Several experts speak about this terminology, suggesting that we should apply the term 'neural organoids' – to be able to encompass all variations – instead of the term 'brain organoids' or 'mini-brains' (see also section 5.5.1). In general, a majority of experts agree that the state of neural organoids research does not currently warrant special ethical or legal concerns, and that the research remains at a stage where sentience is not yet of distinct concern. On the contrary, one expert argues that the unknown status of the issue of sentience calls for specific and deliberate consideration in terms of assigning a moral status at the present stage of research. This view holds that it is important to discuss whether a special legal status should be attributed to organoid entities too, or if a principle similar to the 3Rs within animal research could be implemented.

Nonetheless, the general position among the interviewed experts seems to be very much aligned with the 'ISSCR guidelines for Stem Cell Research and Clinical Translation', that concerns about consciousness are not currently warranted, but that continued ethical awareness is called for as research on neural organoids progresses (International Society for Stem Cell Research, 2021, p.10). While a majority of experts does not assess that any moral status should be attributed at present, many indicate that neural organoids can be perceived as having a more sensitive nature than other types of organoids, which poses certain awareness-raising questions and might require special concern. For instance, it is mentioned that while neural organoids might not cause neurobiological concerns, they do entail a certain 'moral intuition' within the public perception of organoids. Moreover, creating chimeras through neural organoid transplantation is raised as a particular topic of concern (see section 5.2 above). Lastly, while researchers might not intend to create sentient organoids, it is mentioned that this might be an unintentional consequence of their research, which may be difficult to control.

5.4. Informed Consent Procedures and Ethical Oversight

The particularities of informed consent for organoid research and organoid-related technologies have been related to the uncertainties interlinked with future risks, and specific organoid objectives for which patient samples are used (e.g. basic research, proven/unproven therapies, transplantation etc.) (Baertschi

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et al., 2020; Mollaki, 2021) for a field developing apace. Additional issues have been raised in the literature, for instance the scenario that donors may establish a greater sense of attachment to their organoids, e.g., more ethically complex embryoids or cerebral organoids. Donors, attributing greater meaning to the association between organoids and bodily integrity (de Jongh et al., 2022; Mollaki, 2021; Lewis and Holm, 2022), may then ascribe normative values and claims to organoids.

The first published version of 'D.5.1 Operational Guidelines for the Field of Organoids and Organoid-related Technologies' (Chneiweiss et al., 2022) provides a first set of guidelines for the legal basis of informed consent, the context of biological sample collection, and guidelines and checklists for procedural steps to be taken into account during the process. Issues of withdrawal and different models for consent are also discussed but have proven complex, yielding diverse and divergent perspectives on recommendations for best practices. A taskforce has been established to provide additional insights and analysis on the issue prior to an updated version of the operational guidelines. The expert interviews include the topics of consent models and issues of withdrawal to be able to contribute with additional perspectives, assessments, and insights to this ongoing work.

From a legal perspective, the report 'D.6.1. Regulating organoid and Organoid-related Activities: Analysis of the Regulatory Gaps and Areas of Over-Regulation' (Lewis and Holm, 2022) points to several issues of distinct relevance for organoid research regarding informed consent procedures:

- 'EU/EC regulations regarding standards of informed consent do not explicitly include (organoid or organoid-related) research that uses human tissues and cells' (p. 9). This has resulted in national differences in formal requirements and created uncertainty for non-clinical trial purposes such as preclinical or in vitro research (p. 44)
- The nature of organoid research and the difficulties of outlining future uses and risks complicate the obtainment of genuine informed consent. Different models for valid consent may be implemented, such as broad or blanket consent. However, such models pose limitations on standards for actual and genuine consent from tissue donors (p. 44).
- Withdrawal of consent causes challenges for organoid research as it does not extend to derived organoids but only to donated cells and tissues (p. 14). Furthermore, there is also an element of the lack of feasibility of being able to monitor and trace samples back to their donors, e.g. post cell transformation (p. 47).

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On this background, the following sections delve into informed consent, consent models, and withdrawal with regard to the main views and arguments brought forward by the interviewed experts.

When responding to the question of the most important aspects to consider when choosing the best model of informed consent, the interviewed experts recognise the mechanism as the means to inform and secure the rights of the participants donating their cells and tissues to organoid research. For the most important points to consider, the variation of aspects mentioned in the interviews can be summarised according to the following four topics:

1) Proper information and involvement of donors and patients

Providing patients and/or donors with clear, understandable, and sufficient information to enable them to make informed and autonomous decisions while ensuring that the consent is truly voluntary is highlighted as important. As to the latter, patients may be in a state that complicates the provision of consent. Granting participants with decision-making power, involving them in open and disclosing consent processes, where sufficient resources are allocated for questions and dialogue, are other aspects mentioned. Information about medical company research and related issues of commercializing are mentioned as examples of discussion points that should be disclosed in an open conversation about donation. Patients/donors may easily be 'disconnected' from the process, and it remains important that they are given the option of being properly informed about the course of action concerning their own biological material. The information should include a thorough clarification of what organoids are, perhaps through visualisation aids, to avoid misconceptions and science fiction-inspired imaginings.

2) Contextual dimensions: Not 'one-size-fits-all policy'

Providing clear and understandable explanations of research and organoids necessitates an awareness about different factors such as cultural, religious, etc. aspects, which influence meaning-making processes and personal understandings of biological tissues. The contextual dimension is highlighted as relating to the specific use of the donation. For some type of research, standard consent may suffice, whereas more ethically sensitive organoids such as cerebral organoids, gonad organoids, embryo models, and assembloids may call for 'special consideration' in informed consent processes due to their ethical nature and 'moral' positioning within public understandings of different types of organoids. For instance, people may ascribe different meanings to the heart and brain compared to the liver or gut. A

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related point concerns the type of stem cells applied, the two techniques of adult stem cells versus pluripotent stem cells prompting potentially different ethical considerations and concerns in terms of their future use (see also Schickl et al., 2020).

3) Data protection and anonymisation

Another aspect touched upon, is the issues and challenges related to data handling, data storage, privacy protection and traceability and the fact that complete anonymisation is not possible with current DNA sequencing technology. Consequences and risks of data protection measures should be transparently stated in the consent form, including aspects related to distribution and commercialisation (for a review of issues related to complete anonymity and de-identification not being possible or always desirable, see de Jongh et al., 2022).

4) 'Open-endedness' and future use

The 'open-endedness' of biomaterial donated for organoid research constitutes a consideration that relates to the difficulties of specifying future uses and risks in research and medical applications as described above. The open-ended nature of organoids might cause unease and concern among donors and patients in terms of future use of their biological material, also beyond their own lifetimes, as it can be re-used repeatedly since organoids can be maintained for a long time. It is suggested to consider potential time restrictions on the use of donations.

While the protection of donors and patients through proper, responsible, and adequate consent processes is seen as an ethically needed and legally required mechanism, also taking particular challenges for organoid research and consent into consideration, there seems to be consensus that we should not 'hamper science' or 'block any progress' that would also be in the interests of patients and society at large. Striking a balance between providing specific information and allowing some 'grades of freedom' touches upon a profound question and debate, which is also evident in the perceptions of the best models for informed consent.

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5.4.1.Models of Informed Consent

Existing models for informed consent ultimately differ in the specification of information concerning current and future use, type of established communication (one-way/two-way), ongoing (re-contact) or one-off contact, and type of actors involved (e.g. biobanks as intermediaries). De Jongh et al. (2022) provide an overview of available models in their literature review of ethical issues concerning organoids in the table below. The first version of the 'operational guidelines for the field of organoid and organoid-related technologies' within HYBRIDA includes four models of consent: 'specific consent', 'broad consent', dynamic consent', and 'consent entrusted to a third party'. The latter entails that 'exchanges between donors and biobanks be processed by an independent intermediary body, responsible for representing the rights and interests of the donor. Donors retain the right to withdraw from the study at any time (where possible) but delegate consent for the planned research projects to the intermediate organisation' (Chneiweiss et al., 2022, p. 61-62). Similar to the 'governance consent model' (Boers et al., 2019, p. 137), the model focuses on the four elements of privacy by design, participant commitment, benefit sharing, and ethical oversight.

Table 2 Advantages and disadvantages of consent models proposed for organoid research explained in the literature

Type of consent	Summary of the model	Advantages	Disadvantages
Specific consent and re-consent [59, 61, 62, 68]	Donors consent to the use of their tissue for a specific research project and are re-contacted to provide consent for each new potential future study that will be conducted with their tissue		Donors are re-contacted for each scientific (re)use of their sample. Enable to engage the preferences of the donors
Tiered consent [59, 60, 66, 67]	Donors are presented with a list of specific research projects and given the opportunity to provide or withhold consent for specific uses of their tissue	Able to engage the preferences of the donors	Donors are re-contacted for each scientific (re)use of their sample
Broad consent [30, 59, 61, 62, 67, 68]	Donors consent to a broad range of future research purposes, the specific details of which are unknown at the time of consent	Donors are not re-contacted for each scientific (re)use of their sample	Enable to engage the preferences of the donors
Blanket consent [59]	Donors consent to the use of their samples for future research without restrictions	Donors are not re-contacted for each scientific (re)use of their sample	Enable to engage the preferences of the donors
Opt-in [30, 59, 60]	Donors consent explicitly before their samples can be used for scientific research		Donors are re-contacted for each scientific (re)use of their sample. Enable to engage the preferences of the donors
Opt-out [30, 59, 60]	Donor consent is implied, unless the donor explicit refuses to use their biomaterials	Donors are not re-contacted for each scientific (re)use of their sample	Enable to engage the preferences of the donors
Governance consent [30, 59, 62, 68]	Donors consent to governance obligations in the organoid infrastructure to which they contribute. Donors do not exactly know in which studies their tissue will be used, but they do know how researchers will protect their privacy and interests	Able to engage the preferences of the donors. Donors are not re-contacted for each scientific (re)use of their sample. Ongoing communicative (governance) process	
Dynamic consent [59, 60, 62, 67]	Facilitates a two-way communication between donors and researchers through the use of digital interfaces	Able to engage the preferences of the donors. On-going communicative (governance) process	Donors are re-contacted for each scientific (re)use of their sample

Source: de Jongh et al. (2022). 'Organoids: A systematic review of ethical issues', p. 9

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In the literature, there is a longstanding debate about the philosophical and ethical underpinnings of informed consent and the de facto implementation of *genuine* informed consent. Blanket and broad consent have been noted to not provide full information (Lunshof et al., 2008; Lewis and Holm, 2022a). Broad consent allows donors to consent to a broad range of research objectives within a specific area of diseases, for instance, but donors do not have the autonomy or decision-power to enact permissive control of the particular use and/or reuse of their sample, and is therefore seen as a model not providing a *genuine* informed consent. However, blanket and broad consent accommodate the open-ended character of the future uses of tissue donation for organoid research and potential future clinical applications. In turn, the models encompassing two-way communication and re-contact have been criticised for being unfeasible, resource-demanding, creating information-overload, and ultimately potentially impeding research (de Jongh et al., 2022; Lewis and Holm, 2022, 2022a).

In the interviews, experts offer different perspectives on the best model(s) of consent. In many ways, the arguments relate to the complexity of finding a balance between properly and responsibly informing donors while not putting too many constraints on research progress, potential future uses and innovations. The expert opinions reflect different views, also illustrating the debate in the field. However, a majority of opinions reflect the pros and cons of the different models in the recognition that one model does not necessarily fit all purposes.

- *Broad consent*: Eight experts are explicitly in favour of applying other models than broad consent because they prefer a re-approach option and/or because broad consent does not provide sufficient information. One expert does not specify a preferred model but emphasises the need to be as specific as possible and mentions an example of contacting patients for re-use of data, even though permission to share data had been approved by the hospital's research ethics committee. Two experts also do not specify a particular model but point to cases with ethically sensitive organoids for which additional consideration should be addressed in the consent process. Two researchers are primarily in favour of broad consent due to the restraints otherwise imposed on future research possibilities and in consideration of the amount of resources spent on re-contact processes. They do not dismiss other models but are open towards the aspect of re-contacting donors if it can be done in a more feasible way. Another expert does not specify choice of preferred model. One expert is very much in favour of adding as few restrictions as possible, perceiving the donation of tissues not as personal

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property but as donations to medical research at large, highlighting moral aspects in terms of human dignity and 'benefits for humanity'.

- *Dynamic consent:* Three experts explicitly state that they prefer (some form of) dynamic consent to secure a greater level of information and influence of donors, for instance being transparent about the immortality of iPSCs. It is also stated that this model is not without challenges and that re-contact is not always possible, e.g. is it not seen as possible and ethically responsible to contact families of deceased donors. One expert prefers dynamic consent in some cases and in relation to healthy donors. Another expert stresses the impractical nature of implementing dynamic consent procedures.
- *Specific consent*: One expert prefers this model in terms of specifying research objectives while keeping a degree of academic freedom. Two researchers state that they try to specify the consent to the extent possible.
- *Entrusted third party*: Four experts express openness towards having an entrusted third party but also note potential disadvantages: A third party might have an agenda and potential opposing interests, and biobank infrastructures differ significantly from country to country, complicating a cross-national and harmonised model.

Building trust is another important aspect. One expert addresses the patient/donor perspective towards informed consent models for organoid research, and the importance that patients ascribe to sound oversight procedures, good intent, and robust processes of consent (for details, see Bollinger et al., 2021). The three deliberative workshops conducted in the HYBRIDA project with public, patient, and donor representatives displayed similar results and showed that a majority of the participants preferred a model with some restrictions/tiered or a dynamic model for consent (for details, see Ravn et al., 2022).

5.4.2.Withdrawal of Consent

Another related issue concerns the right for donors to withdraw their consent. From a legal perspective, donor withdrawals include only donated tissues and cells, and it remains unclear whether withdrawals extend to derived organoids (Lewis and Holm, 2022, p. 14). Current practices often entail the option to withdraw until the point of cell processing and transformation (e.g. cells thawed for reprogramming).

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Post transformation, the exponential sample growth and sample biobank distribution render the traceability of the original sample very difficult and unlikely. Hence, a recommendation in the 'Operational Guidelines for the Field of Organoids' could be to 'propose a possible withdrawal until the cells are thawed and cultured' (Chneiweiss et al., 2022, p. 60). Additionally, it is recommended to include a time demarcation in the consent form for how long samples can be stored for secondary studies and re-use (Chneiweiss et al., 2022, p. 60). The latter option has also been suggested in some of the expert interviews (please see section on '"Open-endedness" and future use' above).

The general view on withdrawal expressed in the interviews is that tracking down samples may be very difficult, e.g. after the derivation of iPS cells. The withdrawal clause should be very clear and transparent in terms of uses and limitations. One expert questions the 'impossibility' aspect of recalling samples, stating that it is also a matter of priority, and another expert questions the option to withdraw altogether. As for storage and practical implementation, two researchers talk about a pseudonymised registry. One does not operate with a limited time span, and the other is able to track patients for five years before the sample is anonymised. Neither has experienced requests for withdrawals. One expert refers to previously suggested guidelines for the derivation of iPSC, where the issue of withdrawal is included in the first set of guidelines (see Lomax et al., 2013, p. 729).

5.5. Expectations and Scientific Dissemination

Science and society dialogues with multiple stakeholders are recommended for long-term public acceptance of organoid research, and to ensure responsible innovation within the field (Bredenoord et al., 2017; The National Academies of Sciences, Engineering, and Medicine, 2021). In addition, the importance of communicating organoid research findings in a sound and transparent manner is regularly emphasised within the field, since 'the way in which science is represented in public communication can influence expectations and understanding and frame policy debates. Inaccurate or incomplete representation of research may have various negative consequences' (Bredenoord et al., 2017, p. 6). Within the broader field of stem cell research, the recently updated ISSCR guidelines include recommendations for 'public representation of science' for stem cell research and regenerative medicine (International Society for Stem Cell Research, 2021, p. 51-52). This section reports on expert perceptions of potential

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hype within organoid research and their views on how best to address the hype issue in relation to public expectations and scientific dissemination.

With emerging biotechnologies, hype often follows, which has also been the case with stem cell research, personalised medicine, and gene editing, amongst others (Master and Resnik, 2013). Overblown promises can increase expectations, support, attention, and funding, but excessive hype can also negatively influence public trust in science and add to scientific misrepresentations. Ultimately, hype can lead to premature clinical translations and marketing of untested treatments that could severely harm patients (Caulfield et al., 2016; Master and Resnik, 2013).

The majority of the experts assess that a little or some hype can be identified within the field of organoid research, but that it cannot compare to the hype experienced with regard to stem cell therapies for instance. Some interviewees point out that there is a lot of potential for advancements within the field but also that some successes remain to be witnessed in some hyped sub-areas of organoid research. Neural organoids and embryonic models are highlighted as especially hyped areas of research, also in terms of public attention. There seems to be consensus that some hype is a positive prerequisite for scientific progression, attracting awareness and funding, but that it can easily 'backfire' if expectations are overstated and unmet. Examples of negative consequences are the spread of misinformation, increased patient and public misconceptions and mistrust in science, lack of support, marketing of untested treatments, field restrictions, and reduced funding avenues. 'Management of expectations' is seen as an important element in science communication and in clear and transparent dissemination of the current states of research to 'fight misinformation' and avoid 'overpromising'. Researchers and the research community are seen as key actors with 'moral obligations' to practice responsible science communication, but other stakeholders also play a significant role in counteracting incorrect and sensational science representation, overblown promises, and unfounded benefits. Institutional science communication offices, journal editors, science journalists, funding agencies, and politicians are mentioned as stakeholders that can and should enact different responsibilities in promoting responsible health and science communication, including popular (social media) dissemination, publication, and review together with fostering sound science and technology policy decision-making processes.

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5.5.1.Strategies to Address Hype

Overall, the experts agree that guidelines on science communication, such as the ISSCR guidelines (2021), are a valuable way to address hype within the field and help inform and guide researchers and other relevant stakeholders such as funding agencies and policy makers about sound and balanced ways of communicating and representing science.

There is consensus among the interviewed experts that regulating hype is not a fruitful or realistic way forward, as it would be very difficult to envisage such regulation in practice. 'Soft mechanisms' and 'self-regulation' within the research community are seen as more efficient. In addition to providing guidelines and general and clear management of expectations, other strategies to address hype are also recommended: 1. Promote dedicated training and education initiatives of the broad category of science communicators; 2. reinforce efforts to engage in public outreach and dissemination of organoid research to the general public; 3. the research community could invest more efforts in collective activities of coordination and dissemination of accurate science representations, for instance through research networks, collaborations, and social media strategies.

Several experts also stress the role of organoid nomenclature as potentially adding negatively to potential hype within the field and to creating scientific misconceptions and representations. Terms like 'mini-brains' and 'brain organoids' are mentioned as a terminology that does not precisely capture the reality of these entities. One researcher mentions the term 'synthetic embryos' as a problematic and inaccurate terminology that can fuel the wrong connotations and ideas about the state of embryonic models research (see also section 5.3.1). Another expert more generally draws attention to the framing of the organoid terminology itself, pointing out that it might not be as captivating to name them 'cell lines' (for more details on the conceptual aspects of organoids, see Gaillard et al., 2022).

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7. Appendixes

Appendix A: List of Experts

Alexei Grinbaum Paris workshop	▪ Senior researcher working on ethics of emerging technologies at LARSIM, the Philosophy of Science Group at CEA-Saclay ▪ Director of Research at CEA-Saclay ▪ Chair of the CEA operational ethics committee for digital technologies ▪ Member of the French National Digital Ethics Committee ▪ Involved in several EU projects, including TechEthos and observatoryNANO
Alex McKeown Copenhagen workshop	▪ Research Fellow with the Neuroscience, Ethics & Society team (NEUROSEC), Department of Psychiatry and Neuroscience at University of Oxford ▪ Research Fellow with Wellcome Centre for Ethics and the Humanities (WEH) at University of Oxford ▪ Deputy Director of the UK Pandemic Ethics Accelerator
Ana Marušić Copenhagen workshop	▪ Professor of Anatomy at University of Split, School of Medicine ▪ Chair, Department of Research in Biomedicine and Health at University of Split, School of Medicine ▪ Head at the Center for Evidence-based Medicine at University of Split, School of Medicine ▪ Research Integrity Advisor, Doctoral School at University of Split, School of Medicine ▪ Chair at the Research Committee of the World Association of Medical Editors ▪ Council Member of the Committee on Publication Ethics (COPE) ▪ President at The Embassy Foundation ▪ Honorary Professor at University of Edinburgh ▪ Editor in Chief, Croatian Medical Journal ▪ Co-Editor in Chief, Journal of Global Health ▪ Co-Chair of the Cochrane Scientific Committee
Andrea Lavazza Paris workshop	▪ Senior Research Fellow, Neuroethics at Centro Universitario Internazionale ▪ Adjunct, Department of Brain and Behavioral Sciences at University of Pavia ▪ Adjunct, Department of Oncology and Hematology, Adjunct State University of Milan ▪ Founding member of the Italian Society for Neuroethics (SINe)
Andrew Barnhart	

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

Paris workshop	▪ Marie Curie Research Associate and PhD Candidate working on ethics of organoids with a focus on moral status and animal ethics at the Centre for Biomedical Ethics and Law in the Department of Public Health and Primary Care at KU Leuven (Belgium) ▪ Team member in the European Horizon 2020 project 'Organoids for Virus Research – An innovative training-ETN programme' (OrganoVIR)
Anne Forus Copenhagen workshop	▪ Senior Adviser at the Norwegian Directorate of Health ▪ Vice-chairperson and member of the UNESCO International Committee on Bioethics ▪ Chair of DH-BIO/CDBI (2013-2014) ▪ Member of the executive board for stem cell research, Norwegian Research Council (2008-2012)
Carole Chapin Paris workshop	▪ Project manager at the French Office for Research Integrity (OFIS) ▪ Representing OFIS at The European Network of Research Integrity Offices (ENRIO) as a member of board
Christine Dosquet Paris workshop	▪ Clinical Hematologist at Saint-Louis Hospital in Paris ▪ Chair of the Inserm Ethics Evaluation Committee (CEEI - IRB) since 2011 ▪ Permanent guest at the Inserm Ethics Committee (IEC) ▪ Member of the IRB (Institutional Review Board) Paris Nord of the APHP since 2008 ▪ Former member of at the European Network of Research Ethics Committees (EUREC)
Daniel Besser Expert interviews	▪ Managing Director of the German Stem Cell Network (GSCN) ▪ Partner of the EuroStemCell ▪ Former Team Leader of a research group at Max-Delbrück-Center for Molecular Medicine in Berlin
David Townend Paris workshop	▪ Professor of Law in the City Law School at City, University of London ▪ Professor of Health and Life Sciences Jurisprudence at the School for Public Health and Primary Care, Faculty of Health, Medicine and Life Sciences at Maastricht University ▪ Visiting Professor of Health Law at the University of Lincoln ▪ Member of board at the European Network of Research Ethics Committees (EUREC)
Dirk Lanzerath Paris workshop	▪ Professor of Ethics and Research Ethics at Bonn University

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	▪ Secretary General and member of board at the European Network of Research Ethics Committees (EUREC) ▪ Executive Manager at German Reference Centre for Ethics in the Life Sciences (DRZE)
Hannah Schickl Copenhagen workshop	▪ Research Associate and Coordinator of the project "Gene Technology Report" at the Berlin Institute of Health at Charité, Berlin ▪ Involved in the German translation of the "ISSCR Guidelines for Stem Cell Research and Clinical Translation" white paper ▪ Editor of the "White Paper. Organoids - from stem cells to future technologies. State of Research, Core Statements and Political Recommendations for Action on Organoid Technology".
Hanna Seppänen Expert interviews	▪ Gastrointestinal surgeon at Faculty of Medicine, University of Helsinki and Helsinki University Hospital with expertise in gastric cancer and pancreatic cancer surgery ▪ Principle Investigator within the Translational Cancer Medicine Research Program, Faculty of Medicine, University of Helsinki and Helsinki University Hospital ▪ Leading the organoid technology group at Helsinki University with responsibility for ethical aspects
Helle Krogh Johansen Expert interviews	▪ Chief Physician at the Department of Clinical Microbiology, Rigshospitalet (Denmark) ▪ Dr. Med., Chief Physician, Novo Nordisk Foundation Center for Biosustainability Infection Microbiology, DTU Microbes Initiative, DTU ▪ Principle investigator of the Persistent Bacterial Infections (PERFECTION) project funded by the Novo Nordisk Foundation
Hilde De Keyser Paris workshop	▪ Chief Executive Officer at Cystic Fibrosis Europe
Hjördis Czesnick Copenhagen workshop	▪ Head of office of the German Research Ombudsman ▪ Co-Vice Chair of the European Network of Research Integrity Offices (ENRIO) (2019-2022)
Jeantine Lunshof Expert interviews	▪ Member of the Advisory Board of the HYBRIDA project ▪ Ethicist, Philosopher, and Head of "Collaborative Ethics" at the Wyss Institute for Biologically Inspired Engineering, Harvard University ▪ Lecturer at the Department of Global Health and Social Medicine, Harvard Medical School Center for Bioethics ▪ Ethics collaborator to the Church Lab and to the Center for Excellence in Genomic Science at Harvard Medical School

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

	▪ Assistant Professor at the Department of Genetics, University Medical Center Groningen at the University of Groningen
Jeremy Sugarman Expert interviews	▪ Deputy Director for Medicine at Johns Hopkins Berman Institute of Bioethics ▪ Harvey M. Meyerhoff Professor of Bioethics and Medicine at Johns Hopkins Berman Institute of Bioethics, Johns Hopkins School of Medicine ▪ Professor of Health Policy and Management at Johns Hopkins Bloomberg of Public Health ▪ Member of ISSCR Public Policy Committee, ISSCR Ethics Committee, and working group member of the task force to update the ISSCR Guidelines ▪ Co-chair of the Johns Hopkins' Institutional Stem Cell Research Oversight Committee
Johannes van Delden Expert interviews	▪ Full Professor of Medical Ethics and Director of Education at the Julius Center for Health Sciences of the Medical School, Utrecht University ▪ Member of Execute Committee and Immediate Past President of Council of International Organisations of Medical Sciences (CIOMS) ▪ Chair of the International Bioethics Committee of UNESCO (2012-2019)
Kasper Bendix Johnsen Copenhagen workshop	▪ Constituted leader, Danish National Centre for Ethics, The Medical Research Ethics Committees ▪ PhD in Brain drug delivery, Department of Health Science and Technology, Aalborg University
Kris Dierickx Paris workshop	▪ Full Professor of Medical Ethics at the Faculty of Medicine, Catholic University of Leuven ▪ Member of the Committee on Scientific Integrity, member of the Ethics Committee for experiments with animals, and member of board of the department of Public Health and Primary Care, Catholic University of Leuven ▪ Coordinator in the European project "Genetic bio and dataBanking: Confidentiality and protection of data. Towards a European harmonisation and policy" ▪ Member of the Belgian Royal Academy of Medicine ▪ Member of the Flemish Screening Commission ▪ Member of the Deontological Commission of the Superior Health Council

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Krista Varantola Copenhagen workshop	▪ Professor and Rector Emerita of the University of Tampere ▪ Member of The Finnish Academy of Science and Letters and the Council of Finnish Academies ▪ Member of the ALLEA Permanent Working Group on Science and Ethics, and Drafting Group member for The European Code of Conduct for Research Integrity ▪ Member of the ALLEA Board (2016-2022) ▪ Former Chair of the Finnish National Board on Research Integrity (TENK) (2010-2019)and currently acts as an expert to the Board
Kristine Freude Copenhagen workshop	▪ Associate Professor at the Department of Department of Veterinary and Animal Sciences at Copenhagen University ▪ Research focus on neurodegenerative and neurodevelopmental diseases and specialised in disease modelling using iPSCs and CRISPR-Cas9 gene editing
Laurent David Paris workshop Expert interviews	▪ 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
Lisa Diependaele Paris workshop	▪ Policy officer, Ethics and Research Integrity Sector, European Commission with a focus on bioethics and ethics of new and emerging technologies within health research
Lyle Armstrong Copenhagen workshop	▪ Professor of Cellular Reprogramming, Institute of Human Genetics, Newcastle University ▪ Chief Scientific Officer and co-founder at Newcells Biotech ▪ 2018 NC3R Crack-IT challenge 29: ImmuLiver. SME Principal Investigator ▪ NC3R Crack-IT Challenge 24 “3D iPSC derived laminated retinal model as a tool for toxicology studies”. SME Principal Investigator ▪ MRC project grant “An iPSC based screen for candidate pain modulating compounds”. Principal Investigator
Lyn Healy Expert interviews	▪ Senior Research Scientist at the Human Embryo and Stem Cell Unit, The Francis Crick Institute ▪ Involved in the Basic Characterization Working Group and the Undifferentiated Stem Cells and Pluripotency Working Group for the ISSCR Standards Initiative ▪ Member of the Management Committee of The European Network for Stem Cell Core Facilities (CorEuStem)

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

	▪ Member of Stem Cell COREdinates
Majlinda Lako Copenhagen workshop	▪ Professor of Stem Cell Science, Biosciences Institute, Newcastle University ▪ Leader of the Retinal Stem Cell Research group (RSCR), Institute of Genetic Medicine, Newcastle University ▪ Principle Investigator of the "RET-iPSC" project funded by ERC Consolidator Grants
Maria Tenje Expert interviews	▪ Professor in Microsystems Technology, leader of the EMBLA Group, and Head of the Division of Biomedical Engineering at the Department of Materials Science and Engineering, Uppsala University ▪ Visiting Professor at the Pruitt Lab, College of Engineering, University of California, Santa Barbara ▪ ERC Consolidator Grant for the PHOENIX project on organoids ▪ Former member and Chair of the Young Academy of Sweden
Markus Vähä-Koskela Expert interviews	▪ Senior researcher in Biomedicine and Coordinator of the Professional Postdoctoral Career Development Programme FIMMPOD at the research at the Institute for Molecular Medicine Finland, University of Helsinki
Maura Hiney Paris workshop	▪ Adjunct Professor, University College Dublin ▪ Former Head of International Cooperation, Evaluation, and Targeted programmes at the Health Research Board Ireland ▪ Chair of the ALLEA Permanent Working Group on Science and Ethics and Chair of Drafting Group for The European Code of Conduct for Research Integrity ▪ Vice-chair of ENRIO (2019-2022)
Megan Munsie Expert interviews	▪ Member of the Advisory Board of the HYBRIDA project ▪ Professor of Emerging Technologies (Stem Cells), Melbourne Medical School, University of Melbourne ▪ Deputy Director of the Centre for Stem Cell Systems, Anatomy and Neuroscience, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne ▪ Group Leader, Stem Cell Ethics and Policy, Murdoch Children's Research Institute as a part of the Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW) ▪ Head of at Stem Cells Australia ▪ President of the Executive Committee of the Australasian Society for Stem Cell Research

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	▪ Independent Non-Executive Director and Member of the Science and Ethics Committee of National Stem Cell Foundation of Australia ▪ Member of ISSCR Public Policy Committee, ISSCR Ethics Committee, and working group member of the task force to update the ISSCR Guidelines ▪ Member of the Committee on Ethics of Cell and Gene Therapy, International Society for Cellular Therapy ▪ Member of the Policy Committee, Science Technology Australia ▪ Partner of the EuroStemCell
Michaela Th. Mayrhofer Paris workshop	▪ Head of ELSI Services and Research at BBMRI-ERIC ▪ Coordinator for the Code of Conduct for Health Research initiative
Michael Barilan Expert interviews	▪ Member of the Advisory Board of the HYBRIDA project ▪ Professor at the Sackler Faculty of Medicine, Tel Aviv University
Miltos Ladikas Expert interviews	▪ Member of the Advisory Board of the HYBRIDA project ▪ Senior Researcher at the Institute of Technology Assessment and Systems Analysis, Karlsruhe Institute of Technology
Nick Meade Copenhagen workshop	▪ Director of Policy, Genetic Alliance UK ▪ Member of the NIHR Advanced Therapy Medicinal Product (ATMP) Group, National Institute for Health and Care Research ▪ Represents patients in different forums, including e.g., NHS England, the UK Rare Disease Forum, and the European Medicines Agency
Nina Stahl Paris workshop	▪ PhD candidate in public health with a focus on law and ethics, Department of Health, Ethics, and Society, Maastricht University
Signe Mežinska Paris workshop	▪ Associate Professor, Dr. sc. soc., MA, MS Bioethics, Faculty of Medicine, University of Latvia ▪ Senior Researcher, Institute of Clinical and Preventive Medicine, University of Latvia ▪ Rapporteur and member of the International Bioethics Committee, UNESCO ▪ Chair of the Research Ethics Committee for Life Sciences and Medicine, University of Latvia ▪ Member of Central Medical Ethics Committee of Latvia ▪ ELSI expert for BBMRI-ERIC

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Sina Bartfeld Expert interviews	▪ Professor at the Department of Medical Biotechnology, Technical University Berlin ▪ Head of Department at the Bartfeld Lab, at the department for Medical Biotechnology of the Technical University Berlin and the Institute for Molecular Infection Biology (IMIB) at the University of Würzburg
Thomas Lykke-Møller Sørensen Copenhagen workshop	▪ Associate Professor and group leader of the Organoid and Imaging Biotechnology research group at the Department of Biological and Chemical Engineering, Aarhus University
Vicky Mollaki Expert interviews	▪ 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

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Appendix B: Agenda, Co-creation Workshop Paris

Agenda

Expert workshop on operational guidelines for organoid research

Date: 19th of May from 13:00-17:30 PM
Venue: Salle 404, Bâtiment C, étage 4, Cassan Building, Sorbonne University, Paris
Meeting point: Tour Zamansky, the tallest building at the campus at 12:45 PM

12.40 - 12.50	**Arrival at Sorbonne University, Tour Zamansky Tower (Pierre and Marie Curie Campus)**
13.00 - 13.10	**Introduction to workshop by Senior researcher Mads P. Sørensen and Assistant professor, Tine Ravn, AU**
13.10 - 13.20	**Presentation of participants**
13.20 - 14:00	**Presentation of ethical framework by M.D. Dr. Hervé Chneiweiss, Inserm and presentation of version 1.0 of the operational guidelines, followed by a Q&A session regarding the guidelines by Dr. Jean-Luc Galzi, Inserm**
14:00 - 14:10	**Short break**
14.10 - 15.00	**First round of parallel group discussions on selected guideline topics, focus on either 1) the 'MIAOU' and 2) consent form**: a) coverage and quality, b) identification of concerns and "blind spots", c) development of concrete suggestions and recommendations for revisions and amendments, d) prioritised focus areas and action points to be taken into consideration in version 2.0 of the guidelines
15.00 - 15.30	**Coffee break**
15.30 - 15.45	**Group rapporteur relay short summary to the collective group**
15.45 - 16.05	**Plenum discussion on main focus areas and action points for version 2.0. on selected topics**
16.05 - 16.45	**Second round of parallel group discussions on selected guideline topics** (focus on evaluator checklist)
16.45 - 17.00	**Group rapporteur relay short summary to the collective group**
17.00 - 17.20	**Plenum discussion/summation of discussions**

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

17.20 - 17.30 Conclusion and evaluation

17.30 - 20.30 Drinks and Dinner at restaurant 'Le Buisson Ardent'

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

Appendix C: Agenda, Co-creation Workshop Copenhagen

Agenda

Expert Workshop on a Code of Responsible Conduct for Organoid Research

Date: 23th of June from 13:00-17:30 PM
Venue: Hotel Ottilia, Bryggernes Plads 7, 1799 Copenhagen

12.30 - 13.00	**Arrival at Hotel Ottilia**
13.00 - 13.10	**Introduction to workshop by Senior researcher Mads P. Sørensen and Assistant professor, Tine Ravn, AU**
13.10 - 13.20	**Presentation of participants**
13.20 - 14:00	**Presentation of ethical framework by M.D. Dr. Hervé Chneiweiss, Inserm and presentation of version 1.0 of the Code of Responsible Conduct, followed by a Q&A session regarding the Code by Dr. Jean-Luc Galzi, Inserm**
14:00 - 14:10	**Short break**
14.10 - 15.00	**First round of parallel group discussions on the Code of Responsible Conduct. Translation of principles into standards for organoid research**: a) coverage and quality b) identification of concerns c) development of concrete suggestions and recommendations for revisions and amendments d) prioritised focus areas and action points to be taken into consideration in version 2.0 of the Code of Conduct e) a potential add-on to the European Code of Conduct
15.00 - 15.30	**Coffee break**
15.30 - 15.45	**Group rapporteur relay short summary to the collective group**
15.45 - 16.05	**Plenum discussion on main focus areas and action points for version 2.0. of the Code**
16.05 - 16.45	**Second round of parallel group discussions on selected topics**: a) regulatory issues and gaps and b) ethical implications and challenges for responsible organoid research
16.45 - 17.00	**Group rapporteur relay short summary to the collective group**
17.00 - 17.20	**Plenum discussion/summation of discussions**
17.20 - 17.30	**Conclusion and evaluation**

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

18.30 - 22.30 Drinks and Dinner at restaurant 'Pure Madness' (Det Glade Vanvid)

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

Appendix D: Invitation, Co-Creation Workshop Paris

Invitation to expert workshop on organoid research

Dear x,

On behalf of the European Commission H2020 project HYBRIDA (Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies), we would like to invite you to participate in an expert co-creation and consultation workshop on the development of a Code of Responsible Conduct for researchers in the field of organoid research.

The workshop will take place on Thursday the **23th of June from 13:00-17:30 PM in Copenhagen at Hotel Ottilia** followed by a dinner for those who would like to join.

HYBRIDA runs from 2021-2024 and involves eight European partners, including The Danish Centre for Studies in Research and Research Policy (CFA) at Aarhus University, who together with the National Institute of Health and Medical Research (INSERM) in Paris and The Centre for Social Ethics and Policy (CSEP) at Manchester University will organise the workshop. 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 and enhancing existing guidelines, policies and ethics/normative frameworks pertaining to health and life science research.

To help ensure that the ethical and regulatory framework is 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. For this expert workshop, participants representing different research communities (incl. industry), research ethics committees (RECs), research integrity offices (RIOs), policy makers, legal experts, patient organisations and biobanks are invited to consult on and help further develop specific solutions and recommendations for producing a Code of Responsible Conduct for organoid researchers. The Code of Conduct will be the main focus of the workshop. In addition, pertinent regulatory needs and a potential add-on to the European Code of Conduct will be discussed.

In your capacity as X and considering your vast expertise within the field, we would greatly value your participation in the workshop. We will reimburse your travel costs, and we are happy to assist with travel bookings if required. HYBRIDA will also cover needed accommodation, and hotel rooms have been prebooked at Hotel Ottilia (https://www.brochner-hotels.com/hotel-ottilia/)

We would be very grateful, if you could indicate whether you would be able to participate in the expert workshop before the 29th of April. If you wish to participate in the workshop, we will send you a detailed letter of information regarding the workshop.

If you have any questions concerning the project and/or details of the workshop, please contact Tine Ravn, assistant professor at Aarhus University, tr@ps.au.dk, Mobile: +45 8782009.

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

Kind regards
Assistant professor, PhD Tine Ravn and Senior researcher, PhD Mads P. Sørensen, Danish Centre for Studies in Research and Research Policy, Aarhus University, Denmark.

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

Appendix E: Invitation, Co-creation Workshop Copenhagen

Invitation to expert workshop on organoid research

Dear x,

On behalf of the European Commission H2020 project HYBRIDA (Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies), we would like to invite you to participate in an expert co-creation and consultation workshop on the development of a Code of Responsible Conduct for researchers in the field of organoid research.

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If you have any questions concerning the project and/or details of the workshop, please contact Tine Ravn, assistant professor at Aarhus University, tr@ps.au.dk, Mobile: +45 8782009.

Kind regards

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

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

Appendix F: Information Letter, Co-creation Workshop Paris

Letter of information to Experts about the HYBRIDA Project and the Workshop on Operational Guidelines

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.

Organoids

As many of you may very well know, an organoid is an organized cluster of cells generated in vitro (i.e., outside the body in artificial conditions) from different kinds of stem cells. Such entities might serve as "three- dimensional culture models" mimicking the structural and functional properties of different organs, such as the retina, heart, brain, intestine, kidney, pancreas, liver, inner ear and skin.

Human organoids provide unique opportunities for studying both the normal and pathological functioning of organs and human development. Much of what is known about embryonic development and how organ function are knowledge acquired through animal models. However, tissue and organ biology are very difficult to examine through animal models and some biological processes specific to the human body cannot be modelled in animals.

Human organoids have many benefits and advantages compared to existing research models such as animal models, as they can be made from human cells and represent the physiology of humans, making researchers able to study the disease of a single patient. Human organoids also "provide faster and more robust outcomes, are more readily accessible and provide both a more accurate representation of human tissue and a larger quantity of material to work with than animals models do" (Kim, Koo and Knoblich, 2020, p. 579). Some of the challenges that pertain to organoid research are the difficulties related to reproducing organoids and standardize research protocols for generating organoids. In addition, organoids are not as complex as their real counterparts and it is very difficult to study them as whole organs.

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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:

1. 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?

2. 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.

3. 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:

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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).

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

The Aim of the Expert Workshop

While organoid research can be seen as an emerging research field that is still in its early phase, the derivation and use of organoids already raise a number of complex novel as well as familiar ethical questions regarding their current use and their potential application in the future. Organoid researchers have for instance pointed out that,

Organoids should not be seen as a morally neutral alternative. They are grown from cells and tissues obtained from human individuals, and establishing the moral and legal status of human organoids requires ethical discussion and empirical research, particularly for sensitive cases such as brain organoids. The storage and use of organoids in so-called living biobanks raise ethical and governance challenges - for example, questions about the type of donor consent and ethics review needed for long- term storage and use and for feedback of clinically relevant findings to the patient.

Bredenoord et al. 2017, p. 1

By including participants representing different research communities (incl. industry), research ethics committees (RECs), research integrity offices (RIOs), policy makers, legal experts, patient organisations and biobanks in the development of an ethics framework, HYBRIDA will be supported in its efforts to clarify ethical issues related to organoid research and organoid-related technologies as well as identify ethical "blind spots" of current practices. This will help the project to describe known as well as hitherto unrecognized ethical challenges and start developing possible ways to address them. In this way, the project might also help build trust in research institutions and health authorities when it comes to organoid research and the production of organoid-related technologies.

Hybrida applies a three-stage engagement process (1. Exploration of public attitudes, b. co- creation/consultation, and 3 validation) dedicated to involving a wide range of stakeholders and experts throughout the process of developing, designing, producing and validating the four main products in the ethical framework (no. A-D, see above). The expert workshop in Paris is one of two expert workshops in the consultation phase of the project. The workshop in Paris will focus on the set of operational guidelines for organoid research (no. A) and they will address:

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1. Concern assessment of biological material of origin (including donors' informed consent)
2. Efficiency/reproducibility
3. Quality output (size, morphogenesis, cellular composition)
4. Reliability
5. Reducing miscommunication (precise and documented description of materials and methods)
6. Failure to comply with safety, security, RI
7. Research misconduct.

The guidelines aim to aid researchers to uphold the highest standards of RE&RI, while also providing RECs and RIOs, among others, with issues of attention for assessing research performance and addressing field-specific challenges.

Experts in the workshop will be provided with a draft version 1.0 of the operational guidelines prior to the workshop. A main question in the workshop will be to which extent the proposed standards in the 1st version of the operational guidelines are in alignment with the required needs, developments, and conceptualisations within the field of organoid research (please see separately attached workshop agenda). The workshop will focus on discussing standards of conduct and good practices, and assess the coverage and quality of the preliminary set of guidelines. Concerns and lacunas will be considered and suggestions and recommendations for prioritized revisions and amendments will be applied as a basis for developing and refining a version 2.0 of the guidelines.

Date and Venue:

The workshop will take place the 19th of May from 13:00-17:30 PM in Paris at the Sorbonne University.

The address is: L'Auditorium IBPS, Bâtiment C, étage 4, Cassan Building, Sorbonne Université, Campus Pierre et Marie Curie, 7 Quai Saint Bernard 75005, Paris, France.

For participants available to join, dinner will take place at the restaurant 'Le Buisson Ardent', conveniently located close to the workshop venue at Sorbonne University: Carte et Menus 2022 - Le Buisson Ardent à Paris (75005) - TheFork (LaFourchette). Drinks and early dinner will take place in direct continuation of the workshop programme.

Travel and Accommodation

HYBRIDA will be able to reimburse travel expenses to and from the workshop and cover expenses for accommodation (one night). Head of secretariat Jane Irming **jfi@ps.au.dk** at Aarhus University will be happy to assist with any travel arrangements and bookings needed. If participants prefer to book on their own, Jane will subsequently assist with the reimbursement. Please remember to document expenses. As

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

the project is publicly funded, we kindly ask to choose the most economic travel connections (within reason), and book a hotel room within a reasonable price limit. We encourage participants to book via AU or on their own as soon as possible.

Personal Data Protection

Personal data collection, storage and use of the data collected during the expert workshop 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. A consent form will be send prior to the workshop for orientation and may be signed ahead of or at the workshop. If participants consent to take part in the project and the workshop, the personal information provided during the workshop 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 workshop will be audio recorded. The findings from the workshop will be analysed by researchers in HYBRIDA and reported as part of the project deliverables to the EU Commission. Participants attend the workshop in their position as expert representatives within their field and will not appear anonymous. However, the reporting of findings will focus on the data level rather than on an individual expert level. Audio recordings, detailed workshop summaries and notes will only be accessible to members of the project team and handled with confidentiality.

Materials Provided Ahead of the Expert Workshop

Two weeks prior to the workshop, participants can expect to receive:

- A first draft version of the operational guidelines
- An informed consent form
- A detailed and final program for the workshop

We very much look forward to discussing operational guidelines for organoid research in Paris.

If you have any questions concerning the project and/or the details of the workshop, please contact Tine Ravn, assistant professor at Aarhus University, tr@ps.au.dk, Mobile: +45 8782009.

Kind regards

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

Assistant professor, 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).

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Appendix G: Information Letter, Co-creation Workshop Copenhagen

Letter of information to Experts about the HYBRIDA Project and the Workshop on A Code of Responsible Conduct

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.

Organoids

As many of you may very well know, an organoid is an organized cluster of cells generated in vitro (i.e., outside the body in artificial conditions) from different kinds of stem cells. Such entities might serve as "three- dimensional culture models" mimicking the structural and functional properties of different organs, such as the retina, heart, brain, intestine, kidney, pancreas, liver, inner ear and skin.

Human organoids provide unique opportunities for studying both the normal and pathological functioning of organs and human development. Much of what is known about embryonic development and how organ function are knowledge acquired through animal models. However, tissue and organ biology are very difficult to examine through animal models and some biological processes specific to the human body cannot be modelled in animals.

Human organoids have many benefits and advantages compared to existing research models such as animal models, as they can be made from human cells and represent the physiology of humans, making researchers able to study the disease of a single patient. Human organoids also "provide faster and more robust outcomes, are more readily accessible and provide both a more accurate representation of human tissue and a larger quantity of material to work with than animals models do" (Kim, Koo and Knoblich, 2020, p. 579). Some of the challenges that pertain to organoid research are the difficulties related to reproducing organoids and standardize research protocols for generating organoids. In addition, organoids are not as complex as their real counterparts and it is very difficult to study them as whole organs.

Creating an Ethical Framework for Organoid Research

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

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:

1. 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?

2. 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.

3. 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:

A. Operational guidelines for the field
B. A code of responsible conduct (CoC) for researchers (in academia and industry)

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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).

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

The Aim of the Expert Workshop

While organoid research can be seen as an emerging research field that is still in its early phase, the derivation and use of organoids already raise a number of complex novel as well as familiar ethical questions regarding their current use and their potential application in the future. Organoid researchers have for instance pointed out that,

> *Organoids should not be seen as a morally neutral alternative. They are grown from cells and tissues obtained from human individuals, and establishing the moral and legal status of human organoids requires ethical discussion and empirical research, particularly for sensitive cases such as brain organoids. The storage and use of organoids in so-called living biobanks raise ethical and governance challenges - for example, questions about the type of donor consent and ethics review needed for long- term storage and use and for feedback of clinically relevant findings to the patient.*
>
> Bredenoord et al. 2017, p. 1

By including participants representing different research communities (incl. industry), research ethics committees (RECs), research integrity offices (RIOs), policy makers, legal experts, patient organisations and biobanks in the development of an ethics framework, HYBRIDA will be supported in its efforts to clarify ethical issues related to organoid research and organoid-related technologies as well as identify ethical "blind spots" of current practices. This will help the project to describe known as well as hitherto unrecognized ethical challenges and start developing possible ways to address them. In this way, the project might also help build trust in research institutions and health authorities when it comes to organoid research and the production of organoid-related technologies.

Hybrida applies a three-stage engagement process (1. Exploration of public attitudes, b. co- creation/consultation, and 3 validation) dedicated to involving a wide range of stakeholders and experts throughout the process of developing, designing, producing and validating the four main products in the ethical framework (no. A-D, see above). The expert workshop in Copenhagen is one of two expert workshops in the consultation phase of the project. The workshop in Copenhagen will primarily focus on the Code of Responsible Conduct for organoid researchers within academia and industry (no. B)

The Code of Conduct will be drafted having as a basis the four main principles of the European Code of Conduct (ECoC): Accountability, Honesty, Reliability and Respect. The Code will not only relate to personal and

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team conduct but also to society. Context wise, it will include guidelines to support transparency and benefits sharing, and the Code will list these demands and will address the requirements and duties of scientists, research organizations, industries, regulatory instances and States.

Experts in the workshop will be provided with a draft version 1.0 of the Code of Conduct prior to the workshop. A main question in the workshop will be to which extent the proposed standards in the 1st version of the Code is in alignment with the required needs, developments, and conceptualisations within the field of organoid research (please see separately attached workshop agenda). The discussions in the workshop will focus on the coverage and quality of the Code of Conduct version 1.0. Moreover, concerns and existing lacunas and suggestions and recommendations for prioritized revisions and amendments will be discussed and applied as a basis for developing and refining a version 2.0 of the Code. This work will be led by the French National Institute for Health and Medical Research (INSERM). In the workshop, a potential supplement to the European Code of Conduct for Research Integrity (ECoC) will also be discussed.

The Code of Conduct is part of an overall ethical and regulatory framework which also includes contributions to existing ethics and normative frameworks (no. C). This work, led by The Centre for Social Ethics and Policy (CSEP) at Manchester University will primarily focus on identifying gaps in existing ethics and normative frameworks and develop specific proposals for addressing these gaps. Such gaps could be in relation to informed consent, property rights and user rights within the context of organoids and the use and storage of organoids as an institutional practice. One of the parallel discussions for some participants will be to receive feedback on their identification of regulatory gaps and issues, for instance areas of activities that are currently unregulated or under/over-regulated.

Date and Venue:

The workshop will take place the 23th of June from 13:00-17:30 PM in Copenhagen at Hotel Ottilia https://www.brochner-hotels.dk/hotel-ottilia/

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

For participants available to join, dinner will take place at restaurant 'Pure Madness' (Det Glade Vanvid) from 18:30-22:30 PM. The restaurant is located in the city centre at Læderstræde 3, 1201 Copenhagen K and in walking distance from the hotel. The restaurant can also easily be reached by taxa or the metro line.

Travel and Accommodation

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

HYBRIDA will be able to reimburse travel expenses to and from the workshop and cover expenses for accommodation. Hotel rooms have been pre-booked at Hotel Ottilia and will be reserved to participants staying over-night. Head of secretariat Jane Irming **jfi@ps.au.dk** at Aarhus University will be happy to assist with any travel arrangements and bookings needed. If participants prefer to book their own travelling, Jane 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 AU or on their own as soon as possible.

Personal Data Protection

Personal data collection, storage and use of the data collected during the expert workshop 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. A consent form will be send prior to the workshop for orientation and may be signed ahead of or at the workshop. If participants consent to take part in the project and the workshop, the personal information provided during the workshop will be processed based on Article 6(1)(e) of the General Data Protection Regulation.

As a basis for analysing the comments and recommendations provided by participants, the workshop will be audio recorded. The findings from the workshop will be analysed by researchers in HYBRIDA and reported as part of the project deliverables to the EU Commission. Participants attend the workshop in their position as expert representatives within their field and will not appear anonymous. However, the reporting of findings will focus on the data level rather than on an individual expert level. Audio recordings, detailed workshop summaries and notes will only be accessible to members of the project team and handled with confidentiality.

Materials Provided Ahead of the Expert Workshop

Two weeks prior to the workshop, participants can expect to receive:

- A first draft version of the Code of Responsible Conduct
- An informed consent form
- A detailed and final program for the workshop

We very much look forward to discussing a Code of Conduct for organoid research in Copenhagen.

If you have any questions concerning the project and/or the details of the workshop, please contact Tine Ravn, assistant professor at Aarhus University, tr@ps.au.dk, Mobile: +45 28782009.

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

Kind regards

Assistant professor, 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 and Dr Jonathan Lewis, Centre for Social Ethics and Policy (CSEP), Manchester University

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Appendix H: Informed Consent, Co-creation Workshop Paris

Consent Form

Informed consent form for participation in HYBRIDA's co-creation workshop at Sorbonne, Paris, 19th of May 2022.

Short introduction to organoids and HYBRIDA

HYBRIDA works to create a regulatory framework for research and technology related to organoids, with particular focus on ethical issues. Among other things, the framework will consist of guidelines for how to conduct research within this area and a code of conduct for researchers in academia and industry.

The aim of the co-creation workshop

The expert workshop in Paris is one of two expert workshops in the consultation phase of the HYBRIDA project. The workshop in Paris will focus on operational guidelines for organoid research and will address:

1. Concern assessment of biological material of origin (including donors' informed consent)
2. Efficiency/reproducibility
3. Quality output (size, morphogenesis, cellular composition)
4. Reliability
5. Reducing miscommunication (precise and documented description of materials and methods)
6. Failure to comply with safety, security, RI
7. Research misconduct.

The guidelines aim to aid researchers to uphold the highest standards of RE&RI, while also providing RECs and RIOs, among others, with issues of attention for assessing research performance and addressing field-specific challenges.

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 expert workshop will be in

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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 If participants consent to take part in the project and the workshop – by signing this document – information, incl. personal information, provided during the workshop 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 workshop will be audio recorded. The findings from the workshop will be analysed by researchers in HYBRIDA and reported as part of the project deliverables to the EU Commission. Participants attend the workshop in their position as expert representatives within their field and will not appear anonymous in published material. However, audio recordings, detailed workshop summaries and notes 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 workshop with regard to human dignity and integrity, or privacy of persons.

Supervision

Research coordinator Mads P. Sørensen (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).

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 it is not possible to grant full anonymity.
- I give consent to the audio recordings of the workshop.
- I want to participate in the study.

Date and Participant's signature	Date and Project contact's signature

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

Name in Block letters

Name in Block letters

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Appendix I: Informed Consent, Co-creation Workshop Copenhagen

Consent Form

Informed consent form for participation in HYBRIDA's expert workshop at Hotel Ottilia, Copenhagen, 23rd of June 2022.

Short introduction to organoids and HYBRIDA

HYBRIDA aims to create a regulatory framework for research and technology related to organoids, with a particular focus on ethical issues. Among other elements, the framework will consist of guidelines for how to conduct research within this area and a code of conduct for researchers in academia and industry.

The aim of the co-creation workshop

The expert workshop in Copenhagen is one of two expert workshops in the consultation phase of the HYBRIDA project. The workshop in Copenhagen will primarily focus on the Code of Responsible Conduct for organoid researchers within academia and industry. The Code of Conduct will be drafted having as a basis the four main principles of the European Code of Conduct (ECoC): Accountability, Honesty, Reliability and Respect. The Code will not only relate to personal and team conduct but also to society. Context wise, it will include guidelines to support transparency and benefits sharing, and the Code will list these demands and will address the requirements and duties of scientists, research organizations, industries, regulatory instances and States.

Funding

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Use of data and dissemination of findings

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expert representatives within their field and will not appear anonymous in published material. However, audio recordings, detailed workshop summaries and notes will only be accessible to members of the projectteam and handled with confidentiality.

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

Supervision

Research coordinator Mads P. Sørensen (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).

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

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- 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 it is not possible to grant full anonymity.
- I give consent to the audio recordings of the workshop.
- I want to participate in the study.

Date and Participant's signature	Date and Project contact's signature
Name in Block letters	Name in Block letters

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

Appendix J: Interview Guide, Expert Interviews

Interview Guide, Expert Interview, WP4

Introduction

- Short presentation/recap of interview objectives (HYBRIDA product status and process)
- Information about recording/handling of interview material (remember to record!)
- Information about lack of anonymity
- Informed consent

Research Background & field of research

1. Could you please start by telling me about your areas of research and expertise?

Probes:

- Particular focus areas (biomedicine, RE/RI, technology assessment, legal aspects etc.)
- Relation to organoid research or related technologies (stem cell research, Organs-on-chip)
- Introduction to the organoid field and research developments

Prospects and advantages of organoid research and related technologies

2. In your view what are the main advantages of organoid technologies?

Probes:

- Currently (basic research, biobanking, disease modelling, precision medicine etc.)
- In the future – (most promising clinical application of organoids or related technologies such as organs-on-chip - instances where the technologies themselves is used directly in clinical management, and not e.g. drugs developed through use of organoid technology) – bioartificial organs, body-on-chip, eradication of animal models etc.
- Field specific advantages

Prominent ethical and legal issues – field specific

3. From the perspective of your own work and expertise within the field, what do you consider to be the main ethical/legal issues concerning organoids?

Probes:

- Currently (biobanking, regulation and oversight, informed consent, breach of privacy, commodification, and property)
- - In the future (artificial organ development, chimeras/animal hosts, particular sensitive organoids such as cerebral or gonad organoids, embryonic models and assembloids
- - Compared to stem cell research/related technologies such as OOC (the latter, false therapeutic expectations)

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4. How are these ethical/legal issues and challenges addressed within your field of research?

Probes:
- Main barriers/knowledge gaps
- Main enablers/institutional structures, practices, legislation

5. In your view, what can be done to further address these issues?

Probes:
- Within your field/related fields/institutional, national, international level

If relevant: Some commentators have pointed out that precision medicine challenges evidence medicine as it becomes difficult to use e.g. randomized controlled trials when the number of patients with the same condition is low. Against this background, do you think the use of organoid models or organs-on-chip models for personalized medicine/precision medicine imply a change in evidence standards? If so, what kind of standards should in your opinion be required for drug/therapy approval or even drug reimbursement?

In the process of developing operational guidelines for the field, a code of responsible conduct and a regulatory framework, HYBRIDA project partners have identified a number of particular areas in organoid research and some open questions for further analysis, which I would like to discuss with you. The first aspect concerns the issue of informed consent...

Informed consent procedures and ethical oversight
It has proven rather complex to define the best strategy to obtain a genuine informed consent representing the best interest of the donor of cells and tissues and the researchers in terms of them being able to re-use biological samples ('unknown future research uses and risks')

6. In your view, what do you consider to be the most important aspects to consider when choosing the best model of informed consent?

7. Which model would you recommend? Why? (specific/broad (blanket)/dynamic/entrusted to a third party)

8. Another issue related to informed consent concerns the right for donors to withdraw their consent. Currently, withdrawal extend to donated cells and tissues and not to generated organoids. One could argue that donors have a moral and legal claim to their organoids but at the same time organoid researchers have pointed out that this would be very difficult to implement in terms of feasibility

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In your view, what approach would you consider to be most optimal for withdrawal of consent? Why? (Instances where it should not be possible to withdraw – e.g. after transformation of cells)

The HYBRIDA project has shown that some types of organoids are likely to raise particular ethical concerns due to their moral status, for instance cerebral organoids and embryoids.

Sensitive technologies

9. What is your view on cerebral organoids in terms of granting them special ethical or legal concern?

Probes:

- Particular current/future concerns? (Sentience, pain, consciousness – questions of ownership and normative status, complex neural assembloids, human–animal chimaeras etc.)

The International Society for Stem Cell Research has recommended a continued ethical awareness as cerebral organoids develop in complexity.

10. How would you recommend to practice such a continuous awareness? Are particular measures warranted?

Probes:

- Legal measures, ethical oversight, particular responsibilities, technology assessment, ethics by design approach.

11. What do you see as the main legal issues concerning embryonic models?
(non-integrated stem cell-based embryo models (gastruloids) vs. integrated models (blastoids)

Probes:

- Lack of EC regulatory definition of a human embryo, lack of 14-day rule, nomenclature, 'synthetic embryos', moral status

12. How can these issues best be addressed?

Expectations and scientific dissemination

13. It is difficult to assess precisely the many prospects of emerging technologies. Like many other fields, organoids and organ-on-a-chip is nonetheless sometimes accused of benefitting from a “hype” phenomenon, where overblown promises are employed by researchers in the media or research proposals to create expectations and support.
What is your view on potential hype within the organoid field of research?

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How best to address the hype issue? Should hype be regulated and how (for instance in guidelines)?"

Probes:

- Positive influences? Negative influences? public dialogue, communication, public trust, RFOs, regulation needed, marketing of untested treatments etc.

Other issues and debriefing

Before we finish – is there anything else you think we need to cover?

Next steps and sending of report

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

Appendix K: Invitation Advisory Board, Expert Interviews

Dear Professor x,

In your capacity as advisory board member in the HYBRIDA project (Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies) and as a renowned expert within the field of bioethics and X, we take the liberty to contact you to ask whether you will be able to participate in a short online interview concerning organoid technologies.

The interview will last approximately 30 minutes and take place online via Microsoft Teams and, if possible, within the first three weeks of November. You will be interviewed by assistant professor Tine Ravn from Aarhus University and on behalf of project partners from the National Institute of Health and Medical Research (INSERM) in Paris and Centre for Medical Research at University of Oslo.

The interview will focus on current and emerging ethical and legal issues on organoid research from the perspective of your own work and expertise within the field.

As you know, 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 and enhancing existing guidelines, policies and ethics/normative frameworks pertaining to health and life science research.

To help ensure that the ethical and regulatory framework 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. To date, three cross-country public deliberations on attitudes and expectations towards organoid research have been conducted. Moreover, two co-creation expert workshops have been carried out with representatives from different research communities (incl. industry), research ethics committees, research integrity offices, policy makers, legal experts, patient organisations and biobanks with the purpose to further develop specific solutions and recommendations for producing a set of operational guidelines for the field and a Code of Responsible Conduct for organoid researchers.

For the next phase of further developing these guidelines, we wish to conduct interviews with key experts, among here hopefully all members of the HYBRIDA advisory board to further explore existing knowledge gaps, for instance in terms of sensitive organoid technologies and informed consent procedures.

In consideration of your vast expertise within the field, we would greatly value your participation. If you are available for an interview, you are very welcome to respond to this email to arrange the interview appointment.

If you have any questions concerning the interview, please contact me or Tine Ravn (tr@ps.au.dk).

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

Kind regards

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

On behalf of
Assistant professor Tine Ravn and Senior researcher Mads P. Sørensen, Danish Centre for Studies in Research and Research Policy, Aarhus University

Research director Hervé Chneiweiss and Postdoc Ioana Andreescu, French National Institute for Health and Medical Research (INSERM)

Professor Søren Holm, Associate professor Henrik Vogt and Postdoc Maxence Gaillard, Centre for Medical Research at University of Oslo.

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

Appendix L: Invitation External Experts, Expert Interviews

Dear Professor/Dr. X,

As part of the EU funded project HYBRIDA (Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies, 2021-24), we conduct an interview study with leading experts within the field of organoid research and organoid-related technologies.

A key objective in HYBRIDA is to develop a comprehensive regulatory and ethics framework for organoid 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.

As a renowned expert within the field of X, we (hope to be able to draw on your expertise once again and) take the liberty to invite you to participate in a short online interview concerning organoid technologies. The interview will focus on current and emerging ethical and legal issues on organoid research from the perspective of your own work and expertise within the field.

The interview will last approximately 30 minutes and take place online via Microsoft Teams and, if possible, within the first three weeks of November. If you agree to participate, you will be interviewed by assistant professor Tine Ravn from Aarhus University.

In consideration of your vast expertise within the field, we would greatly value your participation. If you are available for an interview, you are very welcome to respond to this email to arrange the interview appointment.

If you have any questions concerning the interview, please contact me or Tine Ravn (tr@ps.au.dk).

Kind regards

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

On behalf of
Assistant professor Tine Ravn and Senior researcher Mads P. Sørensen, Danish Centre for Studies in Research and Research Policy, Aarhus University

Research director Hervé Chneiweiss and Postdoc Ioana Andreescu, French National Institute for Health and Medical Research (INSERM)

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Professor Søren Holm, Associate professor Henrik Vogt and Postdoc Maxence Gaillard, Centre for Medical Research at University of Oslo.

Appendix M: Informed Consent, Expert Interviews

Informed Consent Form

Participation in expert interview study as part of the HYBRIDA Project (Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies), November 2022

Short introduction to organoids and HYBRIDA

A key objective in HYBRIDA is to develop a comprehensive regulatory and ethics framework for organoid 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.

The aim of the expert interview study

To help ensure that the ethical and regulatory framework 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. To date, three cross-country public deliberations on attitudes and expectations towards organoid research have been conducted. Moreover, two co-creation expert workshops have been carried out with a broad range of stakeholders with the purpose to further develop specific solutions and recommendations for producing a set of operational guidelines for the field and a Code of Responsible Conduct for organoid researchers.

The interview with you is part of the next phase of developing an ethical and regulatory framework for organoid research, supplementing the other stakeholder activities by further exploring existing knowledge gaps, for instance in terms of sensitive organoid technologies and informed consent procedures.

The interview will focus on current and emerging ethical and legal issues on organoid research from the perspective of each expert and their expertise within the field.

Funding

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Use of data and dissemination of findings

Personal data collection, storage and use of the data collected during the expert interview 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 If interviewees consent to take part in the project and the interview study – 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.

The interviews will be recorded. The findings from the interviews will be analysed by researchers in HYBRIDA and reported as part of the project deliverables to the EU Commission. Interviewees will not appear anonymous in published material. However, recordings, interview transcripts and notes 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 interview study with regard to human dignity and integrity, or privacy of persons.

Supervision

Assistant Professor Tine Ravn (tr@ps.au.dk) welcomes any questions about the interview.

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 Tine Ravn (tr@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 interview. 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 interview 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 it is not possible to grant full anonymity.
- I give consent to the recordings of the interview.
- I want to participate in the interview.

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Date and Participant's signature

Name in Block letters

Date and Project contact's signature

Name in Block letters

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