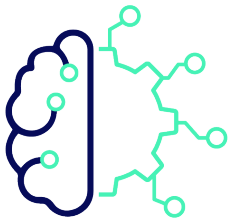

HYBRIDA

D4.2: Report on Participant Selection and Procedures and Criteria for Recruitment

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HYBRIDA

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

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1. Introduction: About HYBRIDA

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

Organoid research comes with ambitious promises of revolutionizing 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 takes place[1].

An organoid is an organized 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.

Following Roman times, all entities have been categorized and regulated either as persons or as things (subjects or objects). Organoids, however, are entities, and organoid research and organoid-related technologies are examples of disruptive research and innovation that 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 categorized as either persons or things? What *are* they? How do we *know* the characteristics of these entities called organoids?

Second, ***epistemological and methodological uncertainty***: How do we address forms of uncertainty that cannot be evaluated through the use of statistical methods, i.e. risk assessment? This is particularly pertinent

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

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where organoids are intended for personalized or precision medicine, where the number of research subjects with a certain characteristic is too low for randomized 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 categorized 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, in contrast 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 (HTA).

Third, ***regulatory uncertainty*****:** This uncertainty emerges because parts of the 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.

1.1 About this deliverable

This deliverable details matters related to participant selection and criteria for recruitment in the studies included in work package 4 in the HYBRIDA project. In this regard, this deliverable/protocol focuses particularly on the sampling and recruitment strategies employed. The complete research design, including methods details, analytical strategy, practical planning issues etc. have been addressed in the main protocol ("Deliverable 4.1. Protocol for WP4"). Parts of the design descriptions, including the particular methods and formats applied, will also be reported in this report to provide a methodological background for the sample criteria and recruitment process in order for this report to be read independently from the main research protocol.

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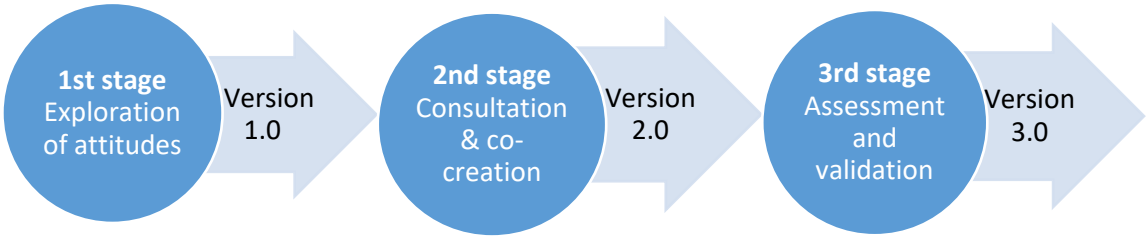
WP4 is dedicated to the engagement and co-creation activities carried out within the framework of the project. It aims to promote effective and inclusive "up-stream" citizen and stakeholder engagement that will include a large number of different stakeholders throughout the process of developing, designing and producing the four main project products: a) operational guidelines for the field, 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). Hence, relevant stakeholders will be included throughout the research process, i.e. from mapping stakeholder concerns across different social contexts and societal groups, to a final validation to ensure that the normative documents produced meet the actual needs and concerns of citizens, patients, the scientific community, among other key stakeholders.

WP4 is divided into three different tasks representing three stages in the engagement process (figure 1); 1) the first stage will explore public attitudes towards organoids through three deliberative workshops. 2) In the second stage, a large number of stakeholders will be involved in a consultation and co-creation process, through which a first draft of the four main products will be co-produced. Two co-creation workshops including 15-20 participants in each workshop and 15 individual expert interviews will be conducted at this stage. 3) At the third and final stage, expert and professional stakeholder groups will contribute to the assessment and validation of a second draft of the four products through the use of six focus group sessions. The three steps and the related sampling- and recruitment strategies will be described separately in the following sections.

Figure 1. Three stages in the engagement process and development of HYBRIDA's products.



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2. Sampling and Recruitment Procedures for Deliberative Workshops/mini-publics

The following section outlines the nature and application of deliberative workshops and describes our approach to participant selection and recruitment in the first stage of the engagement process.

2.1. Exploration of public and stakeholder attitudes towards organoids through deliberative workshops

Three deliberative (mini-public) workshops with 15-20 participants in each will be carried out in Denmark, Italy and Greece, with the purpose of understanding the attitudes of publics, patients, donors and CSOs towards organoid research.

Deliberative (mini-public) workshops are defined as referring to "dialogue events where the focus is on having informed discussions on a complex or controversial issue to gather social intelligence to inform policy, anticipate regulation, exchange opinion or raise awareness" (The Danish Board of Technology, 2014). As with the focus group method, deliberative workshops constitute facilitated in-depth and informed discussions, but contrary to focus group interviews, deliberative workshops place significant emphasis on elements of deliberation, a critical examination of evidence, consideration of experiential knowledge and a fostering of both convergent and divergent views to elicit statements on the particular issue discussed (The Danish Board of Technology, 2014; O'Brien et al. 2020). Furthermore, as a public engagement method, deliberative workshops may additionally be "leveraged to further engage those affected by the research in the knowledge-translation and decision-making phases of the research" (O'Brien et al. 2020, p. 265).

The aim of the deliberative workshop approach is compatible with the characteristics of the method as outlined above and the project's objective to explore and understand public opinion (i.e. worries, concerns, fears, uncertainty and expectations) as well as give voice to citizens, vulnerable groups, patients, donors

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and CSOs to explore societal values and attitudes towards organoids. In addition to understanding attitudes towards organoids, the deliberative workshops will assist with generating a comprehensive and co-produced understanding of the implications of organoid research that will add to the establishment of an ethics framework for organoid research and organoid related technologies. Hence, the three deliberative workshops will provide valuable insights into public and stakeholder concerns and potentially conflicting beliefs and provide a key foundation for the development of the four project outputs, including operational guidelines and an ethics framework.

There is no consensus as to how restrictive or expansive the definition of the design of a mini-public should be. However, often the mechanisms of deliberative polls, citizens' assemblies, citizen juries, planning cells and consensus conferences are included as types of mini-publics (Smith and Ryan, 2012). Despite differences in design, the 'minipopulus' concept, innovated by Robert Dahl in the late 1980s, aims to describe "an assembly of citizens, demographically representative of the larger population, brought together to learn and deliberate on a topic in order to inform public opinion and decision-making" (Escobar and Elstub, 2017, p. 1). Such microcosms of the public are often assembled through stratified random sampling to obtain statistical representation, albeit for smaller mini-publics, and due to the small scale the aim is more often to secure demographical diversity.

In addition, common features include facilitated discussion based on the provision of expert information and close examination of issue positions. Often a five stage process is applied that includes the following stages; planning/recruitment, learning, deliberation, decision-making, follow up (Escobar and Elstub, 2017). While deliberative workshops include these elements to varying degrees, the design allows for greater flexibility in terms of duration, activities, and selection method, even though the latter is being debated and a broader approach to representation and diversity in mini-publics has been suggested (Steel et al. 2020). For the particular design of this HYBRIDA task, the 'deliberative workshop' designation will primarily be applied, but elements from the mini-public format are to a great extent integrated in the design.

2.1.1 Format and setting

The three deliberative workshops will take place as a one-day weekend workshop at a centrally located conference facility (9 hours including a long lunch, coffee breaks and dinner). The workshops will start at 11am to allow time for arrival and will end with a two-hour dinner at 18pm for the participants who would

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like to stay. Each workshop will be facilitated by a professional moderator and expert in deliberation methods and it will be conducted in the respective national language. Project researchers in each of the three countries will be present to assist with group facilitation and provide answers and clarifications. One week prior to the workshop, participants will receive a small information package with lay summaries which include a balanced collection of the evidence and views to be reviewed. The evidence will primarily be drawn from the mapping and review findings from WP1-3 in HYBRIDA. The workshops will include a small questionnaire at the start and the end to survey attitudes, and changes in attitudes, towards organoid research.

The workshops will also bring in a number of expert presentations and allot time for participants to ask questions to the experts as well as questions related to the information package. The deliberation will consist of individual reflections, small group discussions with the inclusion of supporting materials, as well as plenary discussions (for details, see full protocol, D.4.1). Group prioritizations, feedback and suggestions for recommendations will feature as elements in the deliberation, but the primary aim of the deliberative workshops is to elicit a diverse set of attitudes and perspectives and not to reach a consensus or fixed decisions.

2.2 Stakeholder and participants: Selection criteria and sampling strategy

In accordance with the objectives to a) elicit a range of perspectives in terms of participant values and attitudes, and partly b) co-create recommendations, the conceptualisation of representation and diversity are different from the mini-public's third goal of seeking "to approximate the counterfactual public will" through statistical representation. Instead, a purposive design or the use of hybrid recruitment strategies may prove more productive for objective a and b, as greater importance are attached to exploring a diverse set of perspectives as a cross-section of relevant views that are not necessarily an approximation to their population distribution. Hence, in some cases it is reasonable to oversample particular individuals or groups with particular lived experiences, knowledge or representation relevant for the topic of deliberation (Steel et al. 2020).

A purposive or purposeful sampling refers to "selecting *information-rich cases* for in-depth study" (Patton, 2015, 265, emphasis in original) and which can provide deep insight into the topic and the research question(s) posed. In the case of exploring worries, fears and expectations with regard to understandings of

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organoids and implications of organoid research, a diverse set of non-professional actors and stakeholders will be included that not only represent the lay public, but also vulnerable groups, patients, donors, and civil society organisations which possess a set of experience, interest and knowledge particularly relevant for the topic.

2.2.1 Selection criteria and sampling strategy

In particular, a purposeful maximum-variation strategy will be applied to secure diversity in representation and potentially identify common patterns across the diverse groups (Palinkas et al., 2015; Patton, 2015, p. 267). Hence, in relation to the workshop objectives mentioned above, a criteria for assembling the deliberative workshops is both to invite citizens with potentially no knowledge of organoid research as well as key non-professional actors (or enclave groups) representing a minor fraction of the public, who have particular experiences and/or interests in organoid research. For the purpose of exploring a range of attitudes for a particular topic such as organoid research, multiple personal and non-personal experiences and levels of familiarity with the topic are seen as valuable for exploring perceptions, hopes and concerns related to both conceptual (related to conceptual uncertainty) and tangible RI/RE matters such as ownership and informed consent (related to regulatory uncertainty).

For workshop participants, the following non-professional stakeholder will be represented to include intended variation in attitudes, motivation and perceptions:

- The general public (n = 6)
- Vulnerable groups (e.g. and potentially parents to children with genetic diseases; potentially patients) (n=3)
- Patients (e.g. patients with genetic diseases such as Cystic fibrosis (CF), cancer, neurologic diseases, gastrointestinal disease, macular generation among others). Patients may also be donors. (n=3)
- Donors (healthy donors donating different types of biological material) (n=3)
- Civil society organisations (e.g. Sense About Science, ENNA, Civil Society Europe), including religious organisations (n=5)

In addition to ensuring variation among types of patients, donors, CSOs and vulnerable groups, we furthermore broadly aim to secure diversity across age, gender, socio-economic groups, ethnic background

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and religious views. The number of different participants included are merely estimates to secure a fairly equal distribution across participant groups.

The three workshops are distributed across the HYBRIDA partner countries - Denmark, Italy and Greece - to increase cross-cultural and contextual understandings and conceptualizations. Geographical coverage has been sought as to workshop locations, as well as cultural and religious variation, as these factors are known to influence views on emerging and controversial biotechnologies (De Witt et al, 2015). In this regard, Denmark, Italy and Greece represent a Catholic, Protestant, and Orthodox religious orientation, respectively. Variation in science and society clusters and models (e.g. difference in science communication cultures and opportunities for public involvement in science and technology decision-making) are also included as a selection criteria, as the particular role of science in society may influence attitudes towards organoid research and organoid-related technologies. Notwithstanding similar trends in research policy across Denmark, Italy and Greece – and Europe in general – the three countries also represent variation as to their tradition for involving citizens in formalized decision-making processes through different advisory bodies, their consolidation of a science communication culture and with regard to the balance between actual and preferred citizen involvement in science and technology (Mejlgaard et al. 2012).

2.2.2 Recruitment strategy

The different stakeholders will be recruited though various means of strategies. The selection of recruitment strategies for patients, donors and lay people are inspired by three state-of the art studies within the field of organoid research on patient and citizens perspectives on organoids (Boers el al. 2018; Bollinger et al. 2021; Haselager et al. 2020):

- CSO's will be contacted through existing networks, internal experts or directly through organizational gatekeepers.
- Representatives from the public will be broadly recruited through a diverse set of media outlets, such as Facebook groups, twitter, LinkedIn, networks, and well as through newspaper advertisements, political organisations, student organisations, minority organisations etc.
- Vulnerable groups, donors and patients will be recruited through patient organisations, support networks, donation organisations, flyers in outpatient clinic waiting rooms, networks of clinicians among others.

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The recruitment process will be carefully documented in a pre-defined excel sheet, which all partners will apply to document and facilitate the process of recruiting deliberative workshop participants.

2.2.3 Recruitment: Ethical considerations

This section outlines issues related to ethical considerations when recruiting participants for the deliberative workshops, including particular concerns when recruiting vulnerable groups. In terms of the latter, individuals are often "*considered vulnerable if they are susceptible to being harmed, wronged, exploited, mistreated, discriminated against or taken advantage of in the context of healthcare and research*" (Ganguli-Mitra and Biller-Andorno, 2011)

Some of the individuals, groups or populations mentioned as particularly vulnerable include persons who are unable to consent, children, institutionalized persons, homeless persons, refugees or displaced persons, some ethic and minority groups, patients undergoing medical research in combination with medical care, patients with incurable diseases, among others (Solbakk, 2011). As an example of vulnerable individuals or group of individuals/patients in organoid research, a bioethicist interviewed in the HYBRIDA project pointed to the potential risk of participants being exposed to overpromises and hype, and hence being potentially vulnerable in terms of emotional and psychological harm. For instance, parents of a child with an undiagnosed brain disorder could be prone to provide samples or participate in ways not initially considered due to desperation and perhaps an overpromise of benefits from the medical staff (D.3.2. Comparative Analysis, forthcoming).

The precise scope and content of a vulnerability definition has been scrutinized and debated for the past decades. Article 8 of the Universal Declaration on Bioethics and Human Rights represents a definition which combines a minimalist conception with one that applies a human rights-based approach in taking into account universal vulnerability, as well as protecting particular individuals from harm and exploitation that necessitates additional protective measures (Solbakk, 2011). Article 8 reads;

> *In applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected and the personal integrity of such individuals respected* (Unesco, 2005).

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In this regard, there is an attention towards forms of protection that are sensitive to contexts and particular circumstances and take into consideration sub-group differences and needs when creating protective measures (Solbakk, 2011). This will be a guiding principle for the approach to recruit and engage participants for the deliberative workshops, as patients, donors or family members to patients may or may not be deemed vulnerable according to standard definitions, but where an increased sensitivity toward individual and contextual circumstances are required throughout the entire process of designing, conducting and reporting the deliberative workshops. In this regard, there is an equal importance to adhere to the additional values of "respect, responsibility, compassion, and cultural sensitivity" in what can be termed an "recruitment etiquette" and which relate to the Belmont principles of justice, respect for persons, and beneficence, as well as necessary interpersonal skills of recruiters/researchers that all impact on participants, researcher-participants relationships and the representativeness of research findings (Gyure et al. 2015, p. 2).

Measures to safeguard consent, promote voluntariness, protect privacy and confidentiality and inform potential participants in accurate ways will also be taken through a number of formalized steps. Potential stakeholders will be invited to participate in the deliberative workshop, and they will receive an invitation letter (appendix A) with a clear description of the purpose of the deliberative workshops. Additional information about the study, including funding, recruitment, methodologies and issues of voluntariness, processing of personal data etc., will be disseminated in an attached information letter (appendix B). A link will also be provided in the information letter to Aarhus University's privacy policy. Prior to the workshops, participants will receive an informed consent form (appendix C). In the informed consent form, it is very clearly described what the participants give their consent to by signing the form. The informed consent form follows the guidelines of Aarhus University (AU). An ethics approval for the deliberative workshop study will be obtained from the Research Ethics Committee at AU. For further details on ethical considerations in relation to the deliberative workshop study, please see the overall protocol D.4.1.

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3 Sampling and Recruitment Procedures for Expert interviews and Co-creation Workshops

The following section outlines the nature of and procedures for conducting expert interviews and co-creation workshops and describes our approach to participant selection and recruitment in this second stage of the engagement process. While the first stage in the engagement process aimed to explore attitudes towards organoids and implications of organoid research, the second stage consists of a co-creation and consultation phase addressing the first version of the four products in HYBRIDA (see figure 1).

3.1. Co-creation and Consultation through Co-creation workshops and Expert Interviews

Two co-creation stakeholder workshops with 15-20 participants in each will be conducted and include a number of different stakeholders, which include academic & industrial researchers, members of research ethics committees (RECs) and research integrity offices (RIOs), policy makers, legal experts, patient organisations and biobanks. The two workshops will take place in Copenhagen and Paris, respectively, and will each be conducted over one afternoon. Stakeholders will be provided with the initial and collective elements of the operational guidelines for the field, a code of responsible conduct for researchers and a summary of the preliminary assessed gaps in the ethical and regulatory framework which will be produced within WP5 and 6 in the project. Additionally, the need for a supplement to the European Code of Conduct for Research Integrity (ECoC) will be discussed and considered. In this regard, key stakeholders and representatives with a diverse set of expertise and knowledge will assist with co-designing and provide consultation for the first draft of the projects' four products. The particular elements, gaps and additional knowledge required for external co-design and consultation will be assessed and analysed based on the work performed in WP 5 and 6 and in close collaboration with WP 5 and 6 project partners. Hence, the design, structure and progression of the HYBRIDA project support a strong collaboration and feedback loops between the different WPs as they inform and build upon one another. Particular design elements

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pertaining to the second and third stage of the engagement process will then be continuously developed, specified and refined as both WP 4, 5 and 6 evolve.

The four products produced within the timeframe of the HYBRIDA project comprise the following:

Figure 2: Description of HYBRIDA's products

Operational guidelines for the field: Recommendations to organoid researchers. They are designed to streamline certain working procedures according to best practices. They should be open to interpretation, do not need to be followed by the letter and they should provide flexibility for unforeseen circumstances.

The operational guidelines are drafted to support the research community, RECs/IRBs and integrity bodies in matters concerning:

1. concerning assessment of origin of biological material (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.

Code of Responsible Conduct for researchers: Provides ethical standards of good practice to guide researchers in the organoid field, in compliance with the principles of the ECoC: Accountability, Honesty, Reliability and Respect. The Code will list demands for responsible practice, include issues of transparency and benefits-sharing and pinpoint the requirements and duties of scientists, research organizations, industries, regulatory instances and States.

Enhancement of existing ethics and normative frameworks: They represent the normative bedrock of the organoid field, should reflect HYBRIDA's objectives and convey the amount of risk and forms of uncertainty society is willing to accept.

Specific recommendations will be produced to substantiate and complement existing ethics and regulatory frameworks, e.g. concerning issues of the function of biobanks, property rights and user rights, benefit sharing, and informed consent.

Supplement to the ECoC: Will provide an add-on to the ECoC, if needed, in the form of a set of criteria for proper research practices and self-regulation in the field of organoids.

Source: HYBRIDA project description, 2020, p. 7, 13, 36.

Following the two co-creation workshops, 15 individual online and semi-structured expert (8 external and 7 HYBRIDA AB members) interviews will be conducted to further explore key issues in relation to the

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production of the first version of products. Particular issues for clarification, in-depth exploration of emerging questions from the co-creation workshops, and the need for additional expert opinion and guidance, may be potential sub-aims of performing expert interviews. In addition, the expert interviews are also expected to contribute to a comparison within the EU and with other regions of the world with regard to the level of societal awareness and acceptance of the content and framing of products.

3.1.1 Format and Setting

A co-creation workshop is a participatory mechanism/method for involving relevant stakeholders in an open, creative and bottom-up/up-stream innovation process, at where a shared challenge is addressed collectively (Lee et al. 2018; Vandael et al. 2018; Dijk-de Vries et al. 2020). Specifically, co-creation refers to "active and committed decision-making about a meaningful problem through respectful interactions and dialog where everyone's voice is considered" (Norris et al in Dijk-de Vries et al. 2020, p. 2). Co-creation and the related concept of co-design is a very broad concept which is increasingly and widely used both within and outside the field of design, e.g. in science, technology and innovation more broadly. It originated within the design field as a means to bring design products closer to their end users (user-centred design approach) and later to involve relevant stakeholders more actively in the different design phases (the participatory approach) and new modes such as collaboratories, labs, generative design and sprints have emerged (Sanders and Stappers 2008; Jones 2018).

Notwithstanding the particular objectives of co-creation processes or field of application (e.g. health research or STI policy making), it is a general purpose to increase research and societal impact and create better outcomes and innovative solutions that are in greater alignment with the actual needs of citizens and stakeholders and "more likely to be acceptable, valuable, and enduring than traditional research approaches" (Dijk-de Vries 2021, p. 1; Deserti et al. 2020).

This purpose corresponds well with the HYBRIDA objective of engaging affected stakeholder groups in identifying and addressing epistemological, ethical and regulatory challenges in organoid research and co-creating and enhancing new standards and procedures to foster responsible research and support researchers, RECs and RIOs, among others, in tackling the above mentioned challenges within the field and to help ensure that the practice-guiding products build on solid, holistic and interdisciplinary assessments and recommendations from key stakeholders.

The co-creation of the products will be tailored to the specific needs identified subsequent to the first stage of engagement. Overall, the co-creation sessions will be conducted in two phases, in which the first will

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focus on pre-defined cross-cutting themes related to the products and the second phase on specific feedback to 1st product draft versions. Both phases will involve small-group discussions on a) coverage and quality b) identification of concerns and "blind spots" c) development of concrete suggestions and recommendations for revisions and amendments d) co-design of prioritized action points/focus areas to be taken into consideration for the second version of products and followed by a plenum discussion on key action points for the next draft versions (see also Protocol 4.1 for procedural details). Hence, feedback from the co-creation workshops will form the basis for the product versions 2.0. Additionally, feedback will also inform the development of interview guides for the subsequent expert interviews. The entire co-creation process will allow for a "test" of the first product versions (prototypes) by key affected stakeholders; identify challenges and lacunas while revealing agreements and disagreements within the field and co-create and develop solutions that will help refine the guidelines, code of conducts and normative framework as well as provide the basis for the next phase of co-creation and consultation.

The 15 expert interviews will be carried out as semi-structured interviews, adapted to fit participants' individual capacities as experts and be flexible towards the specific need for knowledge (e.g. contextual, technical, interpretative etc.). Hence, bespoke interview guides will be constructed to align expertise with data requirements.

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 characterized as specific knowledge in a certain field of action*" (Mauser and Nagel in Döringer, 2021, p. 265). Expert interviews are often performed for three distinct reasons: a) to explore and thematically become oriented within an uncharted field of study, potentially generating hypotheses b) systematizing interviews to collect 'context information' that can complement insights from other data generating sources, c) to be used as a basis for generating new theories/typologies within the field of research (Bogner & Menz 2009).

The purpose of conducting expert interviews for this study aligns with the explorative (a) and systematizing (b) objectives stated above, in both exploring additional topics emerging from the co-creative processes and gathering opinions, views and recommendations that can deepen and supplement the content and result produced in the workshops.

3.2 Stakeholder and participants: Selection criteria and sampling strategy

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The co-creation and consultation sessions involve a broad range of professional stakeholders, who will be recruited qua their professional experiences, positions and affiliations. Due to the scale and scope of the study objectives (i.e. co-create and consult on four different products including guidelines, codes of conduct and ethics/regulatory framework), a broad range of expertise and specialization are a prerequisite for the data collection process.

A purposeful sampling design (cf. section 2.2.) will be applied as the aim is to identify and select stakeholders for both the co-creation workshops and expert interviews who "are especially knowledgeable about or experienced with a phenomenon of interest" in a way that yields in-depth understandings, while securing and maximizing validity and efficiency (Palinkas et. al. 2015, p. 534). A large number of different stakeholders is chosen to also ensure a broadness in understandings, perceptions and recommendations for needed actions.

3.2.1 Selection criteria and sampling strategy

Within the overall purposeful design, the specific sampling strategy "key knowledgeables sampling", will be applied. As indicated in the designation, "key informants are especially important sources on specialized issues" (Patton, 2015, p. 284). A quality assessment, co-creation and consultation on particular RE and RI related issues on organoid research and organoid-related technologies call for vastly specialized key informants and/or experts who can assist in determining the quality of the first draft product versions, identify gaps and "blind spots" and recommend additions and actions to be taken to develop second draft versions. A key pre-defined criteria will be for stakeholders to be knowledgeable of organoid research and/or organoid-related technologies and have a background and set of experience corresponding to the following occupations or memberships:

- academic & industrial researchers (including practitioners in clinical care)
- members of RECs/IRBs
- members of RIOs
- policy makers
- legal experts
- patient organisations
- biobanks

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To the extent possible, variation with regard to gender, nationality, and age will also be taken into consideration in the recruitment process.

The expert interviews will include 15 individual experts comprising of eight external and seven HYBRIDA advisory board (AB) members. AB members will advise on progress and quality matters throughout the lifetime of the project and will have a unique set of insights into the development of deliverables, as well as being leading experts in the field of organoid research, RE, RI and Technology Assessment. The eight external experts will represent the stakeholder criteria mentioned above; nonetheless recruited in alignment with the specialized issues required for further exploration. AB members can also provide an international dimension in terms of research coverage as well as a comparison of the level of societal awareness and acceptance.

3.2.2 Recruitment strategy

The eight external experts will be recruited from the wide established networks of the HYBRIDA participants. For instance, INSERM is a nationwide organisation for Health Sciences and has a vast network encompassing RECs and RIOs. NTUA participates in EUREC (European Network of RECs) and in ENRIO (European Network of RI Offices) networks. NTUA and AU can also draw on membership of the ENERI network (European *Network* of Research Ethics and Research Integrity) and SOPs4RI (Standard Operating Procedures for Research Integrity) networks and collaborations. In general, the collective consortium has a vast reach-out to key informants and experts across the range of stakeholders included, and these networks will be activated to assist with the identification of experts and, if relevant, act as "mediators" (Kristensen and Ravn, 2015, p. 722) to help facilitate contact and disseminate invitations to partake in an interview. Hence, networks, referrals and chain sampling are contact strategies to be applied in the recruitment phase.

For the co-creation workshops, a similar strategy will be employed, and a multiple search strategy established to reach a broad range of potential participants. A key approach will be to activate relevant networks as their access to participants and the "approval" granted by mediators/gate keepers are likely to add to the success of the recruitment processes. Following each stakeholder group below, potential networks are indicated to help facilitate recruitment:

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- Academic & industrial researchers, including practitioners in clinical care (individuals from the networks of HYBRIDA partners and members from League of European Research Universities (LERU), European University Association (EUA), Young European Research Universities Network (YERUN), Global Young Academy (GYA), All European Academies (ALLEA), The Embassy of Good Science
- Members of RECs/IRBs (members of EUREC, ENERI)
- Members of RIOs (ENRIO, The World Conferences on Research Integrity (WCRIF))
- Policy makers (EC officials, members of CEI)
- Legal experts (members of the Panel for the Future of Science and Technology (STOA))
- Patient organisations (member organisations of Europe's Patient Forum
- Biobanks (members of EuroBioBank)

3.2.3 Recruitment: Ethical considerations

For both the co-creation workshops and expert interviews, an ethics approval for the study will be obtained from the Research Ethics Committee at AU in due course. Participants will be recruited based on their professional merits and positions and there are no foreseen high risks involved in the recruitment of professional stakeholders for this particular study. For the collective discussions in the co-creation workshops, there is a small risk of discovering sensitive information related to institutional handling and management of particular ethical matters concerning organoid research. In the consent form, the issue of confidentiality will be addressed and participants will agree to maintain the confidentiality of the information discussed by signing the consent form. The issue of confidentiality will also be highlighted in the introductions to the co-creation events. Furthermore, the informed consent form follows the guidelines of Aarhus University and in it, it is very clearly described what the participants – both co-creation stakeholders and experts - give their consent to by signing the form. Prior to the workshops and interviews, participants will receive an invitation and information letter detailing study objectives and information regarding funding, recruitment processes, methodologies, issues of voluntariness, and how personal data will be handled etc. In the information letter, a link will also be provided to Aarhus University's privacy policy[2].

[2] These documents will be developed for the ethics approval of this study and the following focus group study.

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4 Sampling and Recruitment Procedures for Focus groups

The third stage of the engagement process concerns the assessment and validation of the second draft of the four HYBRIDA products (see figure 1) and which will contribute to finalizing the third and final versions of the topic-specific products, including an enhancement of ethical, regulatory and normative frameworks of organoid research.

4.1 Assessment and Validation through Focus Group Consultations

The main objective with the third stage of engagement is to obtain expert and professional stakeholder assessment of the 2nd draft of the guidelines, CoC, and ethical framework produced in WP 5 and 6 to help ensure that the outputs of the project meet the actual needs of relevant stakeholders and provide tangible support for researchers, research integrity bodies, research ethics committees (among others), and contribute towards the intended impacts within the field of organoid research and organoid related technologies. Six focus group sessions with approximately 6-8 participants in each group will be assembled to assess and validate the different outputs created.

The focus group method facilitates discussion and, through group interaction, produces data around a pre-defined issue of interest. The reasons for applying focus group interviews can be manifold, but within this context of study, focus groups are particularly relevant when the objectives are to produce data on a complex and potentially uncharted research area and obtain data on interpretations, assessments and practices reflecting stakeholder representation and contextual variation (Morgan 1997; Halkier 2018). The six focus group consultations will provide a structured exploration and assessment of particular open questions and unresolved concerns related to the second draft versions of the documents produced. The focus groups will support a forum for collective discussion, reflection, and idea generation to help ensure that key issues related to ethical (e.g. mundane and contentious issues), conceptual and regulatory matters/uncertainties are addressed. The particular issues to be addressed will be identified in close collaboration with WP 5 and

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6 on the basis of the outcome of stage two of the engagement process and the process of drafting the appertaining document versions.

4.1.1 Format and Setting

Different stakeholder groups representing a number of advisory and regulatory bodies will be composed for the focus group consultations to discuss these key issues, questions and concerns.

The focus group consultations aims to explore the following research question which is successive to the one stated in the second phase of engagement:
1) *To which extent and in what way are the proposed standards (2nd versions of HYBRIDA products) in alignment with the required needs, developments and conceptualizations within the field of organoid research?*

Following this question and an openness towards emerging themes and open questions, the focus group discussions also allow for a thematic exploration of one of the HYBRIDA objectives concerning:

2) *How should these new standards and good practices be implemented*? (HYBRIDA 2020, p. 13).

The six focus group discussions will take place on-site and across Europe to secure a geographical spread, and to lessen the challenges related to travel and recruitment. A preliminary distribution of focus groups based on potential stakeholder participation and location is:

- Two focus groups will take place in the UK (conducted by MAN partner)
- One focus group will take place in Belgium (conducted by NTUA partner)
- One focus group will take place in France (conducted by AU partner)
- One focus group will take place in Germany (conducted by AU partner)
- One focus group will take place in The Netherlands (conducted by AU partner)

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4.2 Stakeholder and participants: Selection criteria and sampling strategy

The six focus group discussions will involve the same type and range of stakeholders as in the second stage of co-creation and will similarly be recruited due to their professional experiences, positions and affiliations within the HYBRIDA areas of research. Due to this main criteria, a purposeful design and "key knowledgeables sampling" (Patton 2015, p. 284) strategy will also be applied (see section 3 above) as a basis for recruitment. For the focus group sessions, we will also aim to construct the groups so that all groups include 2-3 stakeholders who took part in the second stage of engagement (co-creation workshop and expert interviews). The continuation of stakeholders will create a link between the phase of co-design and the final validation of outputs, enhancing transparency and visibility in terms of developments and revisions being implemented in the intervening phase. Repeat stakeholders will also be able to bring former discussions, recommendations and views into the focus group discussions which is expected to - in combination with 'new' stakeholder perspectives – provide an appropriate base for validation.

4.2.1 Selection criteria and sampling strategy

The stakeholders to be recruited for the focus group discussions are:

- academic & industrial researchers (including practitioners in clinical care)
- members of RECs/IRBs
- members of RIOs
- policy makers
- legal experts
- patient organisations
- biobanks

The exact composition of focus groups in terms of stakeholders and end-users will vary depending on the different outputs produced and the elements needed for detailed assessment. As the main purpose of the focus group discussions is to contribute to the final output versions and to assess, validate, and consolidate, rather than co-create the main outputs, we will strive to assemble segmented groups who are "key knowledgeables" within similar areas of required expertise to support focused and detailed in-depth

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discussions (e.g. expertise related to storage of organoids, clinical applications, moral status, data protection and privacy etc.). While the criteria of homogeneity will be applied in terms of area of expertise, we will seek heterogeneity in gender, institutional affiliation and geography.

4.2.2 Recruitment strategy

Focus group participants will be recruited through internal (project affiliated) and external networks as described in section 3.2.2. Furthermore, recruitment through research performing organisations (RPOs), referrals and chain sampling are additional contact strategies that will be applied in the recruitment phase. All stakeholders partaking in the second phase of the engagement process will be asked as to whether they would be interested in taking part in a focus group interview.

4.2.3 Recruitment: Ethical considerations

The ethical considerations related to the focus group discussions follow the same rationale and procedures as described in the second stage of engagement (please see section 3.2.3). There are no high risks involved in the recruitment of focus group participants. Similar to the co-creation workshops, focus groups sessions do involve a small risk of discovering sensitive information concerning the particular handling of ethical issues in relation to organoid research. Confidentiality issues will be addressed in the consent form and focus group facilitators will emphasise in the focus group introduction and debriefing that participants are not to repeat what is said in the focus group interviews to others.

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5 Appendixes

Appendix A: Invitation letter for Deliberative workshops

Invitation letter to potential participants

Invitation to participate in a mini-public/deliberative workshop on the ethics of organoids

Dear Sir/Madam [replaced by name],

In your capacity as **x** [replaced by the group/a description of why they have been invited], we would like to invite you to participate in a mini-public/deliberative workshop **on the x of November 2021** on the ethics of organoids, organized by the project HYBRIDA (Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies).

In the workshop, we will discuss potential worries, fears, and expectations of organoid-based research and technologies. It is important to emphasize that you do not need to know anything about organoids to accept this invitation. Prior to participation, you will receive an information package with a couple of short texts to read and links to relevant videos, which will give you the necessary background knowledge for participating. At the workshop, you will also be given additional information by experts and have the chance to ask questions. The workshop-language will be **x** [either Danish, Italian, Greek].

The workshop will take place **at x** and will last from 11am until 18pm. There will be coffee and a little something to eat from 10am, and we will end the day with a dinner from 18-20pm. We will be able to pay your transport costs (train or own car).

Short description of project

HYBRIDA is funded by the European Commission (grant no. 101006012) and aims to create a regulatory framework for organoid-based research and resulting technologies with a particular focus on ethical questions. Organoid research comes with ambitious promises of revolutionizing 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 takes place.

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As part of the HYBRIDA-project – and as a way to get to know more about the public's worries, fears, and expectations of organoid-based research and technologies – we have planned three mini-publics/deliberative workshops. These will take place in Italy, Greece, and Denmark in November 2021. In each workshop we will have around 20 participants, representing the general public, vulnerable groups (e.g. parents of children with genetic diseases), patients (e.g. patients with genetic diseases such as cystic fibrosis or cancer), donors (healthy donors donating different types of biological material), and civil society organisations, including religious organizations. For more information about the project, see attachment 'Information on the project'.

Personal data

Aarhus University has received you name and e-mail address from **xx** in order to be able to contact you. For more information about our processing of your personal data, please see attachment on how personal data is processed.

Participation

We would be very grateful, if you could indicate whether you would like to participate in this workshop. If you wish to participate in the project, we will ask you to sign a consent form at the workshop.

If you have any questions concerning the project and/or the details of the workshop, please contact **x** [the person recruiting + email + telephone]

Kind regards,

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

Appendix B: Information Letter for Deliberative Workshops

Letter of information to Participants about the HYBRIDA project and the Mini-publics/Deliberative workshops

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

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, both human and non-human such as the retina, heart, brain, intestine, kidney, pancreas, liver, inner ear and skin.

The aim of the mini-publics/deliberative workshops

Organoid based research and technologies come with great hope of revolutionizing biomedical research and medical science, for example, making it possible to develop new and more efficient treatments for illnesses, including diseases that so far have been untreatable. However, organoid based research and technologies can only be sustainable in the long run if they are in line with the general public's ethical standards. Therefore, to take full advantage of the scientific and social benefits of organoids, it is crucial that the public opinion on organoids is considered when developing a regulatory framework for organoid based research and technologies.

Via the three mini-publics/deliberative workshops, HYBRIDA will be able to learn about the publics' worries, fears, and expectations in relation to organoids – and account for them in the regulatory framework it is building. Including patients, patient organisations, vulnerable groups, donors, societal and religious organisations, and representatives from the general public in the three mini-publics/deliberative workshops will make it possible for HYBRIDA 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 describe known as well as hitherto unrecognized ethical challenges and start developing possible ways to deal with 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.

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What is a mini-public/deliberative workshop?

Deliberative (mini-public) workshops are "dialogue events where the focus is on having informed discussions on a complex or controversial issue to gather social intelligence to inform policy, anticipate regulation, exchange opinion or raise awareness" (The Danish Board of Technology, 2014[3]). Deliberative workshops use in-depth and informed discussions, and place significant emphasis on elements of deliberation, a critical examination of evidence, regarding of experiential knowledge and a fostering of both convergent and divergent views to elicit statements on the particular issue discussed.

Who will participate and how will they be recruited?

Participants will include patients, patient organisations, vulnerable groups, donors, societal and religious organisations, and representatives from the general public in the three mini-publics/deliberative workshops. The different stakeholders will be recruited though various means of strategies, for example, societal organisations will be contacted through existing networks, internal experts or directly through organizational gatekeepers, and representatives from the public will be broadly recruited through a diverse set of media outlets, such as Facebook groups, twitter, LinkedIn, networks, as well as through newspaper advertisements, political organisations, student organisations, minority organisations etc. Vulnerable groups, donors and patients will be recruited through patient organisations, support networks, donation organisations, flyers in outpatient clinic waiting rooms, networks of clinicians among others.

Ethical challenges

Since Roman law, all entities have been categorized and regulated either as persons or as things (subjects or objects). Organoids, however, are entities, and organoid research and organoid-related technologies are examples of research and innovation that challenge this dualism. This raises three sets of questions or forms of uncertainty:

1. How should one conceive of entities that cannot be categorized as either persons or things? What *are* they? How do we *know* the characteristics of these entities called organoids? We call this form of uncertainty for conceptual or ontological uncertainty.

2. How do we address forms of uncertainty that cannot be evaluated through the use of statistical methods, i.e. risk assessment? This is particularly pertinent where organoids are intended for personalized or precision medicine, where the number of research subjects with a certain characteristic is too low for randomized controlled trials or other statistically based experiments. As precision medicine and new technologies emerge, evidence-based medicine is challenged to find new footing. In the project, we here speak of epistemological or methodological uncertainty.

3. How should we regulate something that is a mix of a person and a thing? We call this regulatory uncertainty.

[3] The Danish Board of Technology (2014). *Action Catalogue*. Deliberative (Mini-publics) Workshops. Engage2020. Available at: http://actioncatalogue.eu/search

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HYBRIDA will examine these uncertainties, dilemmas and questions, and the input from the deliberative workshops/mini-publics will – together with other inputs – be used to create guidelines for research, a code of conduct for researchers and other products, which together will help regulate organoid research and organoid-related technologies.

Ethical approval of study and personal data protection

The ethical approval of the mini-publics/deliberative workshops study will be obtained from the Research Ethics Committee at Aarhus University before the mini-public/deliberative workshop takes place.

Personal data

Collection, storage and use of the data collected during the mini-publics will be in alignment with the European Union's General Data Protection Regulation (GDPR) and Aarhus University's privacy policy: https://international.au.dk/about/profile/privacy-policy/browse

As mentioned in the invitation letter, we have received your name and e-mail address from **xx**. The legal basis for this transfer of data is Article 6(1)(e) of the General Data Protection Regulation and section 10(1) of the Danish Data Protection Act which entitle Aarhus University to process your sensitive personal data for scientific research purposes without your consent.

If you consent to participate in the project and the workshops, your personal information given to us during the workshops will also be processed based on Article 6(1)(e) of the General Data Protection Regulation and section 10(1) of the Danish Data Protection Act. This entitles Aarhus University to process your sensitive personal data for scientific research purposes without your consent

For more information about the processing of your personal data, see the document on how personal data will be processes.

To be able to analyze the mini-publics/deliberative workshops, the workshop will be audio recorded. On the basis of the recordings, transcription of the discussions will be made. The recordings, transcripts and study reports will be transferred to Aarhus University through a secure pathway. All local recordings of the mini-publics/deliberative workshops will hereafter be deleted. At Aarhus University, informed consent forms for your participation in the project will be stored separately from the recordings and transcripts. The findings from the mini-publics will be analyzed and published. No personal identifiable information will be mentioned or disclosed at any point in these publications.

Each participant in the mini-publics/deliberative workshops may at any time demand removal of their data by a simple request to the coordinator of the study, Mads P. Sørensen (mps@ps.au.dk). However, data, which have already been published, cannot be removed.

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Appendix C: Informed Consent for Deliberative Workshops

Consent Form

Informed consent form for participation in HYBRIDA's mini-publics/deliberative workshops

Short introduction to organoids and HYBRIDA

Organoid research comes with ambitious promises of revolutionizing biomedical research in the future and with it our view of the human organism and life itself. An organoid is an organized 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.

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 mini-publics/deliberative workshops

In order to produce the regulatory framework, we need to understand more about the worries, fears and expectations of the general public, vulnerable groups, patients, donors and civil society with respect to organoids. We will explore these worries, fears and expectations in 3 workshops conducted in Denmark, Greece and Italy. The mini-publics/deliberative workshops are carried out in different parts of Europe to take geographical, religious and cultural differences into account.

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

To be able to analyze the mini-publics/deliberative workshops, the workshop will be audio recorded. On the basis of the recordings, transcripts will be made together with a study report written in English. The recordings, transcripts and study reports will be transferred to Aarhus University through a secure pathway. All local recordings of the mini-publics/deliberative

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workshops will hereafter be deleted. For further details, please see Aarhus University's 'Privacy Policy': https://international.au.dk/about/profile/privacy-policy/browse

The findings from the mini-publics/deliberative workshops will be analyzed and published. No personal identifiable information will be mentioned or disclosed in these publications at any point. The project report detailing the findings of the study will be send to all participants when it is submitted to the European Commission in the spring of 2022.

Personal data

Collection, storage and use of the data collected during the mini-publics will be in alignment with the European Union's General Data Protection Regulation (GDPR) and Aarhus University's privacy policy: https://international.au.dk/about/profile/privacy-policy/browse

The legal basis for this transfer of data is Article 6(1)(e) of the General Data Protection Regulation and section 10(1) of the Danish Data Protection Act which entitle Aarhus University to process your sensitive personal data for scientific research purposes without your consent.

If you consent to participate in the project and the workshops, your personal information given to us during the workshops will also be processed based on Article 6(1)(e) of the General Data Protection Regulation and section 10(1) of the Danish Data Protection Act. This entitles Aarhus University to process your sensitive personal data for scientific research purposes without your consent.

Risk and inconveniences

We do not expect any potentially critical ethical implications of the research results with regard to human dignity and integrity, or privacy of persons. The focus in the deliberative workshops is on the participants' attitudes towards organoid research, rather than their individual life and medical histories. Hence, the study and deliberations do not intend to involve the collection of sensitive personal data. It could be anticipated, however, that participants such as patients and donors will share health details and/or their own or family medical histories, as a way to contextualise their perceptions and attitudes towards organoid research. All data will be pseudonymized in written and published material. This means that no personal identifiable information will be mentioned or disclosed at any point.

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).

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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 give consent to the audio recordings of the mini-public/deliberative workshop.
- I agree to maintain the confidentiality of the information discussed by all participants and researchers during the mini-public/deliberative 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

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