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HYBRIDA

Public attitudes, understandings and perspectives on organoid research

Findings from a series of deliberative workshops

HYBRIDA

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

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Executive Summary

Based on a unique series of deliberative workshops, the report explores and chronicles the attitudes, values and perspectives on organoid research among representatives from the general public, patients, donors, vulnerable groups and CSOs with a particular view to the distinct moral, regulatory and ethical implications of organoid research that emerged from the deliberations. Three deliberative workshops with a total of 51 participants were held in November, 2021 in Italy, Greece and Denmark and hence across three different European countries representing different parts of Europe and different religious, cultural and science-in-society contexts. The deliberations were conducted as part of the Horizon 2020 project HYBRIDA (Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies), which aims to develop a conceptual and regulatory framework including operational guidelines for the field and a code of conduct (CoC) for researchers in academia and industry, partly based on a comprehensive three-stage public engagement co-creation and validation process of which the series of deliberative workshops constitute the first course of action.

Overall, participants expressed a **positive attitude** towards organoid research irrespective of participant category and background characteristics such as gender, religious affiliation and age. They found the prospects of progress as well as both current and future benefits of organoid research promising and attached positive expectations to their application and contribution within biomedical research.

While the participants broadly supported the use of organoids, they also expressed a number of key concerns and worries related to their current and future derivation and use:

Participants expressed **unease towards the commercialisation of organoids** and were concerned that organoid research would add to existing inequalities if not properly and responsibly governed.

Potential **misuse and breach of the privacy of personal data** in connection with data storage and donation was also emphasised as a considerable concern. Another concern, albeit not dominant, was potential misuse of organoids for war purposes.

The two interrelated themes of **informed consent and responsible governance** were highlighted throughout the deliberations as particularly important for participants in order to safeguard ethical and acceptable use. A majority of participants advocated for some restrictions imposed on consent procedures and recommended that issues of ownership and remuneration be specified in the consent form and be contingent on the type of consent provided. Nonetheless, a majority adopted the position that donations of cells should be viewed as a donation or gift transferred without financial compensation.

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In general, it is evident from the deliberations that ethical use of cell donations has to be guaranteed through **strict governance structures, control and ethical oversight procedures**. Both Greek and Italian participants address an association between concerns about misuse of organoid research and a societal distrust in science, which underlines the importance of clear, transparent and objective research dissemination and **science communication**.

It is also evident from the deliberations that **cerebral organoids**/brain organoids raise specific ethical issues and concerns due to questions concerning conscience and moral status.

Participants generally pointed to the **dynamic nature of organoids** and a concurrent need for ongoing societal debate, regular revisions of ethical guidelines and procedures where ethical needs and requirements are aligned with the state-of-the-art in organoid research as it increasingly moves into clinical and translational research.

Participants were divided in their conceptualisations of organoids. While a majority of participants primarily perceived them as **research tools** in their current stage, many participants regarded them as **living organisms**.

The report provides a broad **set of recommendations** from participants for key issues to be addressed in future ethical guidelines on organoid research. The first part of the report reviews the main findings from the deliberations; the second part includes three comprehensive reports from each of the national workshops for a more single-case and detailed exposition.

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1 Introduction: Deliberative Workshops on Organoid Research

1.1. 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.[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. When such a train leaves the station, it is vital that ethics not only follows but is on board 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 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 human and non-human organs such as the retina, heart, brain, intestine, kidney, pancreas, liver, inner ear and skin.

Following Roman times, all entities have been categorised 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 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 statistically based experiments. As precision medicine and new technologies emerge, evidence-based medicine is challenged to find

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

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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. In order to develop ethically and socially robust ways of assessing the effects of organoid research and related technologies, there is a need to include these additional forms of uncertainty in the Health Technology Assessment (HTA).

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

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 the Deliberative Workshops

A key objective in HYBRIDA, and as described in the research protocol for Work Package (WP) 4 in the HYBRIDA project (Ravn and Sørensen, 2021, p. 5-6), ‘is to develop a comprehensive regulatory framework for organoid research and organoid-related technologies that can support the research community and other stakeholders such as RECs and RIOs in ethical matters and implications concerning organoid research, e.g. through enhancing and adapting existing guidelines, policies and ethics/normative frameworks pertaining to health and life sciences and through identifying key ethical elements which could support the ethical dimension of research protocols. To address these ethical matters and related challenges in a socially sound and robust fashion, it is considered essential to a) address the conceptual, epistemological and regulatory uncertainties related to organoid research and b) take into account the knowledge and experiences of a broad range of relevant stakeholders and civil society, 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’.

WP 4 is designed to facilitate the engagement processes within the framework of the project and promote meaningful, inclusive and effective activities for involving citizens and stakeholders throughout the process of developing, designing, producing and validating the four main products to be produced in the project: a)

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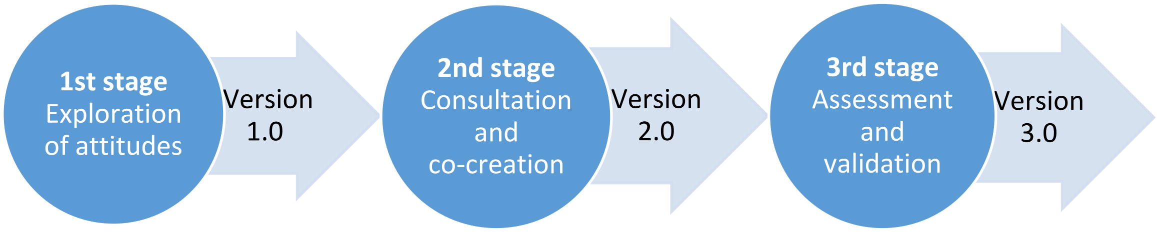
operational guidelines for the field, b) a code of responsible conduct for researchers, c) enhancement of existing ethics and normative frameworks, and d) a supplement, if needed, to the European Code of Conduct (ECoC). The engagement process constitutes a three-part course of action (figure 1) dedicated to a first stage of 1) exploring public attitudes towards organoids through three deliberative workshops in Denmark, Greece and Italy, respectively. 2) In the second stage, a large number of expert and professional stakeholder groups representing research communities (incl. industry), research ethics committees (RECs), research integrity offices (RIOs), policy makers, legal experts, patient organisations and biobanks 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 in Paris and Copenhagen including 15-20 stakeholders in each workshop and 15 individual expert interviews will be conducted at this stage. 3) At the third and final stage, similar expert and professional stakeholder groups will contribute to the assessment and validation of a second draft of the four products through the implementation of six focus group sessions.

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



The findings of the first engagement stage of exploring and understanding the public opinion on organoid research through a series of deliberative workshops will be presented in this report. Three deliberative workshops with a total of 51 participants were held in November, 2021 in Italy, Greece and Denmark with the aim of obtaining insights into and eliciting a diverse set of values, attitudes and perspectives on organoid research from citizens and stakeholder groups such as patients and CSOs and three European countries representing different parts of Europe and different religious, cultural and science-in-society contexts. The main part of the report is dedicated to the individual national reports, attached in appendix A, B and C, delineating and detailing the particular organoid conceptualisations, attitudes and ethical issues raised in each workshop. The first part of the report contains a chapter on the methodological aspects of conducting deliberative workshops (chapter 2) and a chapter reporting on the main cross-cutting results from the deliberations regarding participants' understandings and conceptualisations of organoids as well as key ethical issues discussed (chapter 3). Chapter 4 includes the results from a small pre- and post-survey completed by the participants and the chapter points to a number of deliberative and contextual effects. The final chapter

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5 outlines participant recommendations for issues and concerns suggested to be included in forthcoming efforts to build ethical and regulatory guidelines within the research area.

2 Methodology: Deliberative Workshops

This section outlines the methodological issues related to the design, planning and completion of the deliberative workshops, i.e. the particular research design, research questions and data collection as well as the process of coding and analysing the data and knowledge obtained from the workshops.

2.1. Design: Exploration of Public and Stakeholder Attitudes towards Organoids through Deliberative Workshops

Deliberative workshops can be characterised as “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). Great emphasis is placed on facilitating in-depth and informed deliberations and discussions based on varied expert inputs and an examination of different issue positions with the objective to elicit a broad and diverse range of both convergent and divergent views on the topic in question. Hence, through careful and in-depth considerations of the relevant issue based on evidence assessments and exchange of different points of view, participants are able to develop and produce their own informed opinions. The process may help to foster understandings of how positions, values and attitudes may change due to the type of information given and the nature of the deliberation (The Danish Board of Technology, 2014; O’Brien et al. 2020; Steel et al. 2020, for more details on the method of deliberative workshops, please see the research protocol for the study, Ravn and Sørensen, 2021). The short survey on attitudes completed before and after deliberations is integrated to assist with understanding variation in attitudes and identifying possible changes prompted by the discussions (chapter 4).

As a two-way participatory method, the deliberative workshops were conducted to initiate and facilitate dialogue on the ethical issues pertaining to organoid research and an emerging biotechnological innovation, for which public dialogue has not yet been established, to our knowledge. In general, ‘robust public engagement is important when sensitive new biotechnologies emerge’ (The National Academies of Sciences, Engineering, and Medicine, 2021, p. 91). For organoid research in particular, it has been argued that a broad science and society dialogue with many types of stakeholders is advisable for the long-term public ac-

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ceptance of organoid research and responsible innovation within the field (Bredenoord et al. 2017). Furthermore, increasing and substantiating trust, creating mutual understandings and aligning understandings of and expectations regarding organoids by reducing gaps between realistic and hyped scenarios (HYBRIDA Consortium, 2020, p. 3, 11) remain important,

> *"Establishing and maintaining trust in organoid research will likely be predicated upon proper communication and understanding of it [...] Efforts should be taken to create and disseminate accurate information about organoids that can be used not only when obtaining informed consent for this research, but also for the general public".*
>
> (Bollinger et al. 2021, p. 1881).

In this regard, the purpose of conducting three deliberative workshops is to explore and elicit different views on the use and derivation of organoids and organoid research to understand the public opinion (i.e. worries, concerns, fears, uncertainty and expectations) and key ethical issues and implications related to organoids from the point of view of citizens, vulnerable groups, patients, donors, and CSOs. More specifically, the deliberative workshop was designed to answer the following research questions:

- ***How do non-professional stakeholders and the lay public perceive organoids and organoid research?***
    - What are the participants' main worries, fears and expectations concerning organoid research?
    - How do participants conceptualise and understand organoids? (i.e. persons vs. things, moral status, mythological aspects)
    - What are the perceived current and future benefits of organoid research according to the participants?
    - Which kinds of ethical issues or research pose concern for the participants? (i.e. particular organoid types and uses; particular ethical issues such as informed consent, ownership and commercialisation)?

The valuable public and stakeholder perspectives on these questions will provide key insights and unique knowledge about the continuous process of developing the four HYBRIDA project outputs, including operational guidelines and an ethics framework. These questions were explored in a two-phase deliberation of (1) 'attitudes towards and conceptualisations of organoids' and (2) 'perceived benefits and concerns in relation to the derivation and use of organoids' in terms of key ethical issues and implications to be taken into account in regard to organoid research (see section 2.1.1). The three deliberative workshops followed

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the same protocol and design. All materials were developed by the WP coordinator and translated and adapted (if necessary) by WP partners locally. Processes, materials, practical issues etc. were discussed in a number of coordination meetings between all partners in the planning phase. For specific methodological issues concerning each country, please refer to the national reports in Appendix A, B and C. The following materials were produced to be applied across the three national cases:

Materials for participants:

- An information kit to be sent out to all participants one week prior to the date of the workshop. The information kit compiled three short texts: 1. What are organoids? How are they made, and how can they be used? 2. What are some of the ethical implications of organoid research? 3. How can we understand organoids in a conceptual manner? The kit also included suggestions for extra material, including links to two short YouTube videos on organoid research.
- Invitation to participate in the deliberative workshops (appendix D)
- Information letter to participants (appendix E)
- Consent form (appendix F)
- A note on how Aarhus University processes personal data (appendix G)
- Detailed workshop agenda and workshop material, i.e. questionnaire, guiding questions, dilemmas (appendix H and I)

Materials for partners:

- Excel sheet to document and facilitate the recruitment process of participants
- Template for national reports
- Guidelines for transcription and coding of workshop data

The sampling and recruitment strategy is described in a separate research protocol (Ravn and Sørensen, 2021a) and adapted and refined by each national partner (see section 2.2 in national reports). The study was ethically approved by Aarhus University's Research Ethics Committee (Approval number: 2021-96), and all participants signed written informed consent for their participation.

The 51 participants were distributed across five participant categories: public, patients, donors, civil society organisations, and vulnerable groups, to achieve variation in representation and to include citizens with potentially no knowledge of organoid research, as well as key non-professional actors (or enclave groups) representing minor fractions of the public with particular experiences and/or interests in organoid research.

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In order to elicit a range of attitudes, multiple personal and non-personal experiences and levels of familiarity with the topic are seen as beneficial for exploring diversity in organoid perceptions and understandings. An overview of participant characteristics in term of participant category, age and gender is provided in table 1. Further information concerning the distribution of socio-demographic information is included in chapter 4. In appendix J, an overview of individual participants (anonymised and referred to as P1, P2…) is provided.

Table 1. Characteristics of participants

Workshop	Italy	Greece	Denmark	Total
Participant category (*n* = 51)				
Public	5	9	6	20
Patient	3	1	4	8
Donor	3	1	2	6
CSO	5	1	6	12
Vulnerable	3	-	2	5
Age				
18-40	7	8	5	20
40-60	7	3	8	18
61+	5	1	7	13
Gender				
Female	7	4	7	18
Male	12	7	13	32
Non-binary	-	1	-	1
Total	**19**	**12**	**20**	**51**

2.1.1 Format and Setting in the Deliberative Workshops

The three workshops were structured as a two-phase deliberation with each phase entailing small-group and plenary discussions (table 2). In alignment with the method, participants were introduced to a variation of expert information, views and evidence concerning different topics on organoid research in the first phase, followed by a Q&A session, to establish an informed basis for the subsequent deliberations. In each workshop, professional moderators and national project partners helped facilitate small-group discussions by offering clarifications when needed and keeping track of time. Two main guiding questions were discussed in the first phase of deliberation concerning participants' attitudes towards and conceptual understandings of organoids. Afterward, a rapporteur from each group relayed a summary to the plenary discussion for collective deliberation. In the second phase of the workshop, individual reflections on two case

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dilemmas concerning consent/ownership/compensation and cerebral organoids were followed by small-group deliberations on the dilemmas. Groups were asked to write a set of recommendations for important ethical issues, challenges and concerns to be taken into account regarding organoid research. As the objective was to elicit a broad range of perspectives and suggestions, participants were not asked to reach consensus on a prioritised list of recommendations. As in the first phase, a rapporteur presented the main point from the group deliberation regarding recommendations for ethical issues to be further addressed. The deliberative workshops were audio-recorded for subsequent transcription, data coding and data analysis.

Table 2. Structure and content of the deliberative workshops

Phases	**Deliberative elements**	**Specifications for small-group deliberations**
Phase 1: Attitudes and conceptualisations	• Introduction (ethical issues) • Short ice-breaker exercise. • Short questionnaire. • Presentation by experts • Small-group deliberations • Q&A session with experts • Small-group deliberation. • Rapporteurs from each group relay a summary of the group discussion. • Short summation of the first part of the deliberation.	Collective group preparation of three questions to experts Deliberation based on two guiding questions regarding attitudes towards and conceptualisation of organoids: 1) How do you think of organoids? What are organoids? How can we best describe them? Do you think of them as human, as a thing, or as something in-between? 2) Discuss the feelings organoids evoke in you. Which words come to mind when you think about organoids? Are organoids something to be feared – or do you see a hope in them? Which worries and/or positive expectations do you have regarding organoids?
Phase 2: Ethical implications and recommendations	• Introduction to the second part of the deliberation. • Individual reading of dilemmas and individual reflections • Small-group deliberations. • Rapporteurs from each group relay a summary of the group discussion. • Short presentation of recommendation posters • Plenum deliberation • Short questionnaire.	Presentations of two dilemmas related to a) Consent, ownership, and compensation and b) Cerebral organoids and the issue of consciousness A**)** Discussion of dilemmas based on guiding questions. B) Exercise. List of recommendations for important ethical issues, challenges and concerns to be taken into account in regard to organoid research. Guiding question:

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	• Conclusion and evaluation (debriefing).	1) What are the most important ethical issues that need to be addressed in a regulatory framework for organoid research?

Common guidelines for the transcription and coding of data were provided in addition to an analytical strategy and a template for reporting the findings from the individual workshops. Specific details related to the process of data analysis are included in the national reports. For the 'across-case' analysis reported in the first part of the report, the three national reports were imported to the software programme NVivo 12 and thematically coded according to the main- and sub-themes conveyed in the reports. The findings presented in the following chapters primarily focus on the main themes and the convergent views on organoid research that emerged and were communicated across the three deliberative workshops.

3 Findings

The following section relays the main findings from the deliberative workshops in relation to participants' 1) attitudes towards organoid research, 2) their understandings and conceptualisations of organoids, and 3) the main ethical implications identified.

3.1 Attitudes towards Organoids

Participants across the three deliberative workshops express strong consensus that a continued development and use of organoids should be broadly supported. The **overall positive attitudes** towards organoid research are evident across participant groups and background characteristics such as gender, religious affiliation and age. Despite a range of concerns and ethical implications identified as important for future actions, positive sentiments on organoids characterised the first group deliberations during the morning session and hence the participants' immediate reactions to the feelings organoids evoke in them (see table 2).

Participants find the prospects of progress as well as both current and future benefits of organoid research promising and attach hope and positive expectations to their application and contribution in biomedical research (see also chapter 4). In the Danish and Italian deliberations, it is reported that a particular strong sense of hope is expressed in the group of patients or kin to patients.

Such hope and positive expectations towards the benefits of organoid research were for instance explicitly mentioned to pertain to:

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- Development of new and/or advanced treatments of genetic diseases such as Cystic Fibrosis (CF) and cancer
- Personalised medicine through patient-derived organoids
- Preventive medicine and care
- ‘Auto-transplantation’ of patient cells
- Reduction in the use of animals in research experiments
- Drug testing and screening
- Increase of life expectancy

As a general finding, participants distinguish between current organoid research and future applications. Indeed, a **temporal dimension** plays a significant role in the participants’ argumentation and expression of attitudes. Substantiated by the fact that organoid research is in many ways still in its early phases of development and used as a ‘model system’ (Kim, Koo and Knoblich, 2020, p. 579) in basic research to study human development/disease modelling and to develop and test new medicine, participants highlight a division between current and future benefits and negative implications, paying attention to aligning the possibilities and challenges related to organoid research with current and prospective scenarios. The perspective of time is applied as an important factor throughout the discussions on how to conceptualise organoids and in the ethical implications emphasised (see sections below). In terms of worries, the young Italians and Danes (between the age of 18-40) are reported to focus more on concerns relevant for current and near-future developments and less on potential future disadvantages of organoid research. In acknowledgement of the rapidly advancing field of organoid research and its state of flux, participants broadly highlight the **dynamic nature of organoids** and the concurrent need for ongoing societal debate, revisiting and revising guidelines, procedures and ethical framework on a regular basis, and where ethical needs and requirements are aligned to the state-of-the-art in organoid research as it increasingly moves into clinical and translational research.

In the deliberations about participants’ views and perspectives on organoids, a number of key concerns and worries emerged in relation to the following topics:

3.1.1 Commercialisation, Personal Data and Misuse

Across the three workshops, participants express **unease towards the commercialisation of organoids** and concern about how research results are exploited, the economic interests involved and who the beneficiaries of organoids will be. From a bioethical perspective, participants are broadly worried that industry

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forces will monopolise the technology and on a global scale increase existing health care inequalities as seen with COVID-19 vaccines, for instance. Likewise, they express concern that therapeutics will be overly priced and not properly distributed. Lastly, unease that developments in organoid research will reinforce the hierarchy among different types of illnesses (e.g. resources allocated for funding, research and treatment) is particularly voiced by Danish patient organisation representatives. The concern does not come across as a complete dismissal of market forces or profit-driven private companies, but as a concern that organoid research will add to existing inequalities if not properly and responsibly governed (see section 3.3.2 on governance). The participants find that organoid research, including knowledge, technologies, treatments etc. should be broadly accessible and promote health equality.

A second concern is **potential misuse and breach of the privacy of personal data** (table 3). Protection of private and genetic data in connection with data storage and donation is a considerable concern, and participants envision a number of potential misuses of data, for instance by insurance companies to turn away costumers exposed to certain diseases.

Table 3. Exemplary quotations across deliberative workshops

Commercialisation and increase of inequality	
	As I see it, the results from basic research should be available world-wide. Otherwise, I think it will become even more uneven. And then there's of course the question whether the applied research should be depending on the market forces? And what could an alternative be? (P1, general public, 61+, Denmark) Then state control in science is very important, because then there are companies that if they are not under control do not have a cultural or moral code (man, 31-40 years old, Italy) In whose hands is this research? Why we hear about the EU, which has already told us what the main pillars of, say, are. It is EU policy and economic interests, I think he said that. This is dangerous (P12, donor, Greece).
Data misuse and breaches	
	I guess there's a lot of information in an organoid. Could insurance companies use this to calculate the price of your life insurance? (P3, general public, 18-40, Denmark). We need to make an assessment of the current state or a hypothetical near future. Because I heard a conference on health from the European business community that a truly sci-fi thing was done, but it is not far from reality that in the near future all of our data including cell phone data or our DNA could

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> become the common property of that. What could be the scientific implementation (woman, 51-60 years old, Italy).
>
> When I went to the hospital a month ago, because I had a pain, I was waiting at the radiologist, I was waiting in a place and there was no employee there. So, there was a form of a patient exposed to all the people who came in. So, I do not think there is a protection framework for protecting personal data. (P3, general public, Greece)

3.1.2 Scientific Communication and Distrust in Science

In the Greek deliberative workshop, potential misuse of personal data is closely related to more general mistrust in the capacity of governing bodies to protect personal data as well as an inexpedient ‘entanglement between politics and science’. Science is here regarded as being subject to political interests, which adds to a **societal distrust in science**. Concerns about misuse of organoid research are likewise discursively constructed as an issue of distrust in the Italian context. General distrust in the Italian case is reported to have increased during the COVID-19 pandemic, and participants in the Italian workshop convey challenges for science communication efforts in terms of entangling reliable information from misinformation. A concern that promised benefits of organoids in terms of treatment and medical advancement may never be realised (the hype surrounding organoid research) is also relayed in the Italian workshop. The focus on scientific distrust in the Italian and Greek workshops reflects a **variation in science and society relations** across the three countries, including variation in knowledge, attitudes and involvement in science and technology. As recounted in the Danish report, Eurobarometer data shows significant variation in how well-informed citizens feel about medical advances and discoveries in the three countries. Furthermore, around half of the Italian and Greek respondents (compared to 20% of the Danish respondents) agree with the statement that ‘because of their knowledge, scientists have a power that makes them dangerous’ (see appendix C, p. 5). On a general level, it speaks to the importance of clear and transparent science research dissemination that addresses knowledge uncertainties, sound consent procedures and responsible governance structures, which are also emphasised in the national reports.

3.1.3 Cerebral Organoids Raise Specific Concerns

Akin to overall support to organoid research, participants support and see current and potential benefits of developing cerebral organoids, including studying the human brain and potentially advancing and developing treatments for neurological and psychiatric disorders. Nonetheless, it is evident that **cerebral organoids/brain organoids raise specific ethical issues and concerns**. A participant in the Greek workshop:

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> *There is a set of questions and reservations that are the same for every, applies to everything in particular about patents, access and generally everything we have said so far, but I think the cerebral organoids show a noticeable difference only in the case of one perspective, only if one technology could allow an entire brain to reproduce. And that's exactly where the question comes in, how to define consciousness.*
>
> P10, religious CSO, Greece

The indeterminacy related to the current and prospective derivation of cerebral organoids marks the deliberation on cerebral organoids, for instance the case dilemma 'cerebral organoids and the issue of consciousness' (appendix I), and it generates uncertainties among the participants about their moral, ontological and regulatory status. A primary concern is whether cerebral organoids at some point will be able to exhibit characteristics akin to human sentience, possess cognitive functions or develop some kind of consciousness. A majority of the participants assume a cautious positioning in raising the point that ethical and regulatory guidelines need to be aligned with and be able to respond to potential developments in the field of cerebral organoids. The Italian participants are divided on the need for such attention, as some participants do not envision that future cerebral organoids will ever be able to display consciousness. According to the participants, the **moral status** of cerebral organoids is currently non-comparative to human and animals, but if further developed, they may be compared to the moral status of animals. The Danish participants similarly express that current cerebral organoids have a very low moral status and compare it to animals, some pointing out that cerebral organoids presently have an even lower moral status than mosquitos. As for the prospective moral implications, and perhaps not surprising, participants do not reach a firm positioning as to how and when the moral status may change concurrently with advancements in cerebral organoid research. Hence, specific requirements for rights and special protection are difficult to determine at this point in time.

In addition to the unknown aspects related to organoids becoming sentient and conscious – and the fact that the definition and measurements of consciousness are not agreed upon (Baertschi, 2020, p. 6), a point particularly raised in the Greek deliberation – participants inquire about the possibility of regarding cerebral organoids as individuals:

> *Will it become something similar to something living? Something living as we already know it? You know, people with diseases, people who are lying around and can't do much more than breathe. And will it affect how we see those people, and the fact that it might be us lying like that someday. There is something about our fundamental perception of human life that is important to think about in this.*

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(P11, religious CSO, Denmark).

The question whether cerebral organoids may change our perception, respect and value of human beings was raised as a more fundamental issue in the Danish debate, particularly by representatives from the national church (Evangelical Lutheran Church), and it relates to a concern for a division and devaluation of human worth for some individuals. Some participants raise the concern of unforeseen adverse effects that will be a consequence of treatment procedures and will be irreversible. Furthermore, **the future clinical applications of organoids** are mentioned by a few participants to open the possibility of personality changes and sense of identity, and even manipulation of individuals (e.g., political choices).

> *I'm thinking that if can contribute to e.g. stopping a disease or limit a disease, epilepsy, Parkinson's, then the research is okay. But also that you take it … take the personal things in it, then it becomes … For example, Alzheimer's, if you could adjust on it, how would you get your husband back? Would he be the same or would the personality be different?*
>
> (P10, CSO, identifies as patient, Denmark)

As discussed in chapter 4 on survey results, the majority of Danish participants recognise organoids as something living, and the reaction to seeing a cerebral organoids' physical reaction to light stimulation could increase their attention to the ethical implications of cerebral organoids. The concern for future manipulation was also raised in the Italian workshop, and a majority of the participants expressed the need to address cerebral organoids as a distinct type of organoids.

3.1.4 Dual Use and Science Fiction Aspects

Misuse and dual use of organoid research are raised as a concern, although not a dominant one, in all three workshops, specifically the **potential misuse of organoids for war purposes**. A few of the Danish elderly citizens state that organoid technology might be used for biological warfare, e.g. development of super soldiers. While the possibility for different kinds of misuse is acknowledged and conveyed as potential risks, particularly in terms of data misuse, the more excessive and science fiction-like scenarios are not high on the agenda. In the Greek workshop, references were made to mythological and science fiction aspects with terms such as 'Frankenstein' and 'Wolverine'. The most explicit concern voiced in this regard is a

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resistance to interfering with the natural course of life and enabling human beings to live forever (see also chapter 5 on recommendations).

3.2 Conceptualisations of Organoids

As described in the introduction, one objective in HYBRIDA is to explore and understand the conceptual uncertainty characterising organoids as they are difficult to conceptualise and regulate according to the person/thing dualism (subjects or objects). Due to conceptual uncertainty, and as a starting point, they can be viewed as hybrid entities, something in between persons and things or between nature and artefact because they are complex entities derived from human cells that have the ability to grow into self-organising structures resembling an organ but at the same time does not have the status of a human. A small introduction to the conceptual complexity in regard to organoids and their hybrid status was provided by WP1 and included in the information kit. Participants were given 13 different word options for characterising organoids in the pre-and post-survey. As shown in chapter 4, the most popular descriptors are to perceive organoids as research tools (n=33), cell cultures (n=21), living organisms (n=19) and mini-organs (n=17) at the end of the deliberations (for details, see chapter 4). Participants do not discursively and explicitly construct organoids as something hybrid but discuss them according to the person/thing dualism and to a lesser extent according to the nature/artefact dualism. As to the latter, Danish participants primarily perceived organoids as artificial due to the fact that they are created by humans and would not exist independently. In the Greek deliberation, the issue was discussed in relation to degrees of humanness and human dignity. As reported in the Greek national report:

> *There seemed to be a trend according to which human nature is identical to humanness. Therefore, any intervention in human nature mitigates its humanness. For example, if a person is transplanted with an artificial organ and a prosthetic body part it seems that for some people, this lessens his/her humanness.*
>
> Greek national report, appendix B, p. 19

In addition to the consequences of intervening in natural processes, this aspect is primarily articulated as a concern that organoids could be used to create eternal life and immortality as mentioned above.

Akin to understanding participants’ attitudes as partly depending on the aspect of time/progress (the temporal dimension), participants also emphasise a distinction in their understandings of organoids regarding a current and potential future status of development and advancement. The division between current and

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future progress in organoid research as decisive for organoid conceptualisations is particularly predominant in the Italian deliberation. The large majority of the Italian participants perceive organoids as a research tool and agree that organoids cannot be equated with human beings. Future organoids, especially cerebral organoids, could potentially be considered living beings according to some of the Italian participants (see discussion on cerebral organoids and consciousness in section 3.1.3). As in the Greek discussion, comparing organoids to research tools is reported to be an in-between conceptualisation in terms of the person/thing dualism. Notably, only two of the 51 participants in the survey assign the label ‘thing’ to organoids, which is indicative of the complexity involved in perceiving organoids as ‘something more’ than merely an object. This ‘something more’ causes debate. Based on the survey and deliberations, the majority do not view an organoid as a human being per se, but both Greek and Danish participants define organoids as living organisms and human to some extent.

In both workshops, the definition of a human being was discussed, and divergence exists as to whether human in terms of organoids equals an ability to sense and think, having a beating heart, ‘having properties related to being human’ or something derived/taken from the human body. Table 4 displays different conceptualisations, stressing the human or reification aspects. The Danish and Greek participants are divided on seeing organoids as something human – in the different versions included above – or viewing them as research tools or ‘spare parts’. The ‘spare parts’ metaphor parts is also evoked in the Italian deliberation along with ‘primitive entities’, and participants emphasise the tiny size of current organoids to stress their incomparability with humans. Greek participants who perceive organoids as a research tool do not see organoids as entities that can evolve to having a moral status. This correlation is not clearly identified in the other deliberations. As discussed in the section on cerebral organoids, the question of moral status and when this is to be granted, is not easily settled.

Table 4. Exemplary quotations across deliberative workshops

Conceptualisations of organoids as human	
At present	I also have a concern, and as I understand it, it seems like a natural process. There is an intervention for sure, if I understood it well, it is a natural process the growth of cells in this way, now I get an image, [as if] a flower that grows through the cement. That life, let’s say, finds ways out. (P5, general public, Greece) And I think, some of the things I answered immediately are that it is some living, there is life in it. It is something living, and thereby something human. But it’s also artificial because it has been created. (P11, religious CSO, Denmark)

In the future	Today the brain organ is just a collection of cells (…) Today research must go on [...] if tomorrow we were to have an organism that we can consider to be some living form ..." (P15, patient, Italy)
Conceptualisations of organoids as “things”	
	I distinguish an organoid from an embryo. It is not an embryo. […] So, organoids seem to me like just some research material. That is, I do not want to identify them, I think the questionnaire mentions them as a research tool. Neither an instrument nor a thing, which of course always leaves the question of how it can evolve. But, right now, and based on this data if I wanted to define it just in that way (P12, donor, Greece) My feeling is that it’s a thing created from something human. I wouldn’t consider these, at least at this tiny size, I wouldn’t consider it something human. I would rather see it as a thing that can be used for research or whatever. That was made om something human. (P13, vulnerable group, Denmark) (…) It is difficult to think that "a piece of 5 cm 5 mm could be considered a *person* (male, 41-50 years old, Italy)

3.3 Ethical Issues and Implications in relation to the Derivation and Use of Organoids

The two interrelated themes of informed consent and responsible governance come across as particularly important for participants in order to safeguard ethical and acceptable use and derivation of organoids, and they are closely related to the concerns about commercialisation and insufficient protection of personal data.

3.3.1 Informed Consent and Patient Information

In general, informed consent procedures is a very significant and recurring theme for all participants in the workshops. To safeguard ‘individuals’ and patients’ right to autonomy and self-determination’, it is required from a legal perspective that donors have to give their consent to their cells being used for research and/or clinical purposes, but it can be unclear what specific organoid purposes (e.g. proven/unproven therapies, basic research etc.) individuals or patients are donating their cells to (Baertschi, 2020, Mollaki, 2021, p. 4).

In advocating for **clear, understandable and precise forms of consent**, several participants refer to personal experiences of not feeling properly informed when donating biological samples and that they would have liked to be better informed about the purpose and use of their donation. Consent information should be clear and concise and explain purpose and use, ownership, and distribution of profit. An Italian participant and member of an ethics committee proposes including a short summary in the consent form to increase the transparency of research objectives. Likewise, verbal communication regarding consent should be clear and transparent. Both written and verbal information should focus on **properly and adequately informing donors without over-informing** and providing unnecessary details. Several participants point out that the physical and emotional state of donors might create barriers to processing and relating to too many details and too much information.

Different consent strategies can be implemented in organoid biobanking to obtain and store human biological samples: (a) a blanket consent without limitations, (b) a broad consent with some restrictions, (c) a tiered consent for certain areas (e.g., cancer) or specific diseases (e.g., breast cancer), or (d) continuous consent, which requires re-consent for new uses or purposes (Mollaki, 2021, p. 15). Based on discussions and survey answers (see chapter 4), **a majority of the participants prefer some restrictions imposed on consent procedures**, and only 7 of the 51 participants opt for a broad consent without limitations. In terms of conditions, participants are split in two as to whether informed consent should be broad with some restrictions/tiered for certain areas or dynamic and ongoing and reconfirmed if the donation is used for new purposes and applications. Arguments for the former include a need to secure proper and fair use and avoid misuse, while also recognising the impractical and resource-demanding efforts to identify donors in long-term and large-scale clinical trials for re-consent. In the Greek debate, an argument is made that withdrawal of consent might disrupt the research process and advancement of therapeutics and possibly affect the health of donors/patients. Participants in favour of continuous consent find it most appropriate for donors to give consent in the case of new applications, uses and experiments to avoid future misuse of samples. In the Italian workshop, the example of bone marrow donors in Italy is mentioned as an approach where initial consent is followed by further approvals. The possibility of supervised consent with an ethics committee advising patients is also discussed in the Italian deliberation. A participant in the Greek workshop proposes implementing digital solutions and platforms as a means for donors and/or patients to learn more about their rights prior to a medical test, clinical trial etc. The Greek report points to a correlation between participants advocating for continuous consent and concurrently viewing donors as the rightful owners of the samples donated who should be compensated if profits are derived from therapeutics etc.

3.3.2 Ownership and Governance

In general, the issues of ownership and informed consent are strongly interrelated, as **issues of ownership and remuneration should be specified in the consent form and hence be contingent on the type of**

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consent provided. As a general point of view in the Greek workshop, sample owners – i.e. donors, hospitals, research institutions etc. – should have a share in the profits generated. The question of ownership required careful consideration, as many participants were undecided prior to deliberation (see survey results). After the deliberation the topic was also addressed in a separate case dilemma (see dilemma on ‘Consent, ownership and compensation’ in appendix I), and a majority of participants saw hospitals, research institutions and biobanks as owners of donated biological material. There were different perspectives on whether donors should receive compensation, but a majority of participants adopted the position that donation of cells should be viewed as a **donation or gift transferred without financial compensation** and comparable to blood donation.

While most participants view hospitals, research institutions and biobanks, rather than the state, as owners of donated biological material, participants do not agree on the type of actors who should be in charge of responsible and strict governance of the donated material. Based on the national reports, participants do however seem to favour of the task being managed by the public sector in some form. The Italian participants points to rigorous consent procedures and ethics committees as two avenues for control. Despite inconclusiveness in terms of governance responsibilities, unanimity exist to the position that **ethical use of cell donations must be guaranteed through strict governance structures, control and ethical oversight procedures** to ensure ethically responsible, transparent and safe storage and use of cells, tissues or organoids in biobanks. Likewise, and inherent to ethical governance, strict procedures for protection of sensitive personal data are a key priority for the participants.

4 Deliberative effects and Survey Results

4.1 Deliberative Effects

Participants’ values, attitudes and argumentation related to the benefits and limitations of organoid research were explicitly and partly expressed and informed by lived experiences (personal or family members’ medical stories, and/or experiences obtained through CSO work, for instance) and informed by the expert information provided, among other identifiable factors. Details and exemplary stories are provided in the individual national reports, but in a comparative perspective, the following factors and contextual parameters can be highlighted as having impacted the formation of opinions:

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- Across the country deliberations, participants draw **analogies to related technologies** such as organ donation, blood donation, IVF (in vitro fertilisation) and stem cell research when discussing organoid research. This is reported as particularly noticeable in the Greek deliberation, which might be partly explained by the broad biotechnological perspective in the two Greek expert presentations.
- In relation to the **expert presentations** (see overview of presentation in appendix K of the national reports), the objective of deliberative workshops is to provide participants with the equal opportunity to learn more about the topic in question from a diverse set of perspectives in order to be able to discuss, deliberate and form opinions on an informed basis and to support a more inclusive and efficient process of deliberation (Escobar and Elstub, 2017). All participants were given the same information package prior to the workshops and the opportunity to read about key and varied aspects of organoid research. All participants were also given the same guiding questions and case material in the workshops. The Greek expert presentations focused more broadly on regulation of biomedical research and EU technology assessment, and the Italian and Danish expert presentations addressed organoid research specifically. While it is difficult to measure the effects of the expert presentations, small indications show, perhaps not surprisingly, that the nature of this stimuli influenced the weighting and emphasis on certain topics to some extent. For instance, the discussion on cerebral organoids is more pronounced in the Danish and Italian deliberations, and the topic was specifically addressed in the expert presentations in these two workshops. A reference to EU and EU policy is only made in the Greek workshop, and it is observed that overly both negative and positive perceptions of organoid research developed into more moderate views, presumably due to the nuanced discussions of current and expected benefits of organoids.
- Based on the deliberations and the national reports, **no substantial differences in stakeholder groups or socio-demographics can be inferred to particular organoid positionings or attitudes**. Exceptions from this general observation include the following influences: Most pronounced and as reported above, younger participants seem to focus more on current rather than future challenges and ethical implications in the Danish and Italian workshops. Contrary to initial expectations, **religious affiliation** has not been identified as forming a discernible part of the argumentation in any of the workshops. As stated above, human worth is particularly addressed by especially one religious representative in the Danish workshop. In the Italian case, one Muslim participant explicitly states to be speaking from a religious and spiritual point of view. In regard to stakeholder representation, the Italian and Danish reports point out that **patients groups** focus specifically on current and potential benefits of organoid research, and several participants explicitly express hope for advancing and developing treatments that may benefit close relatives.

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- A comparison of the pre- and post-survey results points to derived **deliberative effects**, i.e. some participants' initial attitudes and understandings of organoids have been revised, clarified and specified based on expert presentations and group deliberations. For example, more participants perceive organoids as a research tool at the end of the workshops, and more participants assume a clarified position on the issue of ownership (see next section on survey results for a complete account).

4.2 Survey Results: Socio-demographic Information, Attitudes, and Opinions

In this section, we first present six diagrams (Diagram 1-6) and accompanying tables (Tables 5-10) with socio-demographic information on the workshop participants, including participant categories, age, gender, religiosity, relation to the job market, and ethnicity/nationality. The tables show the numbers from the three individual workshops as well as the combined figures. The information comes from the questionnaires the participants were asked to fill out at the beginning of the workshop (cf. appendix H) and thus reflects the participants' own understanding of, for example, who they represented in the workshop or which gender category they belong to.

The questionnaire also included four questions on the participants' understanding of and feelings towards organoids as well as questions on ownership and consent. The participants were asked to answer these questions at the beginning of the workshop and again at the end of the workshop to allow us to measure changes in opinions as a result of the workshops. These before and after answers are shown in Diagrams 7-10 with complementary tables.

4.2.1 Socio-demographic Information on Participants

2. Diagram 1: Participant categories and distribution

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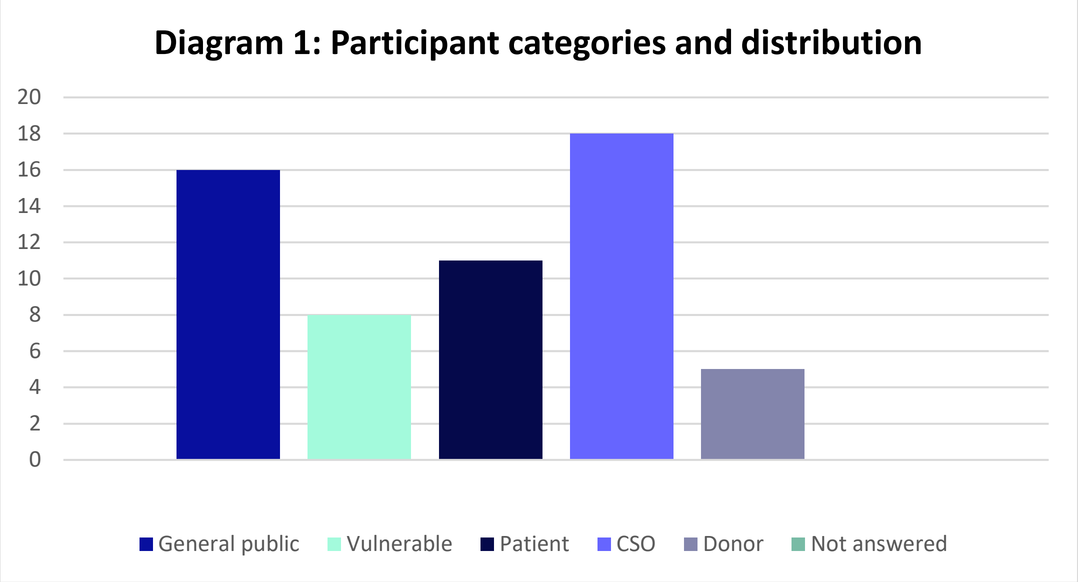

Table 5. Distribution across participant categories – locally and combined

	General public	Vulnerable group	Patient	CSO	Donor	Not answered	Total
Denmark	4	6	5	8	3	-	26
Greece	9	-	1	1	1	-	12
Italy	3	2	5	9	1	-	20
Total	**16**	**8**	**11**	**18**	**5**	**-**	

Diagram 1 and Table 5 show how the participants categorised themselves in the questionnaire. The majority identified themselves as representatives of CSOs (Civil Society Organisations), the general public, or as patients. The Greek participants were mainly from the general public, while the largest group in the Danish and Italian workshops was CSO representatives. It is also worth noticing that most of the participants who identified themselves as 'vulnerable' took part in the Danish workshop (6 out of 8).

Further, Table 5 shows that some of the participants in Denmark and Italy categorised themselves in more than one group (for example, 'CSO' and 'patient'). The 20 Danish participants checked 26 boxes, while the 19 Italian participants checked 20 boxes.

3. Diagram 2: Particiants' age

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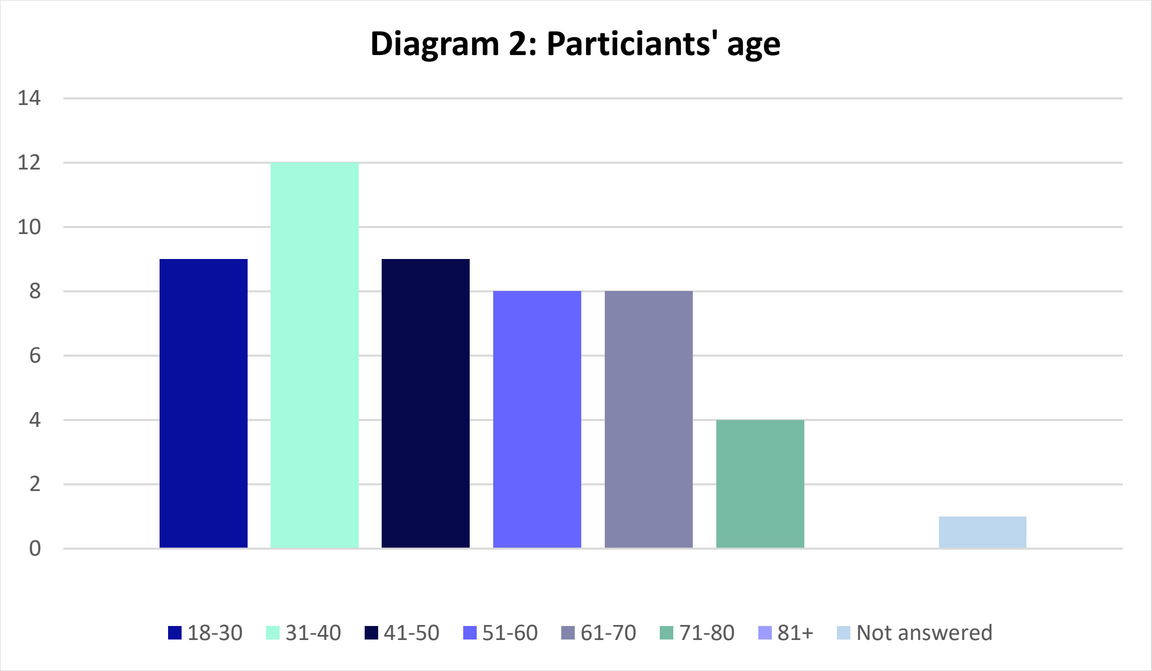

Table 6. Age distribution – locally and combined

	18-30	31-40	41-50	51-60	61-70	71-80	81+	Not answered
Denmark	3	2	3	5	4	3	-	-
Greece	2	6	3	-	1	-	-	-
Italy	4	4	3	3	3	1	-	1
Total	**9**	**12**	**9**	**8**	**8**	**4**	**-**	**1**

Diagram 2 and Table 6 show the age of the 51 participants in the three deliberative workshops. The distribution between age groups is fairly equal. 30 participants were under 51 years old, while 20 were 51 or above. The Greek participants are somewhat younger than the Italian and especially the Danish participants. Only 1 out of 12 participants (8.3%) in the Greek workshop was above 50 years old compared to 12 out of 20 Danish participants (60%).

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4. Diagram 3: Gender distribution

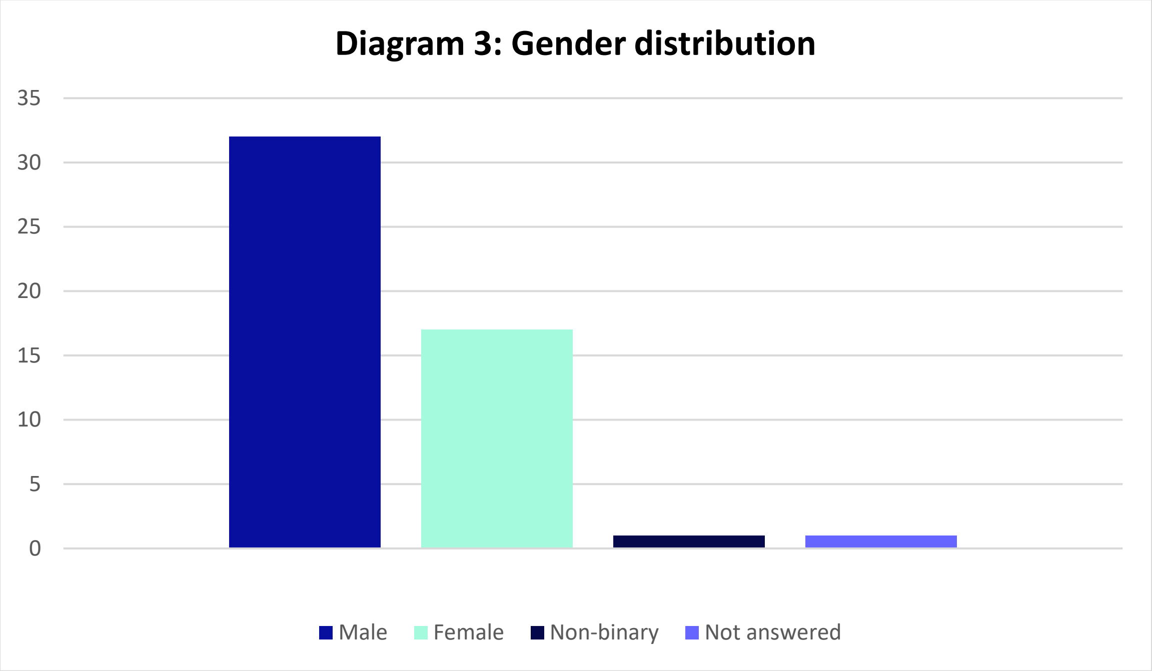

Table 7. Gender distribution – locally and combined

	Male	Female	Non-binary	Not answered
Denmark	13	7	-	-
Greece	7	4	1	-
Italy	12	6	-	1
Total	**32**	**17**	**1**	**1**

The gender distribution among the participants is shown in Diagram 3 and Table 7. There were 32 men, 17 women, and one non-binary person (one participant did not answer this question). In all three countries, there were more male than female participants.

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5. Diagram 4: Religiosity

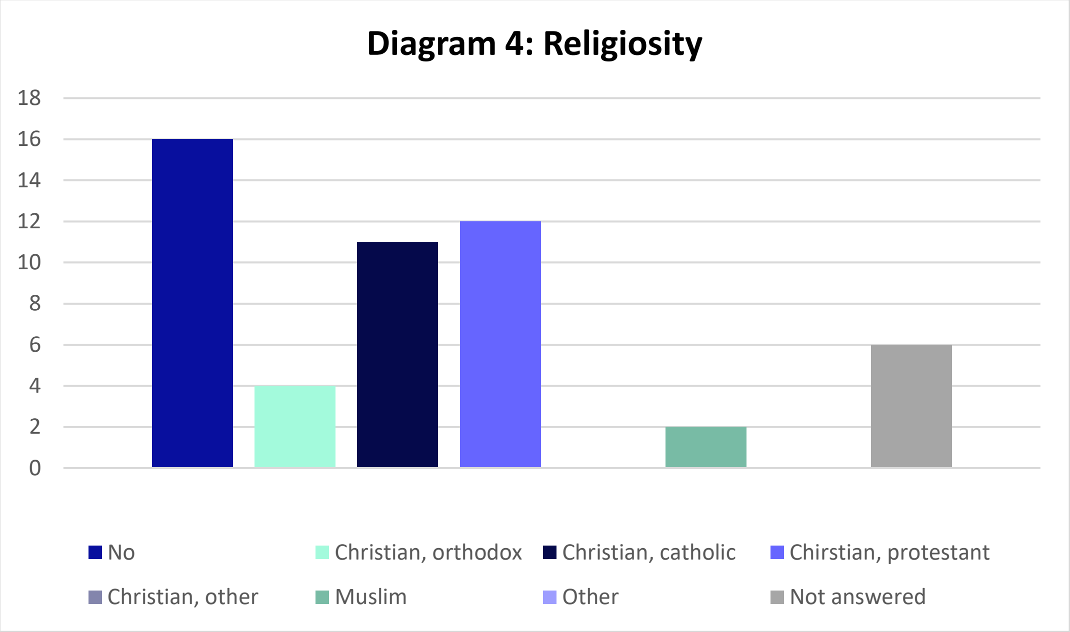

Table 8. Religiosity – locally and combined

	Not religious	Christian, Orthodox	Christian, Catholic	Christian, Protestant	Christian, other	Muslim	Other	Not answered
Denmark	4	1	1	12	-	1	-	1
Greece	7	3	-	-	-	-	-	2
Italy	5	-	10	-	-	1	-	3
Total	**16**	**4**	**11**	**12**	**-**	**2**	**-**	**6**

Diagram 4 and Table 8 show the participants' religious orientations. 16 participants did not consider themselves religious. This group was biggest in Greece with 7 out of 12 participants. Looking at the different religions represented, Orthodox Christianity was dominant among the few religious Greek participants, Catholicism among the Italian participants, and Protestant Christianity among the Danish participants, as expected. One Danish participants checked "Christian, Orthodox" and one checked "Christian, Catholic", however they may have checked the wrong box as there are very few orthodox Christians in Denmark.

Three fourths of the Danish participants considered themselves religious (15 out of 20). In Italy, 11 out of 19, and only 3 participants in Greece.

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It should also be noted that despite a focus on including Muslim representatives in the workshops, this was only realised in two cases.

6. Diagram 5: Relation to job market

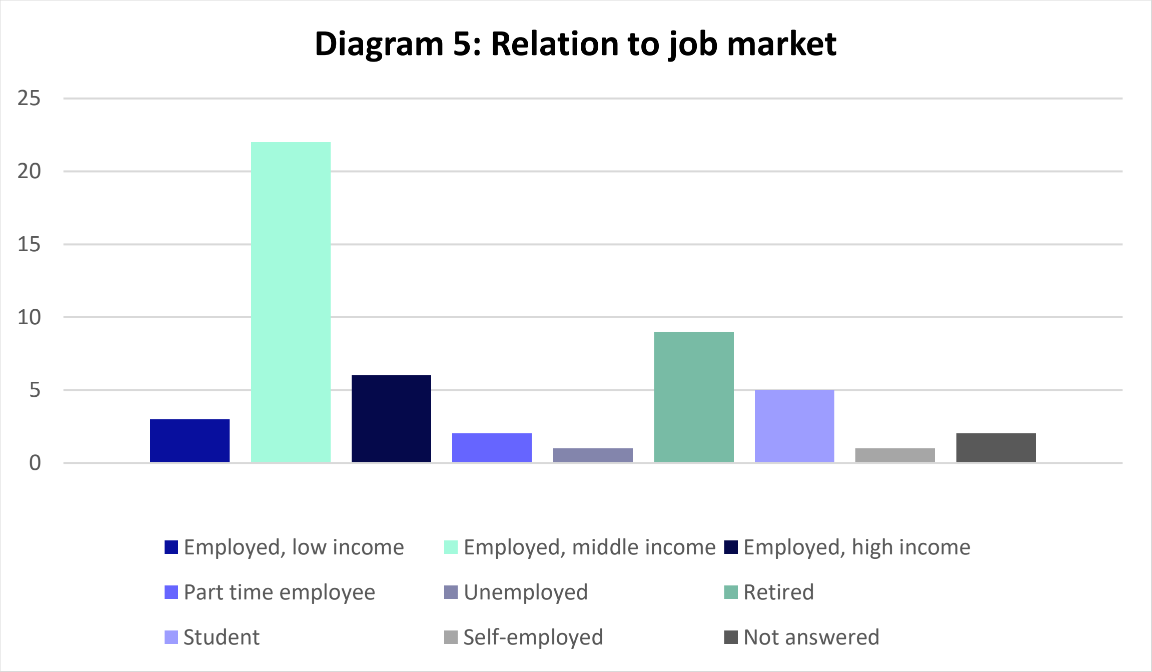

Table 9. Participants' relation to job market – locally and combined

	Empl., low income	Empl., middle income	Empl., high income	Part time empl.	Unem-ployed	Retired	Student	Self-empl.	Not answered
Denmark	-	5	4	2	-	6	2	1	-
Greece	1	9	1	-	1	-	-	-	-
Italy	2	8	1	-	-	3	3	-	2
Total	**3**	**22**	**6**	**2**	**1**	**9**	**5**	**1**	**2**

In this part of the questionnaire, the participants were asked to indicate their relationship to the job market. The biggest group was "Employed, middle income" overall (22 out of 51) and in the Italian and Greek workshops. The biggest group in the Danish workshop was "retired", correlating well with the higher average age of Danish participants, especially compared to the Greek group. Many of the Danish participants were recruited from voluntary organisations, where retirees are traditionally very active. It should also be noted that the questionnaire did not have a ‘self-employed’ category. A participant in the Danish group made us aware of this and created his own category for this.

7. Diagram 6: Ethnicity/nationality

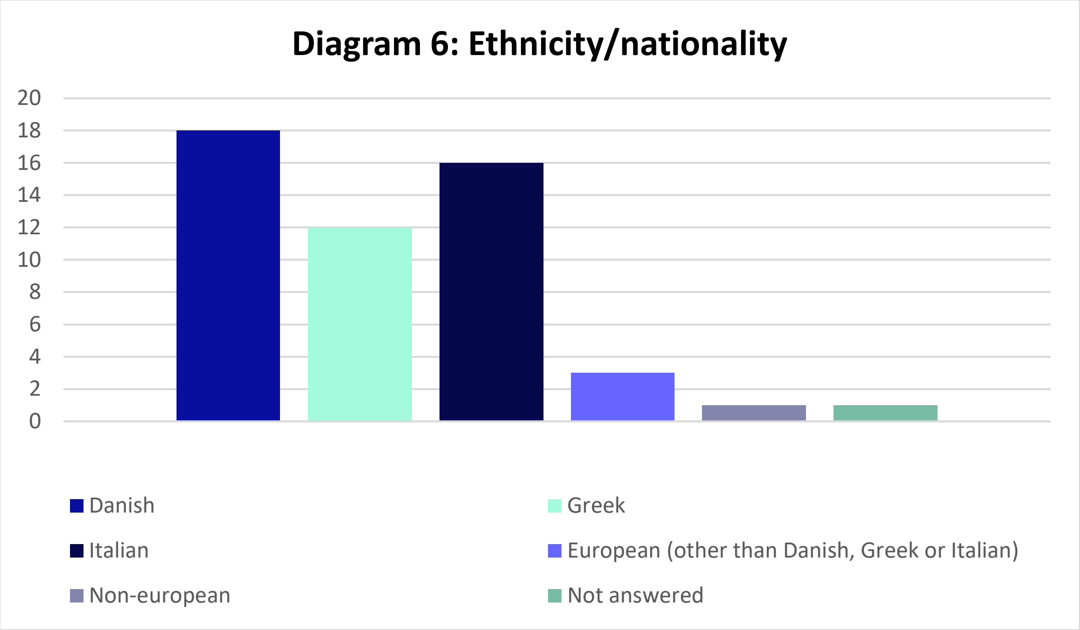

Table 10. Ethnicity/nationality – locally and combined

	Danish	Greek	Italian	European (other than Danish, Greek, and Italian)	Non-European	Not answered
Denmark	18	-	-	2	-	-
Greece	-	12	-	-	-	-
Italy	-	-	16	1	1	1
Total	**18**	**12**	**16**	**3**	**1**	**1**

Diagram 6 and Table 10 show the distribution based on ethnicity/nationality. In general, most participants identified with the nationality of the country in which they participated. This is not surprising since all three workshops and the material used to inform and recruit participants were in Danish, Greek, and Italian, respectively. To participate, one therefore had to be able to speak the language of the given country. 3 participants identified as Europeans (other than Danish, Greek or Italian). Only 1 participant described themselves as non-European.

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4.2.2 Changes in Attitudes, Feelings, and Opinions

Besides gaining knowledge on socio-demographic variables, the purpose of the survey was to document participants' understanding of and feelings towards organoids and organoid research together with their opinions on consent and ownership questions. We also wanted to document potential changes in attitudes, feelings, and opinions as a result of the workshop. Therefore, participants were asked to answer the same questions before and after the workshops. The results are shown in Diagrams 7-10 and Tables 11-14 as side-by-side bars – before and after – for easier comparison.

8. Diagram 7: Which words best describe organoids?

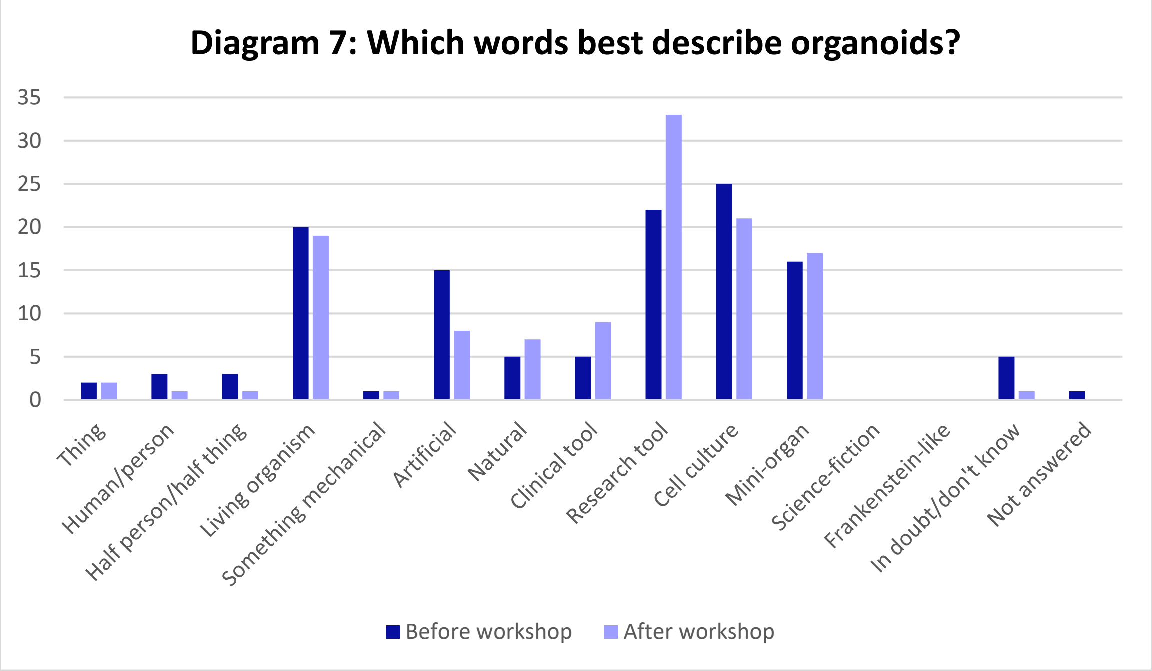

Table 11. Words describing organoids, before and after the workshop

	Denmark		Greece		Italy		Combined	
	Before	After	Before	After	Before	After	Before	After
Thing	-	1	-	-	2	1	2	2
Human/person	1	1	1	-	1	-	3	1
Half person/half thing	-	-	-	-	3	1	3	1
Living organism	10	14	3	1	7	4	20	19

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Something mechanical	-	-	1	-	0	1	1	1
Artificial	3	3	6	4	6	1	15	8
Natural	2	3	1	2	2	2	5	7
Clinical tool	1	2	2	3	2	4	5	9
Research tool	7	11	3	7	12	15	22	33
Cell culture	11	12	7	3	7	6	25	21
Mini-organ	10	11	1	3	5	3	16	17
Science-fiction	-	-	-	-	-	-	-	-
Frankenstein-like	-	-	-	-	-	-	-	-
In doubt/don't know	3	-	2	1	-	-	5	1
Not answered	-	-	-	-	1	-	1	-
Total	**48**	**58**	**27**	**24**	**48**	**38**	**123**	**120**

Diagram 7 and Table 11 show which words the participants found most fitting to describe organoids before and after the workshops. Before the workshops, i.e. before expert presentations and deliberations, the three most used descriptions were “cell culture” (n = 25), “research tool” (n = 22), and “living organism” (n = 20). Also “mini-organ” (n = 16) and “artificial” (n = 15) were popular descriptions. After the workshop, the perception of organoids had changed quite a bit. The number of participants who thought about organoids as “artificial” had dropped from 15 to 8, and “cell-culture” from 25 to 21. “Research tool” was now the most used description across workshops (rose from 22 to 33).

Among the Danish participants, “living organism” became a more popular description during the workshop (rose from 10 to 14), while the number of participants in Greece and Italy who chose this option fell to 1 and 4, respectively. In the Danish workshop, especially a representative from the Protestant Church pointed out that organoids should be seen as something living. Another difference between the three countries is that the Danish participants used more words to describe organoids after the workshop than before, whereas the Greek and Italian participants used fewer.

When interpreting the differences between the three workshops, one has to bear in mind that although we attempted to make the three workshops as similar as possible by operating with a similar design, specifying the themes to be discussed, time used for the different subjects etc. (see chapter 2 for details), there were differences in, for example, the expert presentations, which might have influenced the way participants answered the questionnaire (for a description of the different Expert presentations, see appendix K). Small

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differences in the recruitment process may also have influenced the results. For the Danish workshop, a recruitment poster on social media used the description 'mini-organ' for organoids, and one of the experts in the workshop used the same description. This might explain why so many of the Danish participants both before and after the workshop (n = 10/11) used this description compared to the relatively few participants in the two other workshops (n = 1/3 and 5/3).

Regarding "research tool", the most used description after the workshops, it is worth noticing the difference between the number of participants who after the workshops thought of organoids in this way (n = 33) and the number who thought of it as a "clinical tool" (n = 9). Participants clearly see organoids – in their current state – more as a research tool than something to be applied in a clinical setting.

9. Diagram 8: Feelings related to organoids

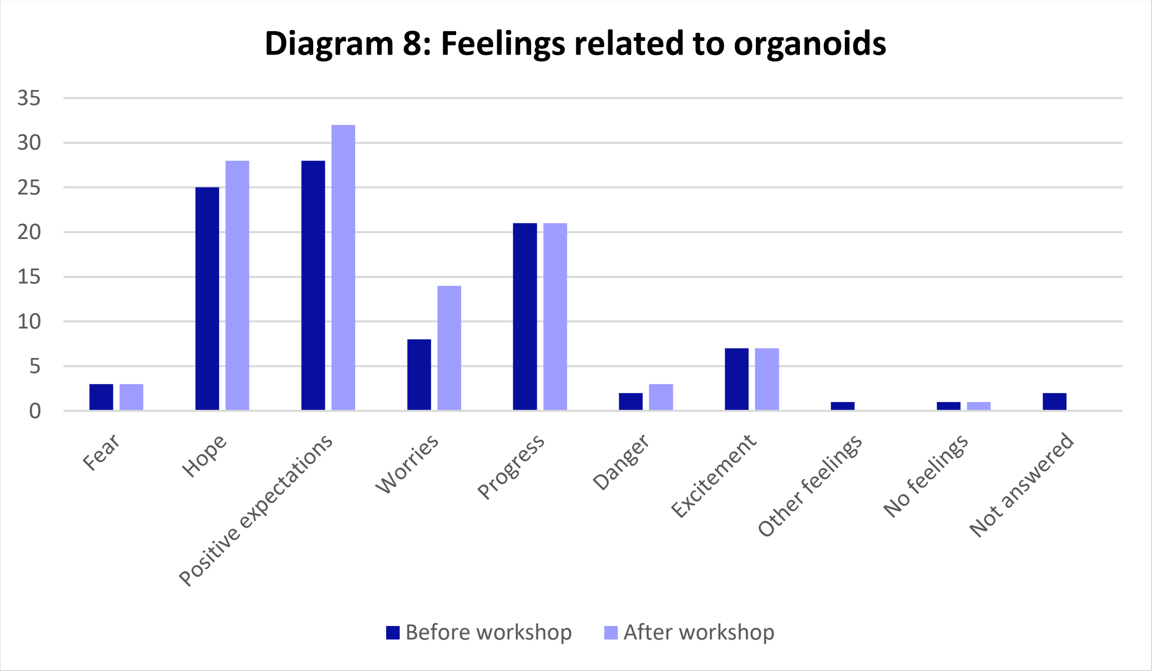

Table 12. Feelings related to organoids, before and after the workshop

	Denmark		Greece		Italy		Combined	
	Before	After	Before	After	Before	After	Before	After
Fear	1	3	2	-	-	-	3	3
Hope	8	10	5	4	12	14	25	28
Positive expectations	13	13	7	10	8	9	28	32
Worries	4	9	3	4	1	1	8	14

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Progress	9	8	3	1	9	12	21	21
Danger	0	1	1	1	1	1	2	3
Excitement	5	6	1	-	1	1	7	7
Other feelings	1	-	-	-	-	-	1	-
No feelings	-	-	1	1	-	-	1	1
Not answered	-	-	-	-	2	-	2	-
Total	**41**	**50**	**23**	**21**	**34**	**38**	**98**	**109**

Diagram 8 and Table 12 show the participants' feelings related to organoids before and after the workshops. Most have positive feelings towards organoids, with "positive expectations", "hope" and "progress" being the dominant answers both before and after, with a small increase in "positive expectations" (from 28 to 32) and "hope" (from 25 to 28).

However, the participants also feel more worried after the workshops (increasing from 8 to 14). This increase primarily stems from the Danish participants (from 4 to 9), and it is probably connected to the point discussed above that many of them understand organoids as something living (see Table 11). However, one of the experts also showed video material of organoids, which, as the deliberations showed, made a huge impression on the participants (see chapter 3). The material included a short video showing a cerebral organoid's reaction (contraction) to light stimulation and another video showing the movements of a bowel organoid.

10. Diagram 9: Who owns the organoids?

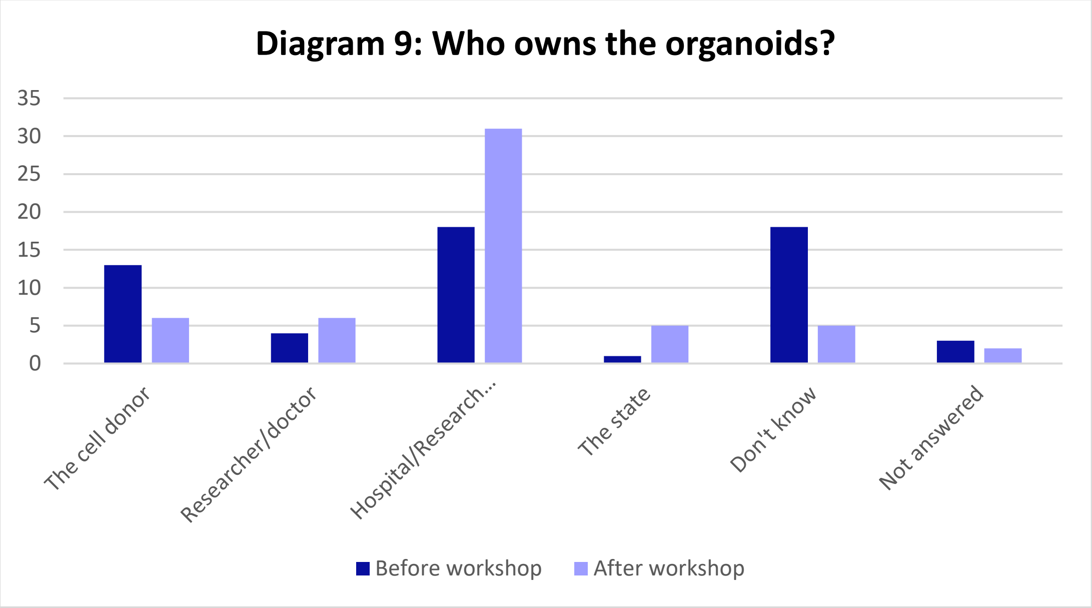

Table 13. Attitudes regarding ownership, before and after the workshop

	Denmark		Greece		Italy		Combined	
	Before	After	Before	After	Before	After	Before	After
The cell donor	5	6	4	-	4	-	13	6
Researcher/Doctor	1	3	1	2	2	1	4	6
Hospital/Research institution/Biobank	6	10	1	5	11	16	18	31
The state	-	4	-	-	1	1	1	5
Don't know	11	1	5	3	2	1	18	5
Not answered	-	-	1	2	2	-	3	2

Diagram 9 and Table 13 show whom the participants consider to be the rightful owner of the organoids. The substantial changes in answers before and after workshops demonstrate the impact the expert presentations and deliberations had on the participants. For example, only 5 answered "Don't know" after compared to 18 before.

Before the workshops, a clear majority of participants (18) believed that "Hospital/Research institution/Biobank" should own the organoids compared to 31 after. In Italy, 16 of 19 participants preferred this option, which is close to a consensus. In written comments, participants pointed out that this question is strongly related to the question of consent, i.e., that ownership depends on the type of consent given.

Moreover, before the deliberations begun, 13 participants preferred the donor as owner of organoids compared to 6 participants after, all from the Danish workshop. 4 out of 20 Danish participants also felt that the state was the rightful owner of the organoids. Only one other, an Italian participant, chose this answer. Here, differences in trust in the state or political system in the three countries might have played a role, as explained in the country reports (cf. appendix A, B and C).

Some participants in the Danish group checked more than one box for this question, so the answers sum to 23 before and 24 after from the 20 participants. Likewise, in the Italian workshop more answers were chosen before the deliberations begun (22 answers from 19 participants), but not after.

11. Diagram 10: Which form of consent is the best?

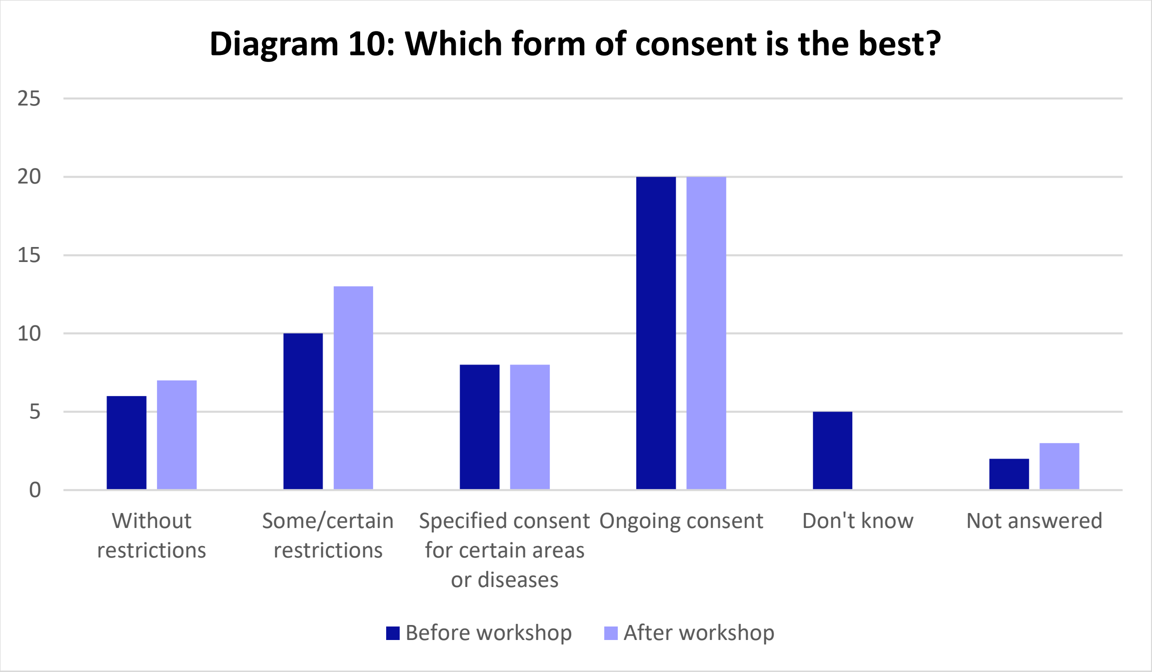

Table 14. Opinions on consent, before and after the workshop

	Denmark		Greece		Italy		Combined	
	Before	After	Before	After	Before	After	Before	After
Without restrictions	3	3	-	2	3	2	6	7
Some/certain restrictions	2	4	4	4	4	5	10	13
Specified consent for certain diseases or areas	4	2	-	1	4	5	8	8

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Ongoing consent	8	10	6	3	6	7	20	20
Don’t know	3	-	2	-	-	-	5	-
Not answered	-	1	-	2	2	-	2	3

Diagram 10 and Table 14 show which type of consent the participants found most relevant for organoid research before and after the workshops were conducted. Both before and after the workshop, the most popular answer (n = 20) was “ongoing consent” (sometimes also referred to as *dynamic consent*) . The number of participants choosing this answer increased slightly after the workshop in both Italy and Denmark, while it decreased from 6 to 3 in Greece. The second most popular answer at the end of the workshop was consent with “Some/certain restrictions” (n = 13). In sum, the questionnaire clearly shows that participants prefer consent to have some restrictions, so that a donor actively has to give a new consent if researchers want to use the donated tissue for new purposes.

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5 Participant Recommendations

The key ethical issues to be taken into account in future guidelines for organoid research can be broadly categorised according to the themes: 1) communication and research dissemination, 2) governance of organoids, and 3) ethical implications. Table 15 summarises the recommendations and priorities identified by the 51 participants. In the aggregate, there is strong consensus on the need to prioritise a) thorough consent procedures and resources for careful patient information, b) responsible, objective and transparent research dissemination, c) ethical oversight and responsible governance structures, d) strict data security and storage, e) mitigation measures for unintended consequences and misuse, f) promotion of equal access to research results and therapies, and e) focus on human value and improvement of the quality of life, not seeking immortality. Additionally, the dynamic and changing nature of organoids call for ethical guidelines, procedures and frameworks to be regularly updated (see section 3.1).

Table 15. Recommendations for key ethical issues to be addressed

Theme 1. Communication and research dissemination	
Informed consent and patient information	Informed consent procedures and forms, as well as all relevant information provided to patients and donors, should be clear, concise, simple and understandable. Some participants suggest that this kind of information can and should be fully digitalised and available in advance to all interested parties, at any given time. Some participants suggest allocating resources to the specific purpose of patient information, e.g. to secure sufficient time to provide information. Some participants highlight the importance of specifying the purposes of the research or the final use of the materials. The consent should be reshaped if new technologies are discovered, and the destination of donated cells changes. Supervised consent through ethics committee that can advise patients can be considered.
Neutral, objective and transparent research dissemination	Clarity regarding how information on organoids is disclosed. It is important that information on organoids is disseminated in a clear, simple and above all transparent way by competent authorities in order to strengthen the relationship between scientific research and civil society.

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	Information on the potentialities of organoid research (stage of development, progress, potential applications) must be provided to the public to allow citizens to contemplate realistic rather than unrealisable scenarios. The terminology is important. Describing organoids as something human may cause fears and worries, while cell cultures or something similar to medication is more neutral. Transparency regarding stakeholders involved in organoid research (RPOs, RFOs, policymakers, public and private sector)
Theme 2. **Governance of organoids**	
Continuous evaluation of ethical guidelines	Regular review and evaluation of ethical guidelines. No agreement on how often this should be performed, since the progress of organoid research is unknown. The recommendation is to stay ahead and as far as possible avoid addressing potential issues after they become problematic.
Ethical oversight	The presence of ethics committees or public institutions to control how donated material and scientific discoveries are used is very important. The need for public control and transparency is highlighted by some participants in relation to the presence of the private sector in the research field. Some participants suggest a regularly updated list, a database of labs and research institutes that conduct organoid research and the current state of research. Strict regulation of organoid research to avoid misuse and maleficent applications, as those developed in other types of research. Transparency in organoid research and governance is important and will cause the public to feel safe and more trusting.
Governance responsibility	Regarding data collection, management and storage, participants broadly feel more comfortable with the perspective of these being governed by the state(s) and, in general, the public sector. A suggestion is to involve the World Health Organization in the governance or monitoring of organoid research. WHO could be in charge of evaluating and monitoring the research and medical development based on organoid research or participate in a council with various stakeholders and citizens. Some participants warn against governance being *too* bureaucratic based on a worry that important decisions and actions will lag behind the development.
Adaptation of guidelines in alignment with type of organoids	Use of specific adjustments when needed based on the particular types of organoids, such as cerebral organoids.

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Learning and best practices implemented from guidelines on related technologies	It would be advisable to follow the examples of other, well-established, analogous types of research/technologies and procedures, such as stem cell research, cloning, IVF, organ donation/transplantation, blood donation.
Data security and storage	Strict focus on data security and storage. This could be managed based on the consent given in the specific case.
Theme 3. Ethical implications	
Equal access to research results and therapies	The results of biomedical research on organoids must be distributed equally and globally based on the principles of solidarity, sociality and subsidiarity. Guidelines should support a development that will not increase inequality, e.g. by avoiding monopolising and commercialisation resulting in treatments being too expensive or non-accessible to the general public. As organoid research and potential applications focus on improvement of treatments, therapies and, in general, quality of life, it should be made sure that there will be no exclusions to access due to origin, sex, sexual orientation, religious orientation, economic status to these benefits for society at large. Organoid research should not increase inequalities.
Human value and course of life	The guidelines should consider our current perception of human value and how organoid research might affect and change this. The extent to which intervention to the course of life is desirable is open to discussion. The goal must be to improve quality of life but without aiming for eternal life and immortality. No participants expressed a desire for immortality.
Intended and unintended negative consequences	The legitimate goal of saving lives, curing disease and improving health must not affect other important ethical issues and harm others, such as the environment or other inhabitants of the earth. Carefully monitor uses to prevent activities against humanity. The guidelines should include rules regarding responsibility in case something goes wrong, e.g. unexpected results of organoid-based treatments.

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7 Appendixes

Appendix A. National report - Italy

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HYBRIDA

Public attitudes, understandings and perspectives on organoid research

HYBRIDA

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

Report factsheet:

Project Title:	HYBRIDA
Title of Report:	Public attitudes, understandings and perspectives on organoid research
Author(s):	Prof. Mario Picozzi Msg. Renzo Pegoraro Dott.ssa Emma Capulli Dott. Giovanni Rasori
Finalised on (date):	First version: 12.01.2022 Second version: 24.01.2022 Third version: 02.02.2022 Fourth and final version: 13.02.2022

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1 Introduction: Deliberative Workshops on Organoid Research

1.1 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[2].

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.

Following Roman times, all entities have been categorised 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 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

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[2] 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 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. In order to develop ethically and socially robust ways of assessing the effects of organoid research and related technologies, there is a need to include these additional forms of uncertainty in the Health Technology Assessment (HTA).

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

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 the Deliberative Workshop in Italy

This report focusses on the deliberative workshop on organoids research that was conducted in Italy in November 2021 as part of the HYBRIDA project.

In Italy, the Catholic religion certainly plays an important role in influencing people's attitudes towards emerging and controversial science and technologies. Specifically, according to a survey (*"Special Eurobarometer 516". September 2021. Retrieved 24 September 2021 - see Volume C: Country/socio-demographics: IT: Question D90.2*), 79% of Italian citizens are Christians Catholic. It differentiates Italy from the other study countries, Denmark and Greece, where the dominant religions are, respectively, Protestant and Orthodox Christianity.

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Italy is classified as a ‘Moderate innovator’ in the European and Regional Innovation Scoreboards 2021 (European Commission 2021a: https://ec.europa.eu/research-and-innovation/en/statistics/performance-indicators/european-innovation-scoreboard/eis).

In the *Eurobarometer Report on European citizens’ knowledge and attitudes towards science and technology*, it is reported that 50% of Italian citizens feel “poorly informed” about new medical discoveries. In the same Report it can be noted that the proportions that agree with the statement: “Science and technology do not really benefit people like you” are amoung the highest in Italy (37%), and amoung the lowest in Denmark (9%).

(https://europa.eu/eurobarometer/surveys/detail/2237)

2 Methodology: Deliberative Workshops

This section outlines and details the methodological issues related to the design, planning and completion of the deliberative workshop, i.e. the particular research design, research questions, participant recruitment and data collection as well as the process of coding and analyzing the data and knowledge obtained from the workshop.

2.1 Design: Exploration of Public and Stakeholder Attitudes towards Organoids through Deliberative Workshops

Deliberative workshops can be characterized as “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). Great emphasis is placed on facilitating deliberation based on expert inputs and an examination of various issue positions with the objective to elicit a broad and diverse range of views on the topic in question (The Danish Board of Technology, 2014; O’Brien et al. 2020; Steel et al. 2020, for more details on the method of deliberative workshops, please see the research protocol for the study, Ravn and Sørensen, 2021).

The purpose of conducting three deliberative workshops is to explore and elicit different views on the use and derivation of organoids and organoid research to understand the public opinion (i.e. worries, concerns, fears, uncertainty and expectations) and key ethical issues and implications related to organoids from the

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point of citizens, vulnerable groups, patients, donors and CSOs. More specifically, the deliberative workshop has been designed to answer the following research questions:

How do non-professional stakeholders and the lay public perceive organoids and organoid research?

○ What are the participants' main worries, fears and expectations concerning organoid research?

○ How do participants conceptualise and understand organoids (i.e. persons vs. things, moral status, mythological aspects)

○ What are the perceived current and future benefits of organoid research according to the participants?

○ Which kind of ethical issues or research poses concern for the participants? (i.e. particular organoid types and uses; particular ethical issues such as informed consent, ownership and commercialisation)

The valuable public and stakeholder perspectives into these questions will provide key insights and unique knowledge into the continuous process of developing the four HYBRIDA project outputs, including operational guidelines and an ethics framework. The exploration of these questions was conducted in a two-phase deliberation at where the first part explored the 'attitudes towards and conceptualisations of organoids' and the second part focused on 'perceived benefits and concerns in relation to the derivation and use of organoids' in terms of key ethical issues and implications to be taken into account in regard to organoid research.

2.2.1 Format and Setting in the Deliberative Workshop in Italy

The Deliberative Workshop in Italy took place in Rome, Via della Conciliazione 1, at the premises of the Pontifical Academy on 20 November 2021. Activities started at 10 a.m. and ended at 5 p.m., with a one-hour lunch break from 12.30 to 1.30 p.m. Present at the event as organisers were Professor Mario Picozzi of the University of Insubria (the Italian contact person for the Hybrida project), Professor Renzo Pegoraro of the Pontifical Academy for Life and University of Insubria doctoral student Emma Capulli. Daniela Mordenti Boresi was present as moderator and 19 participants took part in the deliberative workshop.

All activities were carried out in compliance with coronavirus-related safety measures. The participants seats were spaced apart and the room was ventilated several times during the day. In addition, lunch was served in individual boxes provided by the catering company.

The programme of the day was carried out according to the shared agenda, with no particular variations. The only small variation was the reduction of the time of some activities planned during the morning, as

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the experts' presentations lasted longer than the agenda stated. As an icebreaker exercise, each participant was asked to introduce himself/herself, sharing the reasons for his/her recruitment (membership of patient; associations, donors, students..) and what his/her expectations were regarding the day.

The moderator had a fundamental role in coordinating the event. This role was played by Daniela Mordenti Boresi, professor of communication sciences and journalism techniques at the University of Padua, with experience as coordinator, moderator of events and editor-in-chief.

The programme of the day was divided into two phases.

The 1st phase focused on the participants' attitudes towards and conceptualisation of organoids. This phase included:

- Filling out the first part of the questionnaire (Appendix A).
- Expert presentations. The experts' presentations were essential to introduce the participants to the topic. Two professionals were chosen: Teresa Rinaldi and Andrea Lavazza.
    - Teresa Rinaldi, a graduate in biological sciences, currently works at the Department of Biology and Biotechnology "Charles Darwin" of the Sapienza University of Rome, where she teaches pharmacogenomics, fermentation biotechnology and applied geosciences and bioconservation laboratory.
    - Andrea Lavazza is Senior Research Fellow in Neuroethics at the Centro Universitario Internazionale di Arezzo and Adjunct Professor at the University of Pavia. He is also a lecturer at the Master of Forensic Psychopathology and Neuropsychology at the Faculty of Psychology, University of Padua.

The first expert presentation was an introduction to organoids in general terms, it explained what organoids are, from which cells and how they are produced and the various types of organoids that exist today. The second presentation was a focus on a particular type of organoid: brain organoids.

Group discussions to make questions for the experts. The research team had divided the participants into three groups to ensure that all categories of participants were represented in each group.

- Q&A session with the two experts.
- Group deliberation based on two guiding questions focusing on the perceptions and feelings regarding organoids. Each group presented their main points for the other participants.

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The 2nd phase focused on the ethic perspective of organoid research, including hopes, fears, expectations, and worries related to it. During the second phase, the participants were divided into new groups. This phase included:

- An introduction to two dilemmas and time for the participants two reflect on them individually.
- Group deliberation in two parts: First, they discussed the two presented dilemmas. Second, they had to discuss which ethical issues and recommendations for future guidelines they found most important.
- Group presentations of the main points from their discussions and a plenum discussion.
- Filling out the second part of the questionnaire.
- Conclusion and evaluation of the day.

At the end all participants were provided with a small gift bag. Participants were reimbursed for their travelling expenses, but they did not receive any payment for their participation.

In general, the event ran smoothly. Compared to the initial agenda, the only significant change was in the time allowed for the experts to give their presentations - which was very short (only 10 minutes each). All activities were received with interest and involvement by the participants and the time left for deliberation allowed for good interaction.

2.2 Sampling and Recruitment Procedures for Deliberative Workshops/mini-publics

The recruitment took place in several steps.

As a first step, sub-categories were identified for each category indicated in protocol 4.2, so that they would be suitable to represent the general category and at the same time ensure heterogeneity within it. Efforts were made to ensure heterogeneity in terms of age, gender, education and areas of expertise. For example, in the General Public category, the following sub-categories were identified: university students, consumers, immigrants, volunteers, cultural associations.

As a second step, associations or groups were sought that fell into each sub-category. Thus several student associations, various cultural or voluntary associations and so on.

As a third step, each association was contacted either by phone or email, introducing the project and motivating the reasons for recruitment.

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When a person expressed his/her interest in participating, as a fourth step, he /she was sent the official invitation letter.

For the vulnerable groups it was decided to recruit two members of associations of parents of sick children and one patient. In the patient category, three categories of patients were selected (with priority given to those listed in protocol 4.2), including a cystic fibrosis patient, an ALS patient, and a breast cancer patient. As a third donor, it was decided to recruit a transplanted woman, who had received a liver transplant and was a member of the national association Aido. Amongst the representatives of Civil Society Organisations, it was decided to recruit three religious' representatives (two from the Catholic religion and one from the Islamic religion) and two members of two separate science outreach societies.

The total number of people recruited was 20, of whom 19 took part in the workshop. One person cancelled the morning of the workshop due to illness.

Recruitment does not correspond to the results of the questionnaires because several participants fitted into more than one of the mentioned categories, and some of them categorized themselves as being part of another group than the one they were recruited from.

Table 1. Summary of recruitment results:

Vulnerable group	Patients	Donors
1)Childhood Diabetes As.	1)Cystic Fibrosis patient	1)Organ recipient
2)Children muscular dystrophy As.	2)Breast cancer patient	2)Blood donor
3)Rheumatic patient	3)ALS patient	3)Blood donor

General Public	Civil Society Organization
1)Student Association 1	1)Catholic religion 1
2)Student Association 2	2) Catholic religion 2
3)Consumers Association	3)Islamic religion
4)Immigrant Association	4)Soc. Scientific dissemination 1
5)Voluntary Association	5) Soc. Scientific dissemination 2
6)Cultural Association	

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Table 2. Indicative gender/age distribution of participants

Age/Gender	18/30	31/40	41/50	51/60	61/70	71/80
Women		X	X	XX	X	X
Men	XXXX	XXX	XX	X	XX	

2.3 Data analysis

The data from the workshop was collected through audio recordings from the workshop, posters made by the participants during group deliberations, potential field notes from the present researchers, and questionnaires filled out by the participants during the workshop.

The small-group and plenum discussions were audio-recorded during the event. The audiorecordings were transcribed verbatim. The data from the transcripts was coded using the programme NVivo 12. The coding was mainly based on a deductive approach with predefined codes related to the research questions following the common guidelines shared by Aarhus University.

The coding strategy was primarily directed by a thematic oriented strategy deductively derived from the research questions, themes and guiding questions applied. To structure the coding process as an initial step, we used the list of codes drafted among partners. During the codification we added some more codes emerging through the deliberation in the Italian workshop.

Later, the data were analysed through a within and across-case strategy.

The within-case analytical strategy has three main ambitions:

a) report on in-depth descriptions on the attitudes, perceptions and experiences of participants as to the derivation and use of organoids (phase 1);

b) describe matters related to the perceived benefits and concerns of organoids;

c) report on all recommendations to show the breadth and depth of the ethical concerns (phase 2).

In addition to an account of the perceptions expressed by the deliberators, the analysis within the case will also analyze perceptions and outcomes in relation to contextual issues (e.g. cultural, religious influences)

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and other factors (e.g. variation with respect to the group of participants / stakeholder or type of organoid research, etc.) important for understanding participants' perceptions.

3 Findings

This section presents the main results from the data collected during the deliberative workshop in Italy. The results obtained from the analysis show a general acceptance by the participants of organoids. Those who took part in the discussions showed great involvement and great interest in the event. The first part of the exposition concerns participants attitudes (expectations and fears) towards organoids and the way in which they have been conceptualized. The analysis took into consideration the expressions used by the participants to refer to organoids and the priority that they were recognized in terms of recognition of the protection of interests. The second part of the exposition (par. 3.2) instead relates to more specific issues. In particular, the participants' considerations on some specific issues were reported, concerning the ownership of donated cells, marketing and informed consent. And lastly, the analysis includes an overview of the participants' recommendations for future guidelines for organoids research.

3.1 Attitudes towards and Conceptualisations of Organoids

Participants generally expressed a feeling of positivity and hope towards organoids. In regard to the way in which the latter have been conceptualized, as we will see better in the next paragraph, their position must be identified in a hybrid zone between the thing and the person. None of the participants equiparated the organoid with a human being or even in its entirety with one thing. The analogy that has been most successfully used in terms of conceptual and moral collocation is that with non-human animals. Although the participants expressed some fears on organoids and possible future implications, the prevailing feeling is that of hope on the benefits that can be derived from them.

3.3.1 Commercialization, personal data, misuse and scientific communication

Regarding the possibility of commercialization, the participants expressed some concerns regarding the use of profits by the private sector. Differences of opinion emerged on the topic.

Generally, they shared the idea that the cells should be given to research institutions through a donation, which therefore does not provide any type of remuneration, neither for those who sell the cells nor for

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family members. On this topic, the episode of Henrietta Lacks has been repeated several times. Her story and that of the He-La cells were mentioned by a speaker when she answered the questions expressed by the participants and subsequently the episode was re-discussed and mentioned by two of the groups during the afternoon discussion. Although a feeling of injustice was expressed relating to the aforementioned case, most of those present expressed themselves negatively about obtaining earnings.

The opposition to commercialization has been expressed with frequent reference to the relationship between public and private. Participants expressed greater confidence in public istitute and researchers, while they expressed less confidence in private industry.

According to most of the participants, the transfer must be a donation, made for the community and allow medical research to progress. However, in order to ensure an ethical use of the donated organic material, the latter must be managed by public institutions or private entities but in collaboration with the public and subject to strict control. Earnings in this way should be redistributed or reinvested in research.

Table 3. Some examples of preference for donation and public management

Some examples of preference for donation and public management:
“Since the human domain is basically something public, I think my cells can become the cure for other kinds of diseases tomorrow. I would like to think that there is no economic correlation but the development of research and the implementation of treatments "(woman, 31-40 years old).
“If it happened to me I would say no, because if I decide to donate part of the cells that is a donation, shortly, I do it for research, for a future free from diseases” (woman, 41-50 years old).
"I believe I am a romantic and that the property must remain with the institution which must be public because it must be clear [...] As regards the distribution of the money obtained, I believe that if I make a gift, I make a gift to the whole community and for this income should be redistributed through the public institution and reinvested especially for research "(woman 31-40 years old)
"There must be a framework that must be public, within which both public and private companies operate". (man, 51-60 years old)
"Research is a common good for the society" (man, 31-40 years old)

While towards the private sector some have expressed mistrust while others openness. According to some participants, companies or industries are more interested in profit and less in scientific progress or benefits for the community. Others, on the other hand, have shown greater openness, believing that research and the

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related economic resources can be managed by both the public and the private sector, but subject to public control.

Table 4. Private sector: between mistrust and the control's need

Private sector: between mistrust and the control's need
"There must be a framework that must be public, within which both public and private companies operate. The private ones enjoy more funding and are further ahead. Many new drugs and new discoveries come from the private sector ". (man 51-60 years old)
"Whether it is public or private, the important thing is control. For me, control is essential and the distribution of what is discovered is essential "(woman, 51-60 years old)
"Maybe a company also often goes to look for economic reasons, while the public researcher can think more about good or development" (man, 18-30 years old)
"Then state control in science is very important, because then there are companies that if they are not under control do not have a cultural or moral code" (man, 31-40 years old)

However, opinions are not uniform.

- One of the afternoon groups in responding to the first dilemma stated that the donation must be without payment if it is made to a public institution, while that compensation can be provided to those who sell the cells if the company makes a profit.
- One participant said she does not view profit from private companies or pharmaceutical companies negatively. (woman, 31-40 years old)
- One participant said that the donor of the cells should choose whether to make a donation or receive compensation, if this can be used to incentivize donations. (man, 18-30 years old)

Some have also feared that the findings will not be distributed equally in any case. In this perspective, patents and vaccines were mentioned to highlight how often it is western and richer countries that benefit from scientific discoveries.

Compared to misuse-dual use, a further fear is that organoids could be used for war purposes. In this perspective, what is frightening is the fact that there is no information available on this. In any case, some participants would like more public information on this possibility.

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The fear of misuse emerged in connection with another issue, the collective trust in science. The problem with science communication and trust in science has increased significantly. Communication difficulties were noted by the participants at different levels and at different times related to the research. Generally, there was reference to a widespread mistrust and distrust of science from the society, which increased during the COVID-19 pandemic.

Participants complained of a difficulty in understanding the information that is disclosed and the presence of too many information sources which makes it difficult to know which is reliable.

Consequently, this difficulty also affects more specific communication than in the field of research, that is, informed consent. Some expressed difficulties in understanding the content of the informed consent and also difficulty in having confidence in the real use that will be made of the donated organic material.

An example is the comment of a participant: “Whoever goes to donate that material must understand the research that is being done. We are giving him too specific information, which then very often he is not able to understand. […] If there are things that I cannot understand I am already saying that I do not trust who / to whom I am giving this material. So I don't trust research. Because I am already thinking that there may be a secret goal and what I have given is being used for another reason. This is the problem of science communication which is creating a short circuit between civil society and research. Precisely because civil society does not trust research. When I give in to controlled research, with public guidelines, which is controlled by the rules that I know, I don't think anyone is screwing me”.

3.1.2 Conceptualisations of Organoids

In this section, the issues relating to the conceptualization of organoids will be adressed. The references were made both to the first part of the resolution and to some observations that emerged during the afternoon discussion of the two dilemmas, as relevant. In some points the considerations made during the deliberation were related to the answers that the participants gave in the questionnaires.

During the discussion, the participants gave particular importance to brain organoids and their specificity compared to others. This was probably also due to the presentations of the two experts, the choice to concentrate one of the two exhibitions, that of Professor Lavazza, on cerebral organoids led the participants to give them particular attention.

Generally, we can say that the conceptualization of organoids respect to <u>the thing/person dualism and their moral status</u> has been approached with frequent use of **analogy or contrast** with humans, organs, cells or non-human animals. The analogy with **non-human animals** is the one that has been shared the most. This

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argumentative process showed how the idea of a moral hierarchy of the existing that sees the human being at the top was shared the most among the participants.

3.1.3 Human, thing, artificial, or natural?

Concerning to the thing/person dualism, the results show how organoids have been placed conceptually between these two categories. In the questionnaires very few participants about the question "which word best describes an organoid?" they answered "human being" or "what". Specifically, the answer "human being" in the morning questionnaires was given only once, in association with the words "living organism" and "research tool" (man, 18-30 years old). While in the afternoon questionnaires, at the end of the day, it was never given.

The term "thing" was chosen only once in the morning questionnaires in association with the words "artificial" and "research tool" (man, 31-40 years old). (In another questionnaire it was selected and then deleted, leaving only the answer "mini organ"). It was also chosen only once in the afternoon questionnaires in association with the term "research tool".

The points that emerge from the analysis can be summarized as follows:

1) Relationship between the organoid in general and the human being
2) Relationship between the cerebral organoid and the other organoids
3) Relationship between the organoid and the non-human animal

1) Relationship between the organoid and the concept of human being

The results of the review reveal a non-equivalence between the organoid and the human being/person. The difference between the human being and the organoid was expressed in terms of evolution and complexity / completeness.

During a discussion among the participants, a language emerged that refers to the concept of evolution. Three of the participants used the term "primitive" to refer to organoids. One participant (male, 31-40 years old) defined organoids as "primitive entities" that will never be "more evolved" than the animal models currently used for research. Another (man, 18-30 years old) declared that even a cerebral organoid is a stimulus coordinator in "primitive form". Another participant (woman, 31-40 years old) declared that there is no difference between non-human animals and these "primitive organs" or "primitive entities".

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Furthermore, it has been pointed out several times that organoids lack about the complexity and completeness that instead characterizes the human being. Generally, people have referred to organoids using terminology that refers to lack or partiality. Numerous examples can be given about this.

One participant (woman, 312-40 years old) expressed herself in these terms, believing that "it is difficult for the organoid to reach the complexity of the human being".

In another case a person expressed himself in terms of a dualism where there are humans on one side and animals on the other, explaining that in this dualism the organoids cannot be considered "living humans", so they go "in the other side".

Another participant (woman, 60 years old) during the afternoon discussion, expressing herself in support of the use of organoids to save human lives, used the following expression: "life as an *entirety*, that is, the *whole* human being is more important of *four aggregated cells* because it can never be considered as the *whole* brain, so these cells must be treated as a part of the gastric mucosa". To indicate the human being / person, the participant therefore used words that refer to the entirety: *in toto, all, whole.* While to indicate organoids he has instead used words that refer to something *partial: part, cells* (partial element of the human body) *four* (reduced number).

The same use of partiality to legitimize the use of organoids in research was made by a participant (male, 41-50 years old) according to whom it is difficult to think that "a piece of 5 cm 5 mm could be considered a *person* ". Opposing the terms *piece and person.*

One participant (male, 18-30 years old) talking about brain organoids felt that even if it were possible one day to create a brain that could deliver electrical discharges, "*there is not all the rest of the body*, so they are *simply* interactions. between neurons present in the brain". Later the same participant reiterated his position, asking another "So you consider this brain alive *without anithing*?" and assering that even if the cerebral organoids were to have the ability to interact with the outside, these interactions would be "*limited* to an *on / off* level of consciousness".

The reference to something partial was used by one participant to indicate both the difference between a cerebral organoid and the brain. So the organoid is not a brain, but a *tissue*, therefore a part of it. Both to indicate the difference between a brain and a human being. So a *brain* is not a human being, but rather a part of it.

The organoid has also been settled as a "set of cells" / "aggregated cells".

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Another terminological use that has been made frequently is that relating to size. Several times the participants, when they expressed themselves in terms of a non-equation of the organoid with the human being, emphasized their small size (often using the indicators of the reduced *dimension* of the organoids to justify their lower moral status to that of the human being and usability in scientific research, as is better illustrated in the next paragraph on moral status). Even about the application of size indicators, it is possible to give some examples.

In fact, during one of the afternoon sessions a participant (man, 41-50 years old) explained that we should not worry about an organoid that "*will be 5 centimeters or millimeters thick*, and therefore is comparable to the brain of *an earthworm, a fly or a spider* ".

The same participant repeatedly used the size indicator to justify the impossibility of comparing the organ to the person. He later stated that it is more important to treat an Alzheimer's patient than to consider that 5 centimeters of cells may have a minimum of feeling. The important thing is to treat those who are ill and that "*5 cm* of cell were sacrificed for *us*".

A participant (woman, 51-60 years old) in expressing herself about cerebral organoids stated that "the cerebral organoids today exist even if they are *very small*, but this research is not that it will lead to a *complete* brain, this research will lead to create *segments* ". The point, therefore, according to her, is to understand whether it will be possible to use "*small parts* of aggregated cells that feel" and that in any case they *will never be "a whole brain*, not even in three thousand years". Also in this case the contrast between the partiality and the reduced size of the organoids and the completeness of the human brain emerges.

Finally, the willingness of the participants to affirm the non-equivalence of the organ to the person was expressed through the formulation of sentences that provide for the contrast of two terms, on the one hand the person / human being and on the other something that they do not can be compared.

Examples.

"Today the organoid is certainly something non-human, but a set of cells"

"It's a brain, it's not a human being"

"It is not a person, it is an agglomerate of cells"

The certainly that the organoid is not a human being can be considered a shared point between all the participants in the workshop.

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Table 5. Summary of the language used to indicate the unassimilability of the organ (both cerebral and non-cerebral) to the human being

Human being/person	**Organoid**
Complexity/entirety *complexity of the human being* *In toto* *All* *Entire* *Person* *Entire*	*deficiency/parziality* *Four cells* *Part* *Piece* *There is not everything else* *Simply interactions* *Without nothing* *Limited* *turn on / off* *Tissue* *Set of cells* *Aggregated cells*
	Reduced dimension *5 centimeters / millimeters* *Earthworm / spider / fly (small animals)* *Very small* *Small (parts)*
	Reduced evolution *primeval form* *primeval entity* *primeval organs* *No more evolved than animal models*

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2) Relationship between the cerebral organoid and the other organoids

Although there was no comparability of the organoids to the individual, the participants showed a different attitude towards the cerebral organoids compared to the other types of organoids.

What emerged can be summarized in two points:

- brain organoids are more important than other organoids
- conceptual division between brain organoids of today and those of tomorrow. The development of brain organoids today does not allow them to be compared with the brain and there are doubts about that they can be considered alive. Those of tomorrow could be associated with a human brain, so they could be considered a life form.

During an afternoon debate, a group discussed the relationship between the brain and other organs. One of the participants stated that there is no difference between the liver and the brain. However, the other members of the group disagreed. According to them, what makes the difference between the brain and other organs (and therefore also between the cerebral organoid and the other organoids) is the fact that without any of the other organs it is possible to live, while without brain activity it is not.

This position was supported with two types of arguments, one pragmatic and one legal. In fact, it has been argued that "the heart, like the liver, we can attach it to a machine, while the brain cannot", and reference was also made to the law currently in force in Italy: "today at the legal level, death is established with reference to the brain and not to any other organ. Any other organ is irrelevant".

The different relevance of the brain was also supported by a participant, who stated: "you talk about the cells of the stomach and the heart, but if there is no brain, they have nothing [...] they are like servants of the brain. So we talk a lot about the brain because that is the most important part of our body, if we didn't have the brain I wouldn't be able to talk right now”.

Another participant in the discussion on the relevance of the brain compared to other organs said: "Seeing this debate on the pyramidal status of the organs I think back and make it more a philosophical discussion, in which perhaps the brain with all its synapses can be considered alive".

So it is possible to delineate a greater importance of the brain than the other organs.

However, if the participants were unanimous enough not to consider the cerebral organoid a human being, some conceptual doubts emerge as to whether or not to consider it a **living / living being**. The cerebral organoid has been compared to the concept of **consciousness** and the concept of *life*.

Some participants expressed the view that today brain organoids do not have a conscience and cannot be considered a life form, but this could change in the **future**.

During one of the afternoon deliberations, as part on the discussion of the second dilemma, the participants agreed that the organ is a "*dubious reality*, of which both sentience and conscience must be verified".

For example, one participant said that "today the brain organ is just a collection of cells", but tomorrow it could have a conscience. He also added that: "today research must go on [...] if tomorrow we were to have an organism that we can consider to be some living form ..."

Another (male, 18-30 years old) speaking about the experimentation said: "one of these organoids, which by the way is not even known if it is alive, because we should build the whole body to know if it is alive or not"

Another compared it to mother yeast, saying that it can be considered as: "a cell, a living thing that grows and performs functions [...] that is a tissue, or in any case a set of cells that performs one or more functions". A member of the same group took up this affirmation by clarifying that based on this vision of things: "if you agree we could say what is possible today and what is possible tomorrow. Today the cerebral organoid is a set of cells like other organoids. So today there would be no need to do who knows what at a legislative level. "

In conclusion:

the cerebral organoid is different from other organoids because it is potentially associated with life /living form

It is not clear if actually the current development of the cerebral organoid is enough to consider it alive, but it could be in the future

One participant also attempted an analogy between brain organoids and embryonic stem cells.

3)Relationship between the cerebral organ and non-human animals

It emerged that organoids (especially brain organoids) have been compared with non-human animals. In the previous section we reported how the participants split the conceptualization of organoids into two

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different periods, one present and one future. Importantly, according to the majority of participants, brain organoids are not currently comparable to non-human animals, but will be in the future when they have reached greater development.

The analogy with non-human animals has been used in relation to the presence of a conscience and of a lifeform. Often this relationship has been used to legitimize scientific research on organoids (the topic of research and experimentation will be detailed below [see: moral status]).

The analogy between organoids (especially brain) and non-human animals has been used in numerous passages.

One participant, for example, said that even if organoids “were to develop consciousness systems, these would not be more evolved than those of the animals currently used in research. Therefore, even if organoids were to develop a consciousness like monkeys or mice we should not pose problems, because we are not asking them already now, otherwise research would no longer exist and we would no longer have any kind of evolution ". Two things can be noted in this statement. The first is how he refers to the future, saying they *should develop*. The second is the use of an expression that relates two concepts, that of *future brain organoids* and that of *monkeys and mice*, which are united by the presence of a *conscience.*

Another example already mentioned is that of a participant (afternoon session group 2, Ref. 2), who expressed himself believing that today the brain organ is a tissue, so it does not raise ethical questions. While "if *tomorrow* we will be able to really produce a mini brain" then "we can begin to think about ethics". Because according to the participant, that brain will not in any case be comparable to a human being, but it is difficult to say whether it has "more or less the dignity of a *mouse*" that we use in experiments. Also in this case we can see, as in the previous example, a temporal reference to the future: if *tomorrow*. And the use of a non-human animal, the *mouse*, as a reference for assessing the *dignity* of the organoid.

Let's go back to the example made in the previous paragraph. One participant believed that “if tomorrow we were to have an organism that we can consider some living form […] in this case the regulatory framework used could be the very strict and precise one we use today for animal testing”. Here too there is a reference to the future: if *tomorrow*, and the analogy with animal experimentation. In this case it is not the presence of a conscience that accumulates the cerebral organ with the *animal*, but the fact that this is considered as a *living form.*

We have already given the example of the participant (man, 18-30 years old) who, considering the two human / animal categories, placed the organoid in the animal category.

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In a dialogue that took place during one of the afternoon deliberations when a participant asked another if the brain organ had more or less dignity than a mouse, she replied "it's the same thing".

Some participants, on the other hand, expressed their doubts. A participant (woman, 51-60 years old) said during the afternoon discussion: "I initially thought that animals had much more awareness of these organoids, while now with the last step I have many more doubts".

With reference to the current situation (and not the future one), however, the cerebral organoid has been compared to that of an earthworm, a spider or a fly and to bacteria.

Table 6. Summary of the above examples

future	Identity resembling to organoid	Element of similarity
If they develop by themselves	*monkeys and rats*	*consciousness*
If tomorrow	*mouse*	*dignity*
If tomorrow	*animals*	*living form*

If we want to summarize, in general terms, how the participants conceptually place the organoids within the person/thing dualism, we can say that:

- The organoid is not a person
- The cerebral organoid has undergone a conceptual split between present and future
- The today's cerebral organoid is similar to the other organoids
- The future's cerebral organoid will be comparable to the brain

3.1.4 Organoids' moral status

The moral status attributed to organoids is obviously a consequence of the reflections reported in the previous section. As a premise we affirm that by *moral status* for the purposes of reflection we mean – so very roughly - the fundamental moral considerability, that is, the type of rights which a being is entitled and the importance of his interests. We can consider moral *status* as the normatively significant condition of an existent with respect to the practical and evaluative attitudes that moral agents must have towards him.

The participants' reflection highlighted how the idea of a hierarchy of the living is shared, in which the human being is at the top.

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In trying to outline the moral status that must be recognized to the organoids, the reflections of the participants can be summarized in the following points:

- Superiority of the moral status of human beings
- Superiority of the status of cerebral organoids to other organoids
- Equalization of the moral status of organoids to that of non-human animals

In the previous point it was said how the predisposition of the participants is that not considering organoids as human beings. This obviously also has implications for the relationship between the moral status of brain organoids and the moral status of human beings. In general, it has been believed that the human being is endowed with a higher moral status and as a consequence enjoys higher rights and interests than the cerebral organoids.

This consideration can be traced in some discussions of the participants and particularly in the discussions that involved the second dilemma of the afternoon session.

The second dilemma in fact placed the participants in front of the need to **balance the interests of the human being with those of the cerebral organ.**

The way in which the dilemma is presented led the participants to formulate different positions compared to the current situation and what may occur in the future. Currently, the participants have no doubts about the non-comparability of the moral status of brain organoids to that of humans. Concerns have arisen about the future prospects.

The superiority of the moral status of the human being has been affirmed above all to **legitimize the use of organoids in scientific research** and with frequent use of the analogy with **animal experimentation.**

In conclusion, the participants expressed a general agreement on the possibility of making the good of a patient prevail over that of the organoid and of using organoids in scientific research.

Below are some statements from which it emerges both the equiparation of the status of organoids with that of non-human animals and the superiority of the moral status of the human being (many of which have already been mentioned in the previous section).

1) “Even if they were to develop systems of consciousness, these would not be more evolved than those of the animals currently used in research. Therefore, even if the organoids were to develop a consciousness like monkeys or mice we should *not pose problems*, because we are not asking them already now, otherwise

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the research would no longer exist and we would no longer have any kind of evolution" (male, 41-50 years old). In this statement it is possible to trace: the belief that brain organoids will not even be comparable to humans in the future. The assimilation of the cerebral organoid to the animal used in research. The legitimacy of the use of both *animals* and organoids in research, *to advance research and evolution.*

2) In response to the above, one participant felt "It will be difficult for him to reach the complexity of human nature, so for me it is preferable to think about what is now, to give a better quality of life to those suffering from diseases and postpone this reflection on if it should happen in the future". (woman, 31-40 years old). Also in this case it is possible to detect: Non-comparability of the organ to the human probably *not even in the future*, but it is not certain. Legitimation of use in research to *give a better quality of life to those suffering from diseases.*

3) “I tried to reduce it to a simpler model that is understandable to me. That is, if I find myself with an agglomeration of a few neurons put together, because that are 5 millimetres. Now if we dissect an *earthworm or swat a fly or kill a spider*, we don't have to ask ourselves in the *least* the problem of this organoid that can have a feeling. At most he could have a conscience of existing, but of the typology switch on and off”. In this statement it is possible to trace: the belief that brain organoids will not even be comparable to humans in the future. The assimilation of the cerebral organoid to the *animal* used in research.

4) “Here the comparison is between two realities, the reality of a concrete Alzheimer's patient and a dubious reality, of a cerebral organoid whose sentience and conscience are to be demonstrated. […] We are in a phase of great development and reflection”. From this statement it emerges that today the uncertainties about the cerebral organ make it difficult to attribute rights and interests to it, especially in relation to the human being.

5) “Speaking of species, speaking of survival, unfortunately in medicine and biology these are discourses that occur several times. For me, using it is right to save many more lives ". The whole group, even those who had doubts, was generally in agreement with this perspective.

6) "Referring to my father-in-law that has Alzheimer he talks, sings, does all things, but says nonsense and therefore basically what is the problem? Put my father-in-law back into a state of conscience, I am speaking of my father-in-law of course, and but I also speak of all the people who have a staged dementia of this type, who, as in the past, is a very brilliant person, very efficient or think that a piece of 5 cm 5 mm can feel a feeling and be considered a person? Honestly, I'm too pragmatic. So I think that thos*e who can be saved should be saved* and 5 centimetres of cell *sacrificed* for us. Pass me the deadline *for my son I would exterminate all the rats in the world* to find a cure. So you understand well that it's not that I don't like

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animals but because at the moment there is a different *priority* on the scales ". Also in this case it is evident that the speaker believes that the interests of the human being, when they concern *health,* are *priority*. This given that 5 cm of cell can be sacrificed to save those who can be saved and the mice exterminated to find a cure.

7) "If tomorrow we were to have an organism that we can consider some living form on which we are thinking about whether or not to experiment, in this case the regulatory framework used could be the very firm and precise one we use today for animal experimentation. […] Obviously it must not be done indiscriminately, but when needed for medical and clinical reasons ". In this case, the equiparation of the organoid with the status of animals is postponed to the future, when the cerebral organoid can be considered a living form. In any case, experimentation on both animals and organoids is legitimized for medical and clinical reasons.

8) "The problem is this, it is important to save a person with Alzheimer's and destroy these 5 aggregate cells, which will replace the damaged part of my brain. This is the question. In my opinion it's fine. My idea is that life as a whole, that is, the whole human being is more important of 4 aggregated cells ". [...] "In my opinion these cerebral organoids can also be used, because if we deviate / avoid (difficult word) certain things that happen in ours brain, some degeneration. I think they can also be used ". (woman, 51-60 years old)

9) "So, however, if it is socially acceptable and morally justifiable, it is always possible when I use the organoid to save a human life [...] or heal a disease". (male, 51-60 years old)

10) "In a futuristic discourse in my opinion how to treat the cerebral organ like any other organoid, that is - in a future I repeat - a form of life like the murrine species for the analysis that is done today on animal species" (male, 41-50 years old).

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Table 5. Summary table of the above examples

Object	Expression used to indicate that human interests have priority over organoids and animals	Legitimating reasons
1) Organoid same as monkeys and rats	We shouldn't have any problems	Research / evolution
2) cerebral organoid	Better think about what is now	To give a better quality of life to those who are suffering from diseases at the moment
3)Brain organoid such as earthworm, fly, spider	we dissect / crush / kill… we don't have to ask ourselves the problem at all	Finding cures (implied)
4) cerebral organoid	so much sentience has to be demonstrated	Finding a cure for the Alzheimer's patient
5) cerebral organoid	Speaking of species and survival - for me the use is right	Saving many more lives
6) cerebral organoid/ 5cm of cell	They sacrificed themselves	Save who can be saved
6) Rats	I would exterminate	Finding a cure (for my sick child)
7) Brain organoid / some living form	Whether or not to experiment	For medical and clinical reasons - not indiscriminately
8) Organoid / 5 aggregated cells	destroy	Replace ruined part of my brain
8) Organoids	We can also use them	We avoid brain degeneration
9) Organoid	Utilization	To save a human life or heal a disease
10) Form of life like the murrine species	Treat as animal testing	To advance medical research (implied)

Other people have expressed doubts:

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A) “When do we consider a cell to be life? I agree with my colleague, that there is not much difference in how animals are used in research on these primitive organs on these primitive entities. But then I thought about brain activity, about these synapses that move and I make a more philosophical than pragmatic discourse. At the beginning I was determined: it's like animals, then I stopped and went back so I would increase my doubts, I better stop ".

B) "Compared to this dilemma (the second) I thought I had much clearer ideas, because I also believe that the animal experimentation that is taking place now is somewhat on the same level. Indeed, as far as I'm concerned, at present, animals have a much higher degree of awareness. But I cannot be sure that these organoids cannot develop this degree of awareness and sensitivity ".

C) "A rethinking is taking place (also in the animal question)".

D) "So we must reserve the same protection for the organ as we reserve for the animal?" “In my opinion even less. Those understand (implied the animals). The little dog looks at me ". "5 cells don't look at you?" "Exactly no, I don't feel anything, I have no affection. Emotionally, they don't tell me anything. Emotionally they tell me something if I think they save a life”.

These positions raise some doubts with respect to the generally shared position. Doubts related to: A) philosophical doubt about when a cell is life; B) doubt that in the future the cerebral organoids can develop awareness and sensitivity and recognition - at present - of greater awareness to animals; C) doubt that even the animal question and therefore the use made of non-human animals in research can be rethought; D) doubt that organoids can be equiparated with non-human animals expressed not through a logical but an emotional argument.

Other issues that emerged:

During one of the afternoon deliberations, some participants discussed the difference in status between brain organoids and other organoids. One of the participants stated that a brain should have the same status as other organs, such as the liver, so in the absence of the rest of the body a brain should not be considered human, but just any organ. The other participants instead disagreed, believing that the brain has a different moral status and this because "the heart like the liver we can attach to a machine while the brain does not". Furthermore, death today concerns the cessation of the activity of the brain and not of any other organ. Another participant added that the brain with all its synapses can be considered philosophically alive. In the discussion it emerged that the analogy with the other bodies was not shared by the participants. Only

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one held that a cerebral organoid has the same status as the other organs, while the others believed that the cerebral organoid must have a higher moral status.

An analogy with embryonic stem cells has been hypothesized and in this regard a participant stated that Italian legislation recognizes excessive protection for the embryo. Saying that embryos could be used to advance research and wondering how much ethics in these cases is an obstacle to research.

So in conclusion if we were to do a reconstruction of the moral hierarchy that the participants outlined we can say that:

- The human being has the highest moral status, so much so that both non-human animals and organoids can be used / sacrificed to save lives / treat diseases / medical and clinical reasons / carry out research.
- The cerebral organoid has a higher status than the other organoids.
- To date, the cerebral organoid must be equiparated more to a tissue or an aggregate of cells than to an organ. However, if in the future research were to lead to greater development of brain organoids then their moral status would also be higher. While not equaling the status of a human being.
- The cerebral organoid can be equiparated with non-human animals (according to some already today, according to others it will be in the future when it is more developed).
- The other organoids can be equiparated with tissues or bacteria, but not with organs.

3.1.5 Attitudes towards Organoids

A) Hopes and benefits

In general, the participants showed a positive attitude towards organoids and expressed hope for the advances that organoids can bring in the medical field.

During the deliberation that took place in the first part of the morning, they often used the word hope to indicate the feelings that this research aroused in them.

To do just two examples, a participant with ALS when he introduced himself to the group said that the main reason he was there was to have "a little hope". One of the groups during one of the morning discussions chose to indicate the words: "*benefit, hope, time*" as the focus point of their reflections.

Focus on the present

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Some participants expressed the need to focus on the present, which is positive, and if problems or issues arise in the future that deserve further reflection, they will have to be faced as they arise.

The following statements refer to this:

"Does it make sense to ask these doubts about a possibility that will come in the future when instead we can already save many lives now?" (woman, 31-40 years old).

"In the future they could use them in an unethical way, but now we have these functions, why should we refuse them?"

"At this moment it seems almost all positive, with future discoveries maybe the question will be faced again".

"The point is not to bring back to life what cognitively no longer exists, unfortunately brain death is our limit in biology we cannot go further, and therefore the final limit is always to find a solution to problems that exist, such as tumors, genetic diseases and personalized medicine " (man, 18-30 years old).

"However, it must be considered that at this moment the organoids play this role and we, in my opinion, must evaluate them with the role they have now and in a future that we probably won't even see, they could be so advanced that they could possibly develop feelings, emotions, etc. etcetera but at this moment this is not the goal of our analysis since this is an ethical problem that could arise in the future, but right now we must evaluate the organoid and the organoids as they are at this moment and what we think of they now ".

The determination to focus on the present and understand how organoids can have a concrete usefulness today, referring to the future questions that do not yet arise, was expressed above all by the younger participants of the group (two students aged 20 years or so) and by representatives of civil society, in particular by members of scientific divulgation associations.

Autotransplantation

One of the hopes that has been expressed is that of being able to use organoids for a sort of "auto-transplant" of own cells. One participant, for example, said that "organoids are a set of cells that replicate parts of the human body, so as far as I'm concerned from a research point of view it's something that gives hope." The prospect of a "set of cells that replicate the human body" has generally been welcomed. Participants expressed the hope that numerous benefits in terms of care could be derived from this.

Do not have transplanted organs rejected

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A liver transplant participant expressed the hope that one day organoids could lead to "the study of drugs that are used to prevent the transplanted organs from being rejected, in order to free us from many problems".

Experimentation use

Another positive aspect is what concerns the possible use of organoids in drug testing. In this way it is possible to replace experimentation on human beings (an experimentation that “does not harm the person) and on animals.

Attention to the human system

One participant noted what he believes is a medical problem, namely the attention to the "only sick part". According to him, " we are too often on the slide to look at the only sick part, without then going to see the possible interaction of that therapy on the rest of the human system. So maybe you fix that sick part and go destroy some other healthy part of the body. " His hope / future perspective is that organoids can be used to reproduce all the different parts of the body to understand how the interactions between them work.

Coexistence of positive and negative point of view

Participants believe that research on organoids can bring benefits and expose to dangers; it is not possible to classify research in a single positive or negative meaning: “The truth cannot be declined in black or white, there are a series of shades of gray. There are some very positive aspects of organoids that do not diminish the need to pay attention to critical episodes. But at the same time the negative and critical aspects do not undermine the positive foundations that organoids can bring".

Personalized medicine

One of the possible uses of organoids, most appreciated by the participants, is that of personalized medicine. Those who are not sick have shown interest in the possibilities that could open up in terms of personalized medicine and preventive medicine.

“At the lung level for example, I know the structures of the cystic fibrosis gene. Studying the individual mutations case by case would be perfect because so I am no longer intervening on patients, I intervene on patient x who has that mutation. The work on patients becomes extremely specific, this is the level that medicine must reach" (male, 18-30 years old).

"The aspect of prevention interests me particularly because we say that scientific research has now made a lot of progress for many diseases, right? And I also understand the objection of wanting to challenge death,

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that is, perhaps this is not the point because I believe that instead it is precisely a question of quality of life, that is, living well" (woman, 31-40 years old)

B) Fears

Fear that what is proposed is rejected

One participant expressed fear that what was proposed about organoids could be disregarded. He reported a personal experience that took place in Spain.

"I have a fear because I lived it in Spain. As far as stem cells were concerned, promises were made to the sick which were not kept. For example, a researcher had promised to treat diabetes with stem cells. The government filled the team and this researcher with money by building a huge and very expensive center, but then nothing came of it. So let's say that not only economic but also scientific speculation (I'm saying something that I know cannot come) and moral speculation has been made".

The concern expressed by the participant is that the promised future benefits in terms of treatment and research advancement may never be achieved. The other participants in the group agreed with this danger. Another said that it is a danger that occurs every time there is a new discovery in medicine, but in any case, it is right not to underestimate this point.

Fear that other important issues are neglected in pursuit of health

A Muslim participant expressed fear several times throughout the day that the legitimate goal of saving lives, curing disease and improving health would neglect other important ethical issues and harm others, such as the environment or (to use his expression) other inhabitants of the earth.

“Human life is very important, fundamental. I speak from a religious and spiritual point of view on which a Muslim, wherever he is, must be careful, human life is before all other lives ... But every living being is fundamental. Therefore something that can help people to feel good is positive, but without destroying, without ruining, we must not think that we are the only ones on earth. And this is very important”.

"I agree it is not that I am against (implied: the development of organoids). It's just that we can't manage the things we have in our hands, that is, which are in front of us, such as the environment".

Fear that it is not easy to identify a limit of research

One participant commented that sometimes the goal of achieving ever higher standards of health resembles defying death. While "if that person now (is dead), let's let him go, right?", While we should take care of all those poor and hungry people.

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“What is the limit of this study? that is, sometimes I perceive we want to defy death we no longer want to let anyone leave this world, while we have a million poor and hungry people "

What the participant seems to suggest can be understood from a global bioethics perspective. His statement seems to want to underline the marked disparity present in different world contexts with respect to access to care, for which contexts of poverty are contrasted with others in which there is a strong investment in health in terms of ever more performance and empowerment.

Manipulation

Some have expressed doubts that in the future brain organoids could be used to manipulate individual choices. “As long as anyone who uses these organoids just to repair damaged brains is fine with me. What if someone will use these organoids to make stronger manipulations and to condition man to certain types of political choices and so on?".

Limited collective awareness of non-beneficial uses

During the questions to the experts, the topic of non-beneficial uses that can be made with organoids emerged, for example in the military context. Taking note of this, some participants expressed concern that there may be little collective awareness of the uses that are made of organoids. In this sense, a woman said: "the fact that there is still the possibility of a negative application in my opinion should be sufficiently explained, but not to the scientific community, to the common man. As a potential patient or cell donor, I would like to know these aspects a little better ".

C) particular experiences used in the argumentation (e.g. lived experiences, obtained through CSO work etc.)

Personal experiences were shared by people in contact with the disease, reference was made to a father-in-law with Alzheimer's, a child with disabilities and a participant said she took part in a study related to her disease. They also shared personal experiences from the representatives of civil society, especially the two representatives of the Catholic religion.

Those who reported experiences of sick relatives did so in a context in which they wanted to legitimize the use of organoids in research and to share the reasons that led them to prioritize the discovery of medical treatments that concern humans rather than protect animals or organoids.

“I speak from my personal experience. I have a child with a disability and I hope that the treatment arrives as quickly as possible and I realize that my desire clashes with all the steps of the research. Can anything

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be optimized? Can it be simplified? " […] "For my son I would exterminate all the rats in the world to find a cure". (man, 41-50 years old).

"Referring to my father-in-law *who has Alzheimer's, he talks, sings, does all things, but he says nonsense and so basically what is the problem? Put him back in a state of consciousness, I am speaking of my father-in-law of course, but I also speak of all the people who have a stage of dementia of this type, who, as in the past, is a very brilliant person, very efficient or think that a piece of 5 cm 5 mm can feel a feeling and be considered a person?"*

D) particular concerns (key concerns e.g. related to specific organoid types, use of particular stem cells etc.)

One of the concerns expressed by the participants relates to the possibility that brain organoids may one day develop consciousness or reach a level of development similar to the human brain.

On this point the positions of the participants are divided. Some believe that even if the research continues, it will never reach such a complexity that this possibility must be seriously considered. Others have expressed a more cautious position, believing that in the future the development of brain organoids may become problematic

3.2 Ethical Issues and Implications in relation to the Derivation and Use of Organoids

The current section is divided into five sub-sections, each focusing on different ethical issues and implications discussed by the participants during the workshop. The last of these sub-sections includes the themes, worries, and issues that, according to the participants, should be considered in future guidelines for organoid research and governance related to organoid research.

3.2.1 Informed consent and patient information

The theme of informed consent was central during the workshop, the participants affirmed the importance of this tool from the first discussions. The importance of informed consent has emerged across the board in relation to other topics discussed, for example in relation to ownership, commercialization or society's trust in scientific research.

Consent must be **informed and conditioned**. The information must be adequately communicated even to those who are not competent on the theme and must be **specific, precise and complete**. However, it should

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be avoided that it is too detailed, since the presence of too many details is confusing. Two of the afternoon groups highlighted the importance of specifying the **purposes** of the research or the **final use** of the materials. Another point considered important in terms of consent is the possibility of changing it over time, according to the participants the consent must be **reshaped** in the case of the discovery of new technologies and the new destination of the donated cells.

One group, during an afternoon discussion, also talked about a **supervised consent**, through the presence of ethics committee that can advise the patient.

Regarding the reshaping consent, one participant reported the example of bone marrow donors in Italy, who have an initial consent and then a series of further approvals. The consent is then integrated and reiterated in subsequent activities.

An adequate and clear informed consent also seemed to legitimize the donation. Often, when discussing the issue of commercialization, participants said that the cells must be donated. But this act of transfer to the community must be supported by an adequate awareness of the donor on the use that will be made of the cells. In this sense, informed consent plays a fundamental role.

Regarding the problems that can be raised by informed consent, two participants reported their direct experience.

One woman described her personal experience of participating in a scientific study. The participant complained about the inability of the facility where she was enrolled to give her adequate communication of the procedure she was facing. Personal experience in this case has been reported to highlight the difference that can exist between theory and practice, if in fact in theory a great importance is given to informed consent, in his experience the communication was given superficially and carelessness. With respect to his personal experience, he therefore expressed the desire that in the future not only research will be done, but also the ability to speak with awareness to the patients who participate in the research.

One participant, still on the topic of informed consent, talked about his personal experience in ethics committees. He reiterated the importance of an understandable consent and said that in his experience a functional way to obtain good communication is to include a summary expressed in informative terms in the consent. In his personal experience it is not possible to identify a priori a subject capable of understanding informed consent. This is because "the subject who experiences an important diagnosis on himself can also be a multi-graduate, but his ability to accept the message is strongly influenced by his emotional state".

This reflection has received numerous consents, in fact many have agreed on the fact that patients who experience a disease or are worried about their health are also less able to receive and process information and this must be taken into consideration.

A particular position was expressed by a participant according to which the consent must be reformulated only if the biological samples are traceable to the donor. While if these were completely anonymized, then there is no problem.

3.2.2 Biobanks and governance

The topic of biobanks and storage of data was dealt with across the board by the participants. Many of them did not have sufficient biobank expertise to go into the specific topic, but concern often arose about how cell-derived data could be used.

When the topic of consent was discussed, it emerged that the issue of awareness of the use that will be made of the organic material and also of the information connected to it's of fundamental importance for the participants.

Based on what has emerged, it is very important that biobanks are subjected to forms of control. In particular, two forms of control have emerged. The first is that carried out by donors, therefore by the members of a community at the time of signing the informed consent. Consent that can be reshaped over time as a result of changes in the intended use of organic material or as a result of new scientific discoveries.

The other control is that which must be done by the ethics committees, whose presence was considered essential to guarantee an ethical use of the organic material and of the information transferred.

These two forms of control see an overlap in what one group has called "**supervised consent**" which involves collaboration between the ethics committee and the donor at the time of signing the consent.

The issue of sharing not only cells but also personal data has aroused interest and concern, even if it is aimed at the near future rather than the current situation. Regarding this, one participant stated: "We need to make an assessment on the current state or on a hypothetical near future. Because I heard a conference on health from the European business community that a truly sci-fi thing was done, but it is not far from the reality, that in the near future all of our data including cell phone data or our DNA could become the common property of that. what could be the scientific implementation "(woman, 51-60 years old).

3.2.3 Dilemma 1: Ownership, compensation, and patentability

The first dilemma is based on a case, where a biopsy is taken from a cancer patient in order to find the best possible treatment for him. A part of the biopsy is also used to produce cells for research, which eventually leads to the development of a new vaccine. The doctor who developed the vaccine further wins a Nobel prize. The dilemma raised ethical questions related to ownership, financial compensation, and patents.

Regarding the ownership of the donated cells, many agreed with the fact that when they are given they stop belonging to the donor. A Muslim participant stated that "from a personal and religious point of view you cannot become the owner of something that is used to save other people".It is quite common to assume that the donor of cells waives all rights, including the right to property. This operation is then balanced through a control by the transferor on the use that is made of the cells through the informed consent, as mentioned above.

However, there are more uncertainties about who should be considered the owner. Most of the participants indicated the public institution or the state as the owner, a part of the participants indicated the promoter both public and private (but subject to control), only one expressly indicated the researcher / research group as the ideal owner of cells. Here are some examples:

"The owner is the promoter of the research, so the industry" (man, 41-50 years old)

"The property must remain with the institution that must be public" (woman, 31-40 years old)

"The owner is the research itself; it doesn't matter whether it is a researcher as in the example or a group of researchers. The owner of the cells should be whoever uses them or who conducts the experiment, because they are the ones who use it, they are the ones who know how to move in that field and what research they are doing. Furthermore, according to the participant, the researcher is the best owner of the cells also because he thinks more about good and development, because he hardly has any economic advantages "(man, 18-30 years old).

The theme of commercialization is strictly dependent on the question of the ownership of cells. The issue of marketing has already been addressed in paragraph 3.1.1 to which we refer. In general, what emerged is that, according to most of the participants, the sale must be a donation, made for the community and allow the advancement of medical research. However, in order to guarantee an ethical use of the donated organic material, it must be managed by public or private institutions but in collaboration with the public and subject to strict control. Earnings in this way should be redistributed or reinvested in research.

While some expressed distrust of the private sector while others openness. According to some participants, companies or industries are more interested in profit and less in scientific advancement or community benefits. Others, however, have shown greater openness, believing that research and related economic resources can be managed by both the public and private sectors, but subject to public control.

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Two participants also showed a positive attitude towards economic gains for private industries, believing that if a company decides to invest in research while taking risks, it's fair that it will make profits.

While everyone agrees with the fact that there should be a social impact of the benefits derived from a donation of organic material, not everyone agreed on the possibility of providing or not a compensation for those who donated the cells.

The opening towards a possible remuneration of those who sell organic material was justified either for reasons of justice or for utilitarian reasons. One participant said "it's obvious that if everything started from the case of my son who gave you the opportunity to study, at least recognize something, maybe he can afford a better life than he could have" (man, 41-50 years old) . Another instead adopted a more utilitarian perspective aimed at incentivizing / maximizing donations, saying that the donor of the cells should choose whether to make a donation or receive compensation, if this can be used to incentivize donations (man, 18-30 years old).

However, apart from some isolated positions, most of those present agreed that the donation, to be defined as such, must take place without financial compensation. The donation of organic material was seen as a collective contribution to society and research. Donation and redistribution were seen as complementary to each other, to quote one participant: "Do we want that something like a vaccine that helps society be free? So, let's give society the resources that research needs" (afternoon session group 2 - 12.10 pm).

3.2.4 Dilemma 2: Cerebral organoids

The second dilemma is related to cerebral organoids and leads to discussions about moral status, worries for this specific type of organoids, and animal research.

The second dilemma is closely linked to the issue of the moral status of cerebral organoids, so please refer to section 3.1.4 of the Report.

The way in which the dilemma is presented led the participants to formulate different positions related to the current situation and to what may occur in the future.

Currently, the participants have no doubts about the non-comparability of the moral status of brain organoids to that of humans and non-human animals. Currently, all participants have agreed on the use of organoids in research.

Concerns have arisen about the **future prospects**. Participants struggled to address this issue due to a lack of information on how brain organoids might develop in the future.

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This difficulty led some of the participants to express the need to think about the present and face future issues as they arise.

Others have raised some questions that they have not been able to answer. One of the groups wondered what criteria could be used to define when organoid becomes a living being: when is it complex enough or when is it complete? Faced with the inability to give an answer, some have concluded that in the future the cerebral organoid could also be equated with a human being.

Most of the participants believed that in a future perspective if the cerebral organoids reached a greater development they would be comparable in moral status to that of non-human animals.

Regarding the balance between the good of a patient and that of a cerebral organoid, the participants considered the first to be prevalent. As seen in paragraph 3.1.4, in fact, it emerged that the idea of a hierarchy of the living is shared, in which the human being is at the top. The table inserted in paragraph 3.1.4 shows numerous examples of how the participants prioritized the interests of humans with respect to both brain organoids and non-human animals. Many have in fact believed that if in the future the cerebral organoids reach a greater development, the same regulation that is applied today to non-human animals in research can be applied to them.

Most of them, however, highlighted that the prevalence of the moral status of the human being must be supported by a legitimate reason, and this reason was identified in the possibility of advancing research and finding new treatments.

3.2.5. Recommendations for future guidelines

The recommendations for future guidelines for organoid research are shown in Table 8. They are based on the previous analysis and the posters made by the participants during the last deliberation at the workshop, where they discussed which subjects, they found most important to include in future guidelines. Following the model developed by the University of Aarhus, the recommendations are sorted into the following categories: Communication, governance, and ethical implications[3].

Table 8. Recommendations for future guidelines.

Recommendations for future information and communication on organoids

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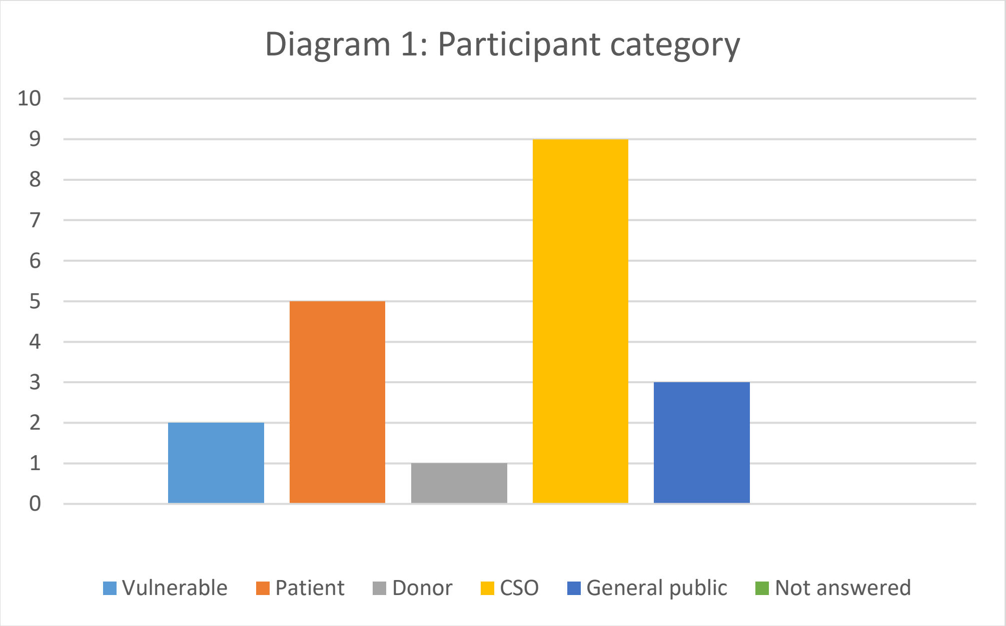
[3] The recommendations are not mentioned in a prioritized order, though the listed recommendations are the ones the participants expressed as most important to them.

Clarity regarding how information on organoids is disclosed. It is important that information on organoids be disseminated in a clear, simple and above all transparent way by competent authorities in order to strengthen the relationship between scientific research and civil society.
Consent must be **informed and conditioned**. The information must be adequately communicated even to those who are not competent on the theme and must be **specific, precise and complete**. However, it should be avoided that it is too detailed, since the presence of too many details is confusing. Two of the afternoon groups highlighted the importance of specifying the **purposes** of the research or the **final use** of the materials. The consent must be **reshaped** in the case of the discovery of new technologies and the new destination of the donated cells. Consider a **supervised consent**, through the presence of ethics committee that can advise the patient.
Recommendations related to the governance of organoids
Clear rules for how organoid research and data related to it is governed. In addition to clear guidelines, the presence of ethics committees or public institutions that can control the use made of both the donated material and scientific discoveries is very important. The need for public control and transparency is felt above all in relation to the presence of the private sector in the research field.
Use specific adjustment when needed based on the specificity of particular types of organoids, such as those of the brain.
The results of biomedical research on organoids must be distributed equally and globally. The principles to be followed are those of solidarity, sociality and subsidiarity.
Strict focus on data security and storage. This could be managed based on the consent given in the specific case.
Ethical implication to take into account
The legitimate goal of saving lives, curing disease and improving health must not affect other important ethical issues and harm others, such as the environment or other inhabitants of the earth.
The goal must be to improve the quality of life but without aiming for eternal life and immortality, the dead must be accepted. In this sense it is important to be able to see the limit.
Carefully monitor the uses that are made to avoid the use that would be made for activities against humanity.

3.3 Survey and Change of Attitudes towards Organoid Research

As previously stated, the participants had to fill out the first part of a questionnaire at the beginning of the workshop, before any deliberation had taken place, and a second part repeating some of the same questions at the end of the workshop. The answers from the questionnaire are displayed below in a number of tables and diagrams.

First of all, we have created basic diagrams on demographic information on the participants (Diagrams 1-6), on participant categories and distribution, age, gender, religiosity, relation to the job market, and ethnicity/nationality.



The Italian workshop had a total of 19 participants (the total of morning questionnaires is 18). The diagram show how they were distributed across the five participant categories based on their answers in the questionnaire, which may differ from the category they were recruited as.

One participant only writes: Association representative (he/she was count as CSO)

Two participant who choose *patient* also indicate *CSO*

Two participant who choose CSO specified their competence writing: scientific divulgation association and bioethics specialist.

Table 9. Participant category distribution – Recruitment vs. questionnaire

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Participant category	Distribution from recruitment	Distribution based on questionnaire at workshop
The general public	6	3
Vulnerable groups	3	2
Patients	3	5
Donors	3	1
CSOs	5	9
Total	**20**	**20**

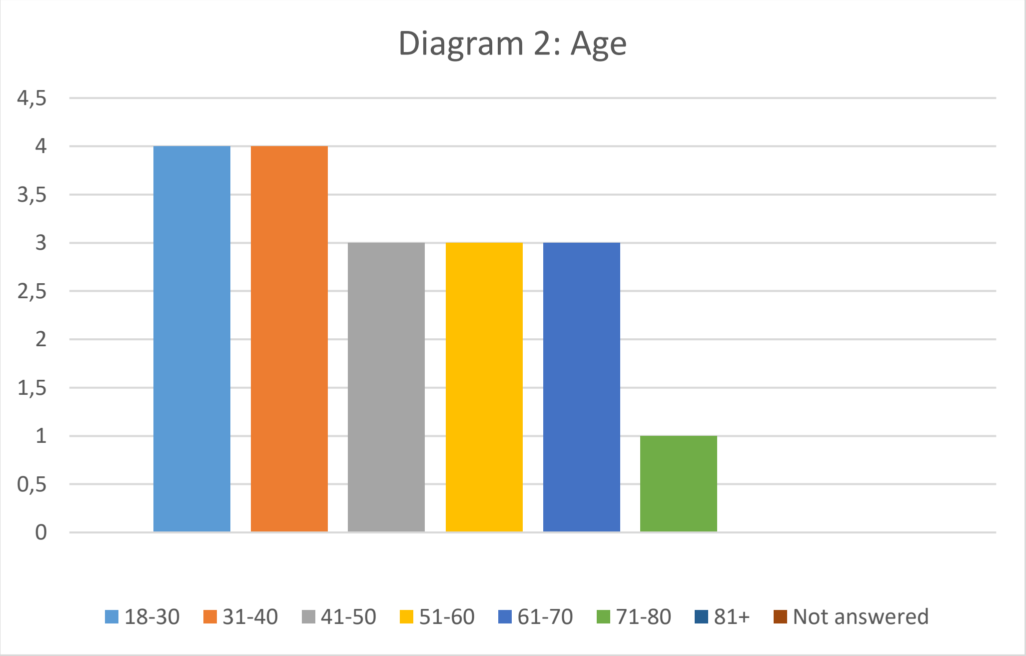

Diagram 2 shows the age distribution among the 19 (18) participants in the Italian deliberative workshop. As the diagram shows, there was a fairly equal distribution of participants between the different age groups. 11 participants were under 51, 7 were 51 or above.

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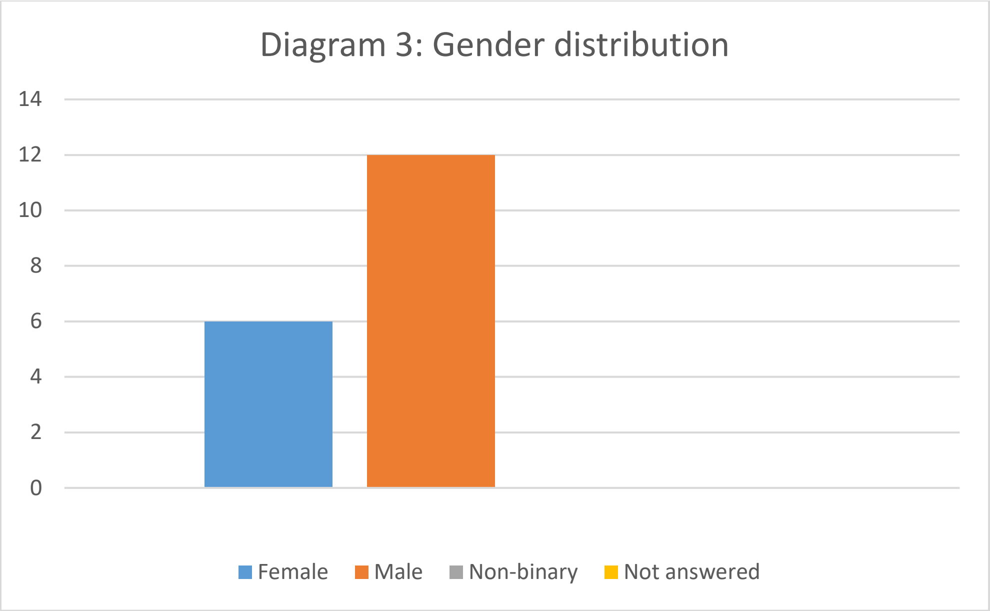
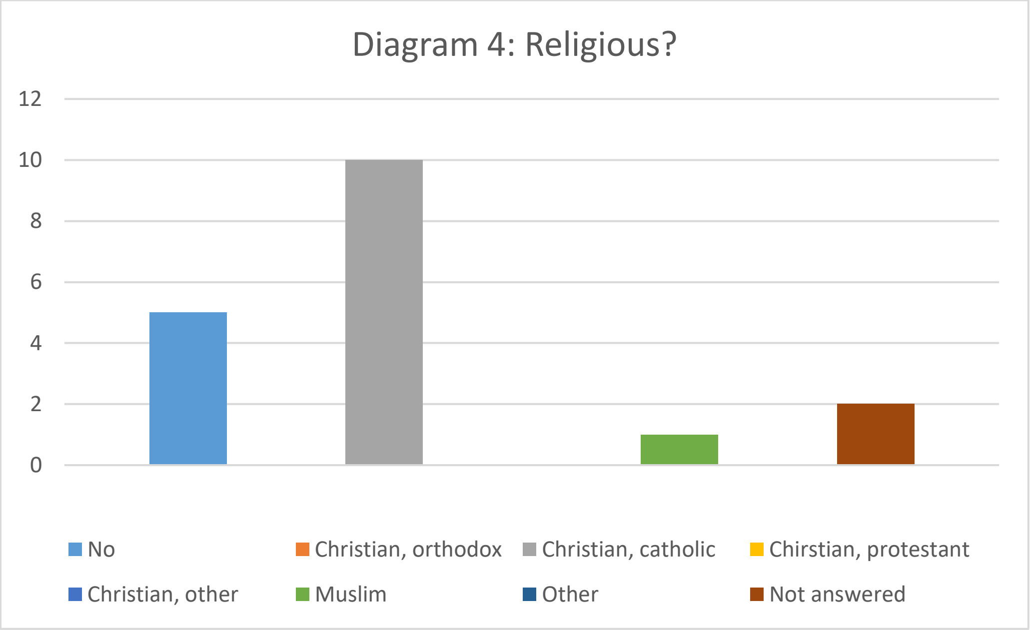


The diagram shows the gender distribution of the 18 participants at the deliberative workshop in Italy. 6 women and 12 men participated in the workshop.



The diagram shows how the 18 participants are distributed related to whether they consider themselves being religious, and which religious orientation. As diagram 4 shows, most of the Italian participants described themselves as Christians (Catholic).

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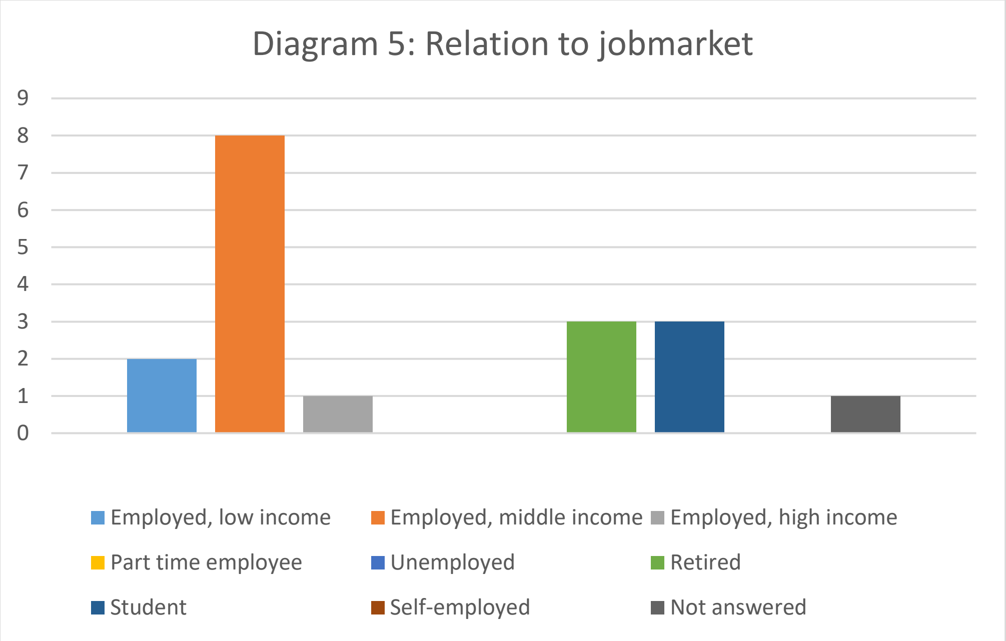
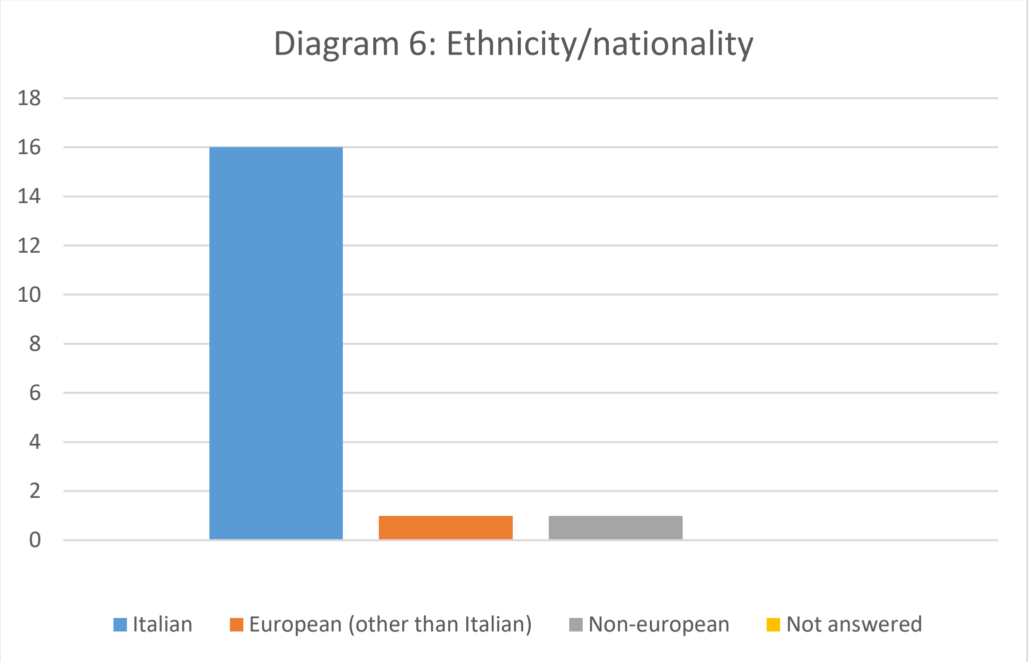


In this part of the survey, the participants were asked to indicate their relationship to the job market. The biggest group was ‘employed, middle income’ (8 participants).



The diagram shows how the 18 participants categorized their ethnicity/nationality.

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3.3.1 Potential changes in attitudes

Besides using the survey for sociodemographic background information on the participants, we also wanted to use it to capture changes in attitudes towards organoids and organoid research as a result of the expert knowledge and deliberations at the workshop. Diagram 7-10 show the participants' answers from the beginning as well as the end of the workshop. The results are shown as side-by-side bars for easier comparison.

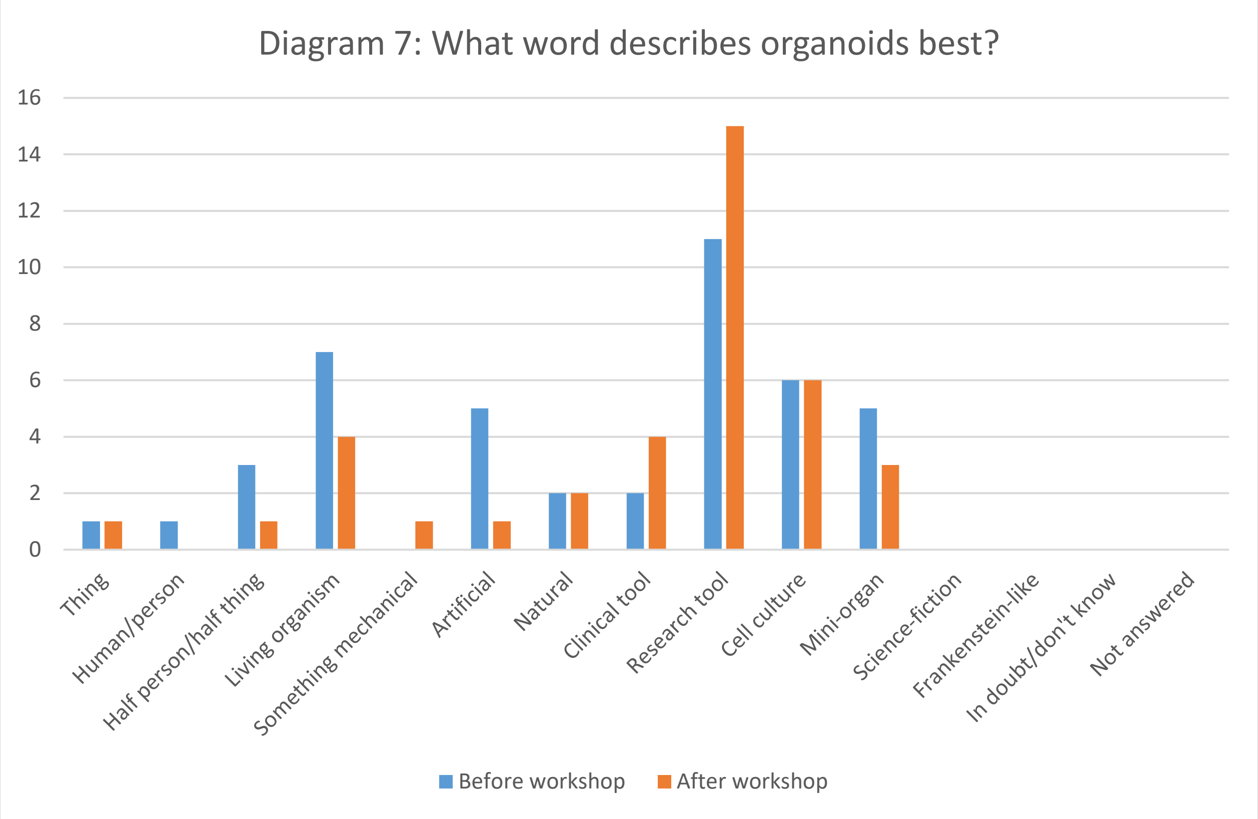
Diagram 7: What word describes organoids best?

Diagram 7 shows which words the participants found to be the best words to describe organoids – before and after the deliberations at the workshop. They could choose up to three words. We see the biggest changes in the words *artificial*, *living organism* and *research tool*. After the workshop, 7 participants considered organoids to be a *living organism* as opposed to 4 at the beginning of the day. For *research tool*, the figures shifted from 11 to 15, and for *artificial* it shifted from 6 to 1. At the end of the workshop the participants had a clearer understanding of organoids, as they used fewer words to describe them.

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Table 10. Words describing organoids – Before and after the workshop

	Before workshop	After workshop
Thing	1	1
Human/person	1	0
Half person/half thing	3	1
Living organism	7	4
Something mechanical	0	1
Artificial	5	1
Natural	2	2
Clinical tool	2	4
Research tool	11	15
Cell culture	6	7-6
Mini-organ	5	3
Science-fiction	0	0
Frankenstein-like	0	0
In doubt/don't know	0	0
Not answered	0	0
Total	**47**	**38**

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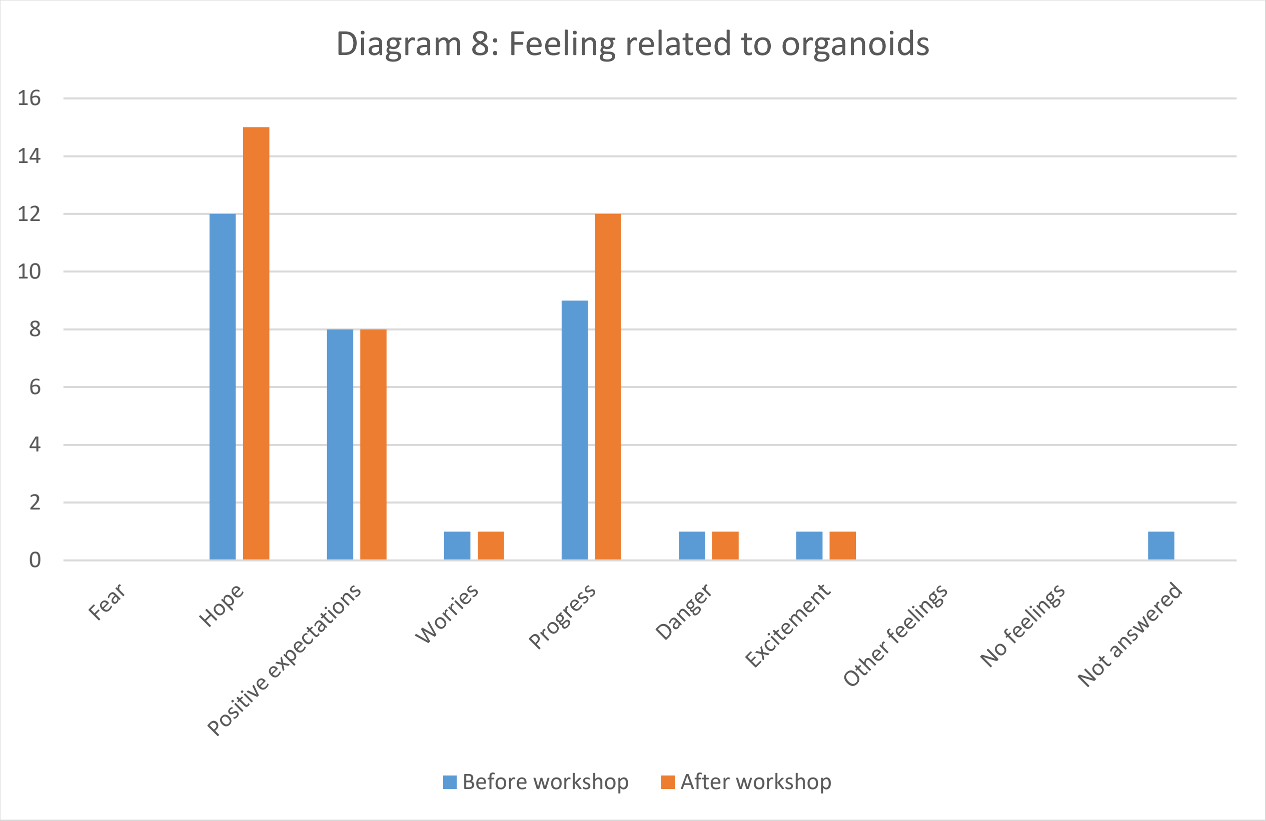

Diagram 8 shows the distribution of the participants' answers on the feelings they had in relation to organoids before and after the workshop. Both before and after the workshop, positive feelings such as 'hope', 'positive expectations' and 'excitement' are dominating.

As Table 11 shows, the participants have also in this case used more words to answer the question at the end of the workshop than at the beginning of it.

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Table 11. Feelings related to organoids before and after the workshop

	Before workshop	After workshop
Fear	0	0
Hope	12	15
Positive expectations	8	8
Worries	1	1
Progress	9	12
Danger	1	1
Excitement	1	1
Other feelings	0	0
No feelings	0	0
Not answered	1	0
Total	**33**	**38**

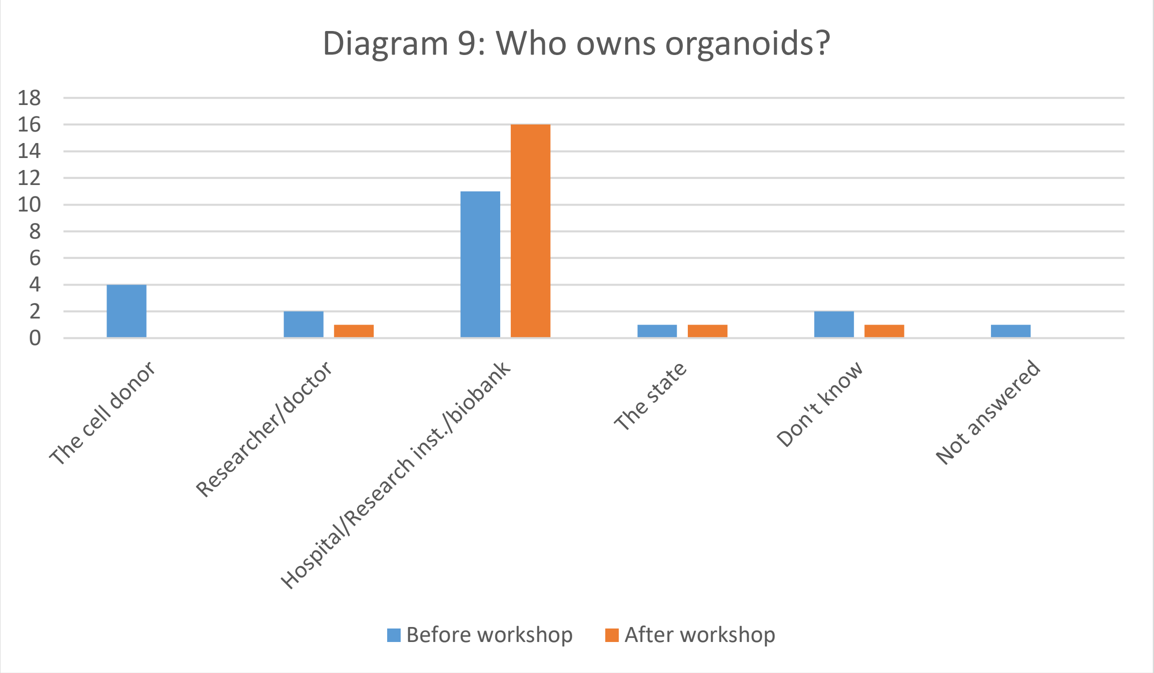

Diagram 9 shows how widely it is shared by the participants that the cells must belong to the *hospital/research institution*. At the beginning of the workshop this answer was given by 11/18 participants and at the

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end by 16/19. It is also significant that if at the beginning of seminar 4 they had answered cell donor, at the end of the seminar no one chose this answer.

The total number of morning answers is 21 because one participant chose 4 answers: cell donor + researcher + hospital + the state.

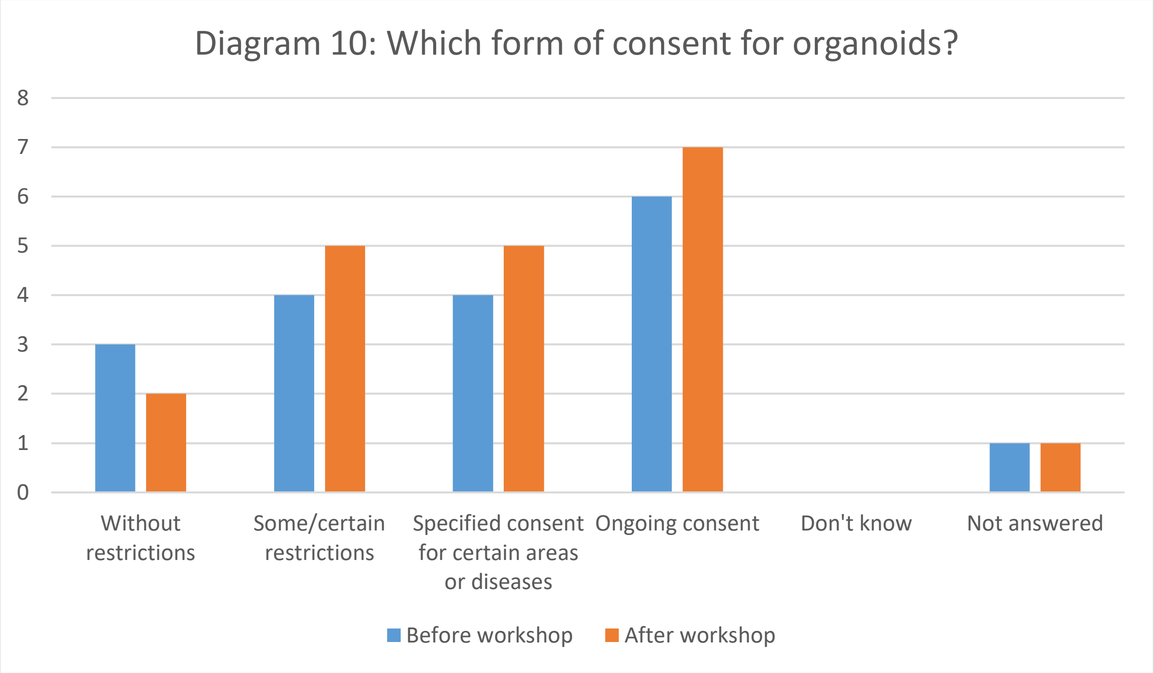

Diagram 10 shows the distribution of answers from the participants - before and after the deliberations - on the question of which form of consent they prefer. Here, almost half of the participants prefer *ongoing consent*. One of the participants who choose the answer “ongoing consent” specified: “Except in cases where it isn't possible to trace donor's DNA”.

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3.4 Conclusion

The Italian deliberative workshop has shown that the participants were mainly positive and hopeful regarding research with organoids and the ways it can contribute to important knowledge about diseases and development of new treatments and medications. This positive attitude was found in all participants, regardless of age and category for which they were recruited. There was a strong sense of hope about the perspectives opened by organoids on the part of patients and parents of sick children. During the deliberations it emerged that the participants in order to orient themselves on an unknown topic made frequent use of analogies, referring in particular to animal experimentation and the current donation system of cells and organs. While the sentiments expressed are generally positive, fears have also emerged. The fears and concerns mainly concerned the cerebral organoids, not so much in relation to the current situation, but to the possible future implications and the possibility that these could develop a form of consciousness. Generally a great difficulty has emerged in addressing this issue with current knowledge and conceptual tools. Participants also express worries related to misuse of data and the risk of the technology leading to an increase in inequality and access to treatment. A topic to which a lot of attention has been dedicated is the issue of consent, the methods of obtaining consent were considered fundamental with respect to the need to ensure the ethics of research. Furthermore, the need for transparency and research control by ethics committees or public institutions has emerged. The results must be distributed equally and globally and the principles to be followed are those of solidarity and transparency.

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Appendix B National Report – Athens

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HYBRIDA

Public attitudes, understandings and perspectives on organoid research

HYBRIDA

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

Report factsheet:

Project Title:	HYBRIDA
Title of Report:	Public attitudes, understandings and perspectives on organoid research
Author(s):	Eleni Spyrakou, Vana Stavridi, Panagiotis Kavouras
Finalised on (date):	First version: 14.01.2022 Second version: 21.01.2022 Final version: 04.02.2022

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innovation programme under grant agreement No 101006012.

1 Introduction: Deliberative Workshops on Organoid Research

1.1. About HYBRIDA

The HYBRIDA project is a 3-year project funded by the Horizon 2020 framework programme. The main aim is to build a comprehensive ethical dimension for organoid-based research and resulting technologies[4].

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.

Following Roman times, all entities have been categorised 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 innovationthat 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

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

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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. In order to develop ethically and socially robust ways of assessing the effects of organoid research and related technologies, there is a need to include these additional forms of uncertainty in the Health Technology Assessment (HTA).

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

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 the Deliberative Workshop in Athens

This report provides a concise overview of the discussions that took place and the survey that was conducted during the deliberative workshop in Athens, Greece. Greece is a country with strong religiosity among its population, relatively to other European countries. Specifically, according to a survey ("Religious Belief and National Belonging in Central and Eastern Europe". Pew Research Center, 10 May 2017. Retrieved 21 January 2022), 90% of Greek citizens are Orthodox Christians. Greece holds the last place of the group of European countries that are Moderate Innovators, according to the European Innovation Scoreboard of 2021. In economic terms, Greece is among the weak countries in Europe. Its Gross Domestic Product per capita ranks Greece at the 31st place of the 42 European countries (https://en.wikipedia.org/wiki/List_of_sovereign_states_in_Europe_by_GDP_(PPP)_per_capita). Greece, in 2020, had the highest rate of unemployment among the EU countries with 16.85%. The most striking factor for Greece is not these absolute numbers but the relative decline of its economy at large after 2010.

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2 Methodology: Deliberative Workshops

This section outlines and details the methodological issues related to the design, planning and completion of the deliberative workshop, i.e. the particular research design, research questions, participant recruitment and data collection as well as the process of coding and analysing the data and knowledge obtained from the workshop.

2.1. Design: Exploration of Public and Stakeholder Attitudes towards Organoids through Deliberative Workshops

Deliberative workshops can be characterized as "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). Great emphasis is placed on facilitating deliberation based on expert inputs and an examination of various issue positions with the objective to elicit a broad and diverse range of views on the topic in question (The Danish Board of Technology, 2014; O'Brien et al. 2020; Steel et al. 2020, for more details on the method of deliberative workshops, please see the research protocol for the study, Ravn and Sørensen, 2021).

The purpose of conducting three deliberative workshops is to explore and elicit different views on the use and derivation of organoids and organoid research to understand the public opinion (i.e. worries, concerns, fears, uncertainty and expectations) and key ethical issues and implications related to organoids from the point of citizens, vulnerable groups, patients, donors and CSOs. More specifically, the deliberative workshop has been designed to answer the following research questions:

- *How do non-professional stakeholders and the lay public perceive organoids and organoid research?*

o What are the participants' main worries, fears and expectations concerning organoid research?

o How do participants conceptualise and understand organoids (i.e. persons vs. things, moral status, mythological aspects)

o What are the perceived current and future benefits of organoid research according to the participants?

o Which kind of ethical issues or research poses concern for the participants? (i.e. particular organoid types and uses; particular ethical issues such as informed consent, ownership and commercialisation)

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The valuable public and stakeholder perspectives into these questions will provide key insights and unique knowledge into the continuous process of developing the four HYBRIDA project outputs, including operational guidelines and an ethics framework. The exploration of these questions was conducted in a two-phase deliberation at where the first part explored the 'attitudes towards and conceptualisations of organoids' and the second part focused on 'perceived benefits and concerns in relation to the derivation and use of organoids' in terms of key ethical issues and implications to be taken into account in regard to organoid research.

2.1.1 Format and Setting in the Deliberative Workshop in Athens

The deliberative workshop in Athens took place in a conference room of a hotel, located at the centre of the city. This was preferred in order for all participants to be able to reach the venue by means of public transport. Also, it would be easier for the participants coming from Thessaloniki, since they resided at the hotel were the deliberative workshop took place.

The deliberative workshop took place on Saturday, in order to facilitate participation of people who otherwise would not be able to participate, due to the fact that they would have to obtain a permit of absence from their work if the deliberative workshop was going to take place in a working day. This choice was decided collectively, by all three groups that conducted the deliberative workshops in Aarhus, Athens, and Rome.

The NTUA team had recruited 22 participants. However, 12 participants showed up at the venue. 4 of them notified the NTUA team about their absence a couple of days before the meeting, and 4 of them on the same day of the deliberative workshop, more specifically less than one hour before the deliberative workshop was scheduled to start. 2 other individuals that had accepted to participate did not show up at the deliberative workshop, without notifying the organisers.

The only modification at the programme was that the session with the questions to the experts took more time than anticipated. This resulted that this session was cut in two successive sessions, since the organisers had to make the lunch break.

The ice breaker used by the facilitator was to ask all participants to describe their prior knowledge on organoids. This “provocative” question was used in order for all participants to realise that everyone was not aware of the organoid research and feel comfortable with this fact. One happy occasion, during this ice-breaker session, was that one of the participants started describing that he had deep knowledge of organoids

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and that this was one of its favourite games from his childhood. This, of course, caused the amazement of everyone to be followed by its statement that this was just a joke that he thought about spontaneously. It also provided the explanation of this initiative by the fact that it is an amateur stand-up comedian. That provided a nice opportunity to the organisers to explain again the novelty of the organoid field of research in a much more relaxed atmosphere.

All present at the deliberative workshop had to wear protective face masks and were seated with at least two meters distance from each other. For this reason, the participants, the experts and the organisers (making a total of 17 people) were spread in an area of 10 m × 4 m. Only the two experts, during their presentations removed their masks to be clearly audible.

The workshop was moderated by a professional moderator, with a background in Molecular Biology, from a non-profit organisation, called "Sci-Co", specialised in science communication to the public via innovative and entertaining means. The moderator was successful in making the transition between different sessions, while he took the correct initiative to break the answers from the experts session in two, in order to facilitate the lunch break and to provide some time for rest to the participants. The moderator also presented, in specific "strategic points" of the deliberative workshop, some elements from his experience that helped the participants to grasp the essence of a deliberative workshop; i.e. that they are participating not only to make questions to the experts and to the organisers but also to provide valuable responses to issues that are still to be clarified.

At the beginning of the morning session, there were two presentations made by two experts:

- Dr Olga Tzortzatou-Nanopoulou, Legal counselor and President of the Intellectual Property Committee of the Biomedical Research Foundation of the Academy of Athens (BRFAA), European Commission Expert, specialised in GDPR/informed consent issues and IP/patents.
- Dr Miltos Ladikas, senior researcher at the Institute of Technology Assessment and Systems Analysis, Karlsruhe Institute of Technology, Germany, adviser to the European Commission, the European Research Council, the European & Developing Countries Clinical Countries Partnership, and a number of National Research Organisations, on social-ethical issues in Science & Technology developments, specialised in Global aspects of Technology Assessment, Responsible Innovation, Ethics in Science and Technology Policy, as well as, Science Diplomacy.

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The first expert presentation (*"Information Society and the current role of Bioethics: Personal data and informed consent"*) was on issues of data management and GDPR in the context of biomedical applications, focused on stem cell technologies. The second presentation ("*Technology Assessment and Policy making"*) was about the way policy making is affected by disruptive technological advances. Both presentations did not target the organoid field of research directly, but they described the ways disruptive technologies affect everyday life. This proved to be a sound choice, since participants followed back with many questions that were relevant to the experts' presentations put in the context of organoid research.

During the debriefing/evaluation session the participants made the following comments:

1. The deliberative workshop would be better if it had started earlier, e.g. at nine o' clock in the morning. The rationale was that people are more used to start their more active part of the day at this time.
2. The deliberative workshop could have a smaller duration, i.e. four hours
3. The participants found that the two case studies with the dilemmas should be somewhat connected; i.e. the second case study should present a "*progress*", that was the word that was used, with regard to the first. Going through two completely different case studies seemed to create confusion, at a time that the participants had already went through quite a lot of mental strain.
4. A comment was that the information given, before the deliberative workshop, should be significantly less. There were concerns that the participants became biased from the informative material that was circulated before the deliberative workshop. Less information, according to one participant, might help them think more "*out of the box*", again according to the words used. The discussion on the amount of necessary information on organoids continued; specifically, concerns were raised on the issue of how to balance the input on pre-conditioned attitudes/feelings versus a genuine evidence-based reaction towards organoids. If too little or no information is given, then the information obtained by the participants will be closer to "*a simulation of the general public's awareness*".

2.2 Sampling and Recruitment Procedures for Deliberative Workshops/mini-publics

The sampling procedure that we applied indented to secure diversity in representation and potentially identify common trends across the diverse groups. Hence, in relation to the workshop objectives as they are mentioned on D4.2, a criterium for assembling the deliberative workshops was both to invite citizens with potentially no knowledge of organoid research as well as key non-professional actors representing a minor fraction of the public, who have particular experiences and/or interests in organoid research. For the purpose

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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 were 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). In addition, we tried to ensure the diversity between age, gender, socioeconomic groups, ethnic origin and religious views by approaching and inviting representatives from all these categories, while ensuring confidentiality.

However, it is worth noting that the pandemic imposed a restriction which affected the sample and precluded the emergence of additional attitudes. In particular, due to the COVID-19 pandemic restrictions and since the deliberative workshop should have been a physical meeting, there was a further condition that had to be met and affected the recruitment process: all participants had to be fully vaccinated or to have the relevant certificate of disease at their disposal. This condition should be considered restrictive for the representation of certain groups to the deliberative workshop sample, namely of groups that have certain attitudes (critical and of disbelief) towards science and progress. In other words, if we consider that a large percentage of unvaccinated citizens constitute a group with a specific attitude towards science and its progress, then it should be noted that no specific concerns that exist in society were recorded and would certainly affect the findings of our survey. Furthermore, there was an additional restriction regarding possible attendees that had to do with the fact that some patients and people related to patients were hesitant to attend as they were afraid of being exposed to potentially COVID-19 affected environment.

The approach of stakeholders happened in the following ways:

- CSO’s were contacted through existing networks, internal experts or directly through organizational gatekeepers.
- Representatives from the public were recruited through personal contacts and through a diverse set of media outlets, such as Facebook groups, networks.
- Vulnerable groups, donors and patients were recruited through the websites of patient organisations, support networks, donation organisations.

The approach of stakeholders was done gradually. Initially, we contacted the participants either by phone or via email in order to inform them about the workshop and to explore their initial interest in attending it. Then, if they expressed interest, we sent an e-mail with the invitation and the information letter. We then called to ensure that they had received the documents we had sent them, and in addition to confirm their attendance to the deliberative workshop. Finally, a week before the workshop, we sent an e-mail to those who expressed their desire to attend the workshop with the information material, the consent form and the

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agenda of the deliberative workshop. After sending the email we then confirmed by phone that they had received it and answered more specific questions posed by some of the participants. The following Table 1 shows the intended distribution of the recruited participants compared to the actual distribution.

Table 1. Distribution of participants – planned and actual

	Planned distribution of participants	Distribution of recruited participants before the workshop
The general public	6	6
Vulnerable groups	3	4
Patients	3	4
Donors	3	3
CSOs	5	5
Total	**20**	**22**

Finally, the Greek workshop had actually a total of 12 participants out of 22 that we had recruited. Table 2 shows the distribution of stakeholder groups with the persons that actually attended the deliberative workshop**.**

Table 2. Final distribution of participants at the workshop

Participant category	
Vulnerable	-
Patient	1
Donor	1
CSO	1
General public	9
Not answered	-
Sum	**12**

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2.3. Data analysis

All parts of the deliberative workshop were recorded in the following way: all three organisers from NTUA recorded the discussions via their laptops. All recordings were then moved to RNanoLab's secure server and deleted from the organisers' laptops. The reason this recording procedure, i.e. having three recordings, was to make sure that all participants were audible in the recordings. The participants were seated in a conference room with at least two meters distance from each other, due to pandemic measures. As a result, the participants occupied a space of 10 m × 4 m, so the organisers had to spread throughout this area.

Then, the three organisers allocated transcription responsibilities among them. Before the start of the transcription the organisers used the best of the three recordings, i.e. they used the recording that the sound was optimal. The organisers tested two applications for automatic transcription, but they proved inefficient due to the fact that the deliberative workshops took place at the Greek language. For this reason, the transcriptions were made manually.

The coding of the transcripts was based on the codes the Aarhus team sent. Firstly, the codes that were sent in English were translated by the NTUA team. Then, all three organisers read the whole transcript of the deliberative workshop and added additional codes, while working separately. Then the organisers compared these three sets of additional codes and produced the final set of codes that was about to be used for the analysis of the deliberative workshop.

The analysis of the deliberative workshops was made independently by two NTUA members. The third NTUA member had the role of the referee, in case of disagreement between the two other members. The results were discussed among the NTUA team and the conclusions were included in the Greek national report.

3 Findings

In the next following sections, we report the findings of the deliberative workshop focusing on the following issues:

- Conceptualisations of organoids
- Attitudes towards organoids

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- Ethical issues and implications in relation to the derivation and use of organoids (informed consent and patient information, biobanks, misuse/dual use, animal research, commercialisation, science communication)
- Recommendations for future guidelines.

One general comment that reflects the discussion conducted as a whole is that for the participants seemed to be very helpful to contemplate on organoids by using analogies and comparing potential applications of organoids with other technologies that are considered similar. This is something that was happening spontaneously during the discussion.

The participants, also, considered as very important and promising the fact that lay people are being asked to contribute to the formulation of regulating procedures at a quite ‘early’ stage of a particular scientific field. In the words of one participant:

> *“It is very unique, very innovative that something like this is discussed at first and then a certain plan is implemented; I have never seen such a thing before.”*

3.1 Attitudes towards and Conceptualisations of Organoids

The findings related to the conceptualisation of organoids and the attitudes towards organoids derived from the first part of the deliberative workshop and specifically from the “group deliberation: collective preparation of three questions to experts” and from the part of “deliberation based on two guiding questions regarding attitudes towards and conceptualisation of organoids”.

The conceptualisation process and the attitude formation took place through the use of analogies and correlations with technologies and procedures of which the participants were aware. The use of analogies to other technologies has also been a means of conceptualising organoids and giving them relevant ethical dimensions. Regarding technologies and procedures which are related to organoid research, participants found analogies with stem cell research, IVF, organ donation, blood donation. The analogies were mainly about the deficiencies of the legal framework for the aforementioned technologies and procedures. The discussion on legal framework covering these technologies and procedures gave rise to fears and worries of participants. However, the attitudes of participants towards organoid research could be characterised as positive. The positive attitude of participants towards organoids was mainly expressed at two phases of the workshop:

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- The first was during the deliberation based on two guiding questions regarding attitudes towards and conceptualisation of organoids
- The second was during the deliberation on two dilemmas and mainly at the discussion on the types of informed consent.

The analysis of results, which are related to the conceptualisation of organoids and attitudes towards organoids will be presented in the next two sections. The results ensued from the coding of the transcript and from the observations of the organisers. In order to provide a comprehensive picture of the participants' views we will quote specific excerpts of the deliberative workshop.

3.1.1 Conceptualisations of Organoids

As all participants stated that they were not aware of organoids, they tried to define and conceptualise them, in order to form their questions and discuss on specific ethical dimensions that each conceptualisation indicates. The concepts that participants gave to organoids formed their attitudes towards organoids and towards specific ethical issues that organoid research raises. In both parts, group deliberation: collective preparation of three questions to experts" and "deliberation based on two guiding questions regarding attitudes towards and conceptualisation of organoids", participants conceptualised organoids through the following terms: living organism, with its own life, machine, something artificial, natural, research tool, clinical tool, mini organ, skin without wrinkles, replacing part e.tc. However, there were participants who did not proceed directly to the conceptualisation of organoids, but the conceptualisation became evident through the concerns they raised during the group discussion.

Most of the conceptions remained constant from the beginning to the end of the workshop and we could say that the discrepancies were not significant. In the process of conceptualising organoids, participants took into account the current stage of the research, the possible future possibilities of the organoids, or both.

The concepts that participants gave to organoids seemed to be different at first, but the way with which each participant expressed his/her concerns on the discussion indicated some similarities. The analysis of these similarities shows the trend of ethics on organoid research and helps us to draw fruitful conclusions. The similarities which were ensued from the discussion could be deduced to the common characteristics related to their relation to the job market/work and specifically the scope of their work and their religious orientations.

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In the following sections (3.1.2, 3.1.3) we will present the specific directions that the deliberation on organoids took and the main concepts that dominated the discussions in sub-groups and plenary.

3.1.2 Human, thing, artificial, or natural?

The guiding questions for the discussion, as well as the questionnaires circulated to the participants, emphasised two major distinctions regarding possible conceptualisations of organoids: **human/person vs thing** and **artificial vs natural**. This discussion was initiated using these distinctions. However, due to the way that the participants conceptualised the very concepts of 'human', 'person', 'thing', the discussion was broadened and included the notions of **living organism, with its own life**. Moreover, it should, also, be taken into consideration the difference between the word 'human' as a noun and 'human' as an adjective (namely, something that has some properties related to being human or something that derives from a human) in the Greek language. This direction of the discussion affected, consequently, the relevant results during the coding process. Having these differentiations in mind, some participants expressed the following concerns as displayed in Table 3:

Table 3. Quotes on human conceptualizations of organoids.

Organoids as human
May I ask a question over the question? There is this question of whether an organoid is a human being. I would like to ask how, by asking this question, you defined what a human being is because, in my mind, at least in different contexts, it can mean different things of what a human being is and it may sound very 'post-structural' or 'post-anything'. So, having no idea how the human brain works, are there any specific functions of the brain that we can determine as important, constitutive, and to say that it has this function, and, therefore, it is human (*the adjective*) or a human (*the noun*)? (P2, general public)
I think that a very strong framework of reductionism is introduced here. That if we put the parts together, a whole person will come out, let's say, which may not be the case, in the sense that if we recognize that every level of organization has extra properties, then the human body is not just a set of organs, nor the brain. If I take a part of it and multiply it and make something looking like a brain, will it

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be a brain, will it have functions, will it have intelligence? It's a very powerful reductionist framework, we need to explain it. (P7, general public)

Therefore, the discussion was developed around the different conceptions of what is a human, and the different perspectives of the notion, namely from a biological, a legal and a social point of view. Moreover, the participants expressed their concerns on how a gradualist approach on the mater may affect the conception of a human. For instance, how we conceive someone who is brain dead or has been born with Anencephaly malformation. Should these examples be considered as less human? Do their conditions affect their humanness?

Regarding the conception of an organoid as a thing, as it is shown also in the relevant diagram 6 and table 11 on the questionnaires, no participant conceptualised organoids as things actually, in the sense that they did not use this specific term. Instead, as it will be analysed in the following paragraphs, some participants used the term ‘tool’.

Moreover, during the conceptualisation of organoids, participants took account of the current stage of organoid research and/or the future potentialities of organoids. Most participants faced organoids as a **dynamic entity** and organoid research as a **dynamic procedure**. In this context as well, the issue of person vs thing appeared. Participants who deliberated from the point of view the **future potentialities** of organoids had the tendency to give organoids characteristics, features similar to a **living entity**. This tendency is captured in the following terms, as already mentioned: **living organism, with its own life**. As a participant stated:

> *“I would be more concerned with the level at which it (organoid) can acquire its own life, that is, if it can acquire both emotions and nerves.”* (P2, general public)

Another participant stated:

> *“But we assume that it is a living creature, we assume that it is a living organism, it is something alive. We assume it has some features of life in it in an artificial way.”* (P6, general public)

And another participant stated with metaphors, in an almost artistic way:

> *“I also have a concern and as I understand it, it seems like a natural process. There is an intervention for sure, if I understood it well, it is a natural process the growth of cells in*

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> *this way, now I get an image, [as if] a flower that grows through the cement. That life, let' say, finds ways out."*(P5, general public)

Simultaneously, an interesting part of this discussion was an additional conceptualisation of organoids that appeared. We observed a different conceptualisation of organoids forming another one dominant trend in the deliberation. Participants who shared common professional characteristics, but not a common religious orientation, conceptualised organoids as "extension of stem cell research" and "research tool''.

According to these concepts, there was a participant who, in his/her attempt to define and conceptualise organoids in order to discuss specifically the ethical issues that organoid research raise, proceeded to the analogy between organoid research and stem cell research and he was wondering if organoids are an extension of stem cell research. The participant asked the following:

> *"I still have a question about stem cells and organoids, whether organoids are an extension of stem cell research or whether they are something completely different. That's something I have not clarified."* (P7, general public)

And while initially the participant posed the analogy between stem cell research and organoid research during the deliberation as a question, it seemed that this participant reproduced this analogy as a certainty by making relevant arguments. Taking into account the stem cell research, its development and its ethical issues, the participant opposed to the idea that an organoid could acquire the characteristics of a living organism or even more consciousness. As himself/herself argued:

> *"Stem cells and gamete lines, generally cell lines are not easily maintained, it is not that we have things from the science fiction now and they (organoids) will pull tentacles"* (P7, general public)

And also:

> *"I do not think guys, the research is still at a very early stage, here we do not have very basic tools. That's why I do not care about this question, it seems so distant to me…"* (P7, general public)

In the same context, other participants conceptualised organoids as **a research tool**, but not as a thing. They kept a middle position giving to an organoid a status which is **neither person nor thing.** And although they

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mentioned that an organoid is not a thing, they took distance from those who claimed that an organoid could evolve into an entity that could have a moral status. As a participant claimed:

> *"I distinguish an organoid from an embryo. It is not an embryo. [...] So, organoids seem to me like just some research material. That is, I do not want to identify them, I think the questionnaire mentions them as a research tool. Neither an instrument nor a thing, which of course always leaves the question of how it can evolve. But, right now, and based on this data if I wanted to define it just in that way.''* (P12, donor)

During the conceptualisation of organoids there were also some references to **mythological aspects** of organoids. In the context of common assumption that organoid is a dynamic entity, there are participants who gave to organoids mythological or science fiction characteristics through terms such as "*Frankenstein*", "*Wolverine*'' or "*an eye that blinks and puts mascara on*''. As two participants discussed:

> "- *Yes, yes, exactly. The question, I think, that you raise is 'should Mr. X proceed with his research with the danger, at some point, to get very close to creating a brain?'* (P10, religious CSO)
>
> -*To make a Frankenstein!''* (P4, general public)

And, also:

> *"Now, if, at some point, they make an eye that blinks and can put mascara on, what can I say?! I don't know, then we will have to see it differently!"* (P12, donor)

The **mythological and science fiction** aspects emerged in the context of discussion around the management of biological samples, the advancement of technology and the informed consent of donors. The use of such aspects seemed to be equivalent with the use of analogies and examples from other, similar or more familiar, technologies. At the same time a position which defended the delimitation of research and the protection of the donors or patients against the organoid research development was, also, expressed.

Finally, one of the important issues raised was that of nature. There were participants who believed that the applications of the organoid research despite its usefulness for the well-being of humans is an intervention in human nature for which there should be a limit. As a participant stated:

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> *“Surely all this is in the interest of people to prolong life, etc. etc. The moral, however, is that you intervene too much in nature, but will the nature of man himself… in levels… reach immortality through technology?”* (P4, general public)

And another one that claimed that organoid research treats a human as a device/machine and stated:

> *“This makes me a bit like a human being, let's say, becoming a machine. When something breaks, okay, nothing happened […] we put a spare part, let’s say”* (P11, patient)

The claim about **intervention in natural processes** and of the consequences that such intervention brings, has greater ethical weight when combined with the argument concerning **human dignity**. There seemed to be a trend according to which human nature is identical to humanness. Therefore, any intervention in human nature mitigates its humanness. For example, if a person is transplanted with an artificial organ or a prosthetic body part, it seems that, for some people, this lessens his/her humanness/human dignity. It is, also, possible that such an intervention will affect the self-perception of this particular person.

3.1.3 Moral status

The correlation of an organoid with a living entity and its conceptualisation as a living organism that has the potentiality to acquire **consciousness** and as something which has its own life gives rise to the issue of **moral status**. Participants who gave to organoid the features of a living entity deal also with the moral status of this entity and proceed to the recommendations about the legal framework, which would regulate organoid research and the potential evolution of a new entity. One of the participants made this recommendation with a very clear way:

> *“Maybe the time has come and as technology advances and we make new inventions to define a new category of entities that could potentially acquire self-awareness, whether it is a big data algorithm or a tissue or an organoid and therefore to create a legal framework for anything that, theoretically, can acquire a relevant status, let’s say, before we find it ahead? Because this thing will happen.”* (P8, general public)

From this statement, but also from other points of discussion, it seems that the concept of consciousness is implicitly linked to the concept of moral status, recognising that an entity with consciousness needs special treatment. However, moral status and consciousness do not coincide in all cases. As it has already been presented in section 3.1.2, there examples of people who lack or have limited consciousness, but who are attributed with moral status and need to be treated as moral entities. All creatures that have consciousness

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have been considered as worth being attributed with moral status. Nevertheless, moral status needs to be also attributed to entities that do not have consciousness or self-consciousness (as in the case of patients with dementia).

Furthermore, it is worth mentioning that the participants recognised a significant difference in the way we tend to approach the idea of the creation of chimeric entities, based on whether the host organism is an animal (e.x. a mouse) or a human. It seems that the reaction to such perspective is different, and that the audience was less hesitant to endorse the perspective of non-human chimeras. As a participant pointed out:

> *But what you say about mice, it was okay to put a human brain into a mouse, okay cool, but to put a mouse brain into a human it's a shame. How does this, really, come about? The first option is ok, but the other is not? I wonder, what is the element that makes someone, something human? I understand that there is a taboo, it is okay to make a chimerical entity to be a'mouse-', but to make a chimeric entity that will be a 'human-' would cross a red line. Philosophically, I mean, how do we isolate the concept 'human' and say "we do not touch it" or that we only 'touch' it for reasons of life preservation?* (P2, general public)

There seems to be a 'gradual' attainment or possession of moral status, in other words an hierarchy, among living creatures, depending on whether they are humans, animals or organoids. The participants showed the tendency to choose humans over animals, but, also, animals over organoids, in hypothetical scenarios in which they would have to choose which creature to 'sacrifice' in order to save the other. For example:

> *I try to answer here the last question which says that we should weigh our interest for a patient with Alzheimer's disease in relation to the possibility of the suffering of an entity that looks like a very simple form of life. Thinking, then, I think I would probably end up saving the human, the Alzheimer's patient.* (P3, general public)

The following part of the discussion is, also, relevant:

> *-Look, I'm with these questions… Deep inside, I'm a cynical [reference to profession] … We have no problem taking the guts out of a guinea pig, we do anything with each guinea pig, we insert electrodes and, suddenly, we worry for an entity that…* (P7, general public)
>
> *-Here I agree, I do not agree with the experiments on frogs in general but…* (P9, general public)
>
> *-Here is another question, very, very different from what we do with guinea pigs in general.* (P7, general public)

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- *Yes, then you go to animal testing in general.* (P9, general public)

- *Okay, now this, about consciousness and so on, we have a very narrow perception of consciousness here. In this sense, why do we consider that the frog does not have consciousness and we disembowel it?* (P7, general public)

-Doesn't the frog have consciousness? (P9, general public)

-It does have and if we can find ways not to use frogs, we have to look for it. This dimension mentioned here seems very interesting to me, namely that we can replace this frog, so we could look for it further. (P8, general public)

-Yes, so I agree if we can stop researching on frogs and do experiments on cells, we should do experiments on cells, of course.

[…]

-[…] if they made steaks by artificial cells, I would eat artificial cell steak. If I could eat meat without animals dying, it would be great. Not that I have many moral inhibitions but I would feel much better if I knew that for the meat I eat no animal died. (P9, general public)

Closing this section, we could say that the discussion among the participants covered all possible conceptions of organoids and through them important ethical issues were raised that concern the ethics of organoid research. The conceptions that participants gave to organoids and the variations that emerged should not be considered consolidated or absolute. During the deliberation, especially in the first part of the deliberative workshop, most of the participants expressed their opinions in the form of question and with a sense of uncertainty about the categorisation of these entities. This is advocated by the fact that they asked for more information about what organoids are and about their applications. They formed judgments based on hypotheses, intuitions, and analogies with technologies and procedures of which they had prior knowledge.

3.1.4. Attitudes towards Organoids

The attitudes of the participants towards organoids were formed through analogies with other technologies (organ donation, blood donation, IVF). Participants used their prior knowledge of related to organoid research technologies and procedures for the purpose of forming their attitudes. Also, specific experiences of

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participants set the context of discussion about how they feel towards organoids. At this point of deliberation, fears and worries emerged, but expectations and hopes were, also, expressed. Worries, fears, expectations and hopes were expressed though personal experiences and facts that had happened in the context of other technologies and procedures. Worries and fears concerned the management of the biological material and the consequent use or misuse of personal data, access to potential benefits from the development of organoid research (access to therapies) and the consequent broadening of social inequalities, commercialisation in science (for example with stem cells) and the absence of a regulatory and legal framework for organoid research.

Positive attitudes towards Organoids

Despite the fears and concerns that were not directly related to organoid research, but had to do more with the legal and ethical issues related to similar technologies, the participants formed positive attitudes towards organoid research. All participants identified the research in organoids with terms such as 'treatment', increase of their life expectancy', 'reduction in the use of animals in research experiments'. This attitude was also supported by the views of the participants during the deliberation on the type of consent. Most of the participants were in favor of some kind of informed consent that will favor the progress of the research but will not affect the rights of donors. This conclusion will be further analysed in section 3.2.3 on Dilemma 1.

A general sense throughout the deliberative workshop was that the participants had positive expectations towards organoid research. This sense was further confirmed by the answers given by the participants to the relevant question in the questionnaire (see Diagram 7 and Table 12). This positive attitude was expressed, more or less, by all participants, regardless of age, gender, participant category.

Table 4. Quotes expressing positive attitudes towards organoids.

I'm a bit biased into this as a [reference to profession) and this type of research is not disgusting or dangerous or negative for me. I would characterize them as interesting and hopeful with the concerns that obviously exist as in many other research fields. But I'm biased into that. (P7, general public)
I am also a little biased because as a [reference to profession] I do not feel anything… but looking at the questionnaire I thought that I would check some positive expectations along with reservations. It is

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interesting that there is no choice 'reservation', there is 'concern', I do not know, maybe it is more intense. I do not feel any particular feelings. (P10, religious CSO, self-identified as scientist also)
When we hear about science and technology it comes to mind that it is also a good thing. And even that we discuss this, I have positive emotions but as P10 said 'with a limit'. There are too many questions to be answered, there are dangers as to whether they can be applied to humans. We are at a very early stage as we said, but I see it with a very positive sign. Okay, there are definitely a lot of doubts and especially in relation to whether this is possible. (P4, general public)

Worries related to organoid research

Throughout the deliberation, there were particular recurring questions, such as: Who defines the purposes and scope of research? Who benefits from research advancements? How stakeholders involved in research exploit research results? As one participant mentioned:

> *"Do we know, at the EU level, which labs are registered somewhere, which labs work on organoids? We could say that these labs every six months need to report on what they are working on."* (P8, general public)

It should be mentioned that a participant namely expressed **fear and distrust** towards processes related to the **donation of biological material**, as well as towards the way research is conducted generally nowadays, as a particular case:

> *"I, however, wrote in the questionnaire that I am afraid of expectations and I am afraid in a corresponding question of the questionnaire, because a key question mentioned by the first speaker and for the trade of learning, in general for the trade in science, is who ultimately owns all this. . . all this research. In whose hands is this research. Why we hear about the EU, which has already told us what the main pillars of, say, are. It is EU policy and economic interests, I think he said that. This is dangerous. It is the example the expert mentioned with the stem cells of children. That they ended up in a normal trade in stem cells while the hematologists themselves had concluded that in Greece we want a sample of ten thousand stem cells to solve at least the hematological problems. So one question is how much can we trust the EU in the sense of a council, with the structure it has, to deal with these issues?"* (P12, donor)

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Serious concerns were also expressed during the discussion of the **type of consent** provided by donors and patients. There were also some contextual issues related to racism and homophobia. It was interesting that all the participants in the deliberation on the type of consent were placed against a consent, which would give absolute freedom to the cell donor to decide on what will happen to the cells provided, at each stage of the research, and on who can benefit from the results of the research conducted by processing of his/her cells. In this scope, one participant expressed the following scenario:

> *"What if a donor, after some years, finds out that the majority of those who take part in these trials or research are black, say. And he is a racist, let's say. What is he going to do; Will he get the cells back? That is, we move back to these issues again… I do not know, I do not see how…"* (P10, religious CSO)

Concerns and fears were also expressed through **particular experiences**. Several participants gave examples of **misuse and breaches** of the privacy of personal data. For instance, a participant mentioned the following:

> *"When I went to the hospital a month ago, because I had a pain, I was waiting at the radiologist, I was waiting in a place and there was no employee there. So, there was a form of a patient exposed to all the people who came in. So, I do not think there is a protection framework for protecting personal data."* (P3, general public)

Worries related to different types of organoids

Regarding the particular concerns related to specific organoid types, use of particular stem cells etc., we could say that some were expressed in relation to cerebral organoids. At this point it is worth quoting the point of view of a participant, which summarizes the specificity of the concerns of cerebral organoids:

> *"[t]here is a set of questions and reservations that are the same for every, applies to everything in particular about patents, access and generally everything we have said so far but I think the cerebral organoids show a noticeable difference only in the case of one perspective, only if one technology could allow an entire brain to reproduce. And that's exactly where the question comes in, how to define consciousness."* (P10, religious CSO)

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In the context of the discussion concerning cerebral organoids, the notion was expressed that a theory of consciousness is missing. There the concept of human in relation to consciousness was re-introduced, as already analysed in section 3.1.3 on the moral status of organoids. A debate took place in which the question raised was whether incomplete consciousness, in the sense of the absence of self-consciousness, makes one less human, and, moreover, if consciousness is the mere sense of pain.

3.2 Ethical Issues and Implications in relation to the Derivation and Use of Organoids

Throughout the discussion it proved to be important for the participants to know the current state of research on organoids and related technologies, as well as, in general, the limits of science and particular research. This piece of information seemed crucial for them in order to be able to think realisable/realistic scenarios for future developments on organoids and to set some limitations on their imagination.

It is worth to be mentioned that throughout the meeting there was actually no particular direct reference to God or matters of faith or mitigating circumstances religion-wise, with the exception of a reference to the example of people who deny donating blood for people that belong to a different religious group than theirs. Despite the fact that one of the participants was an Orthodox Christian priest, he himself made no reference or connection to this occupation – he contributed to the discussion mostly with his capacity as a doctor – and the rest of the participants did not seem to attribute certain characteristics to him as a priest. They did not make any comment or expressed any queries relevant to matters of faith that could affect in any way the conceptualisation of organoids and the perception of their applications.

3.2.1 Informed consent and patient information

This consideration on informed consent and information related to patients, namely personal data and information provided by patients or referring to patients, runs through the whole discussion, from the beginning, during the deliberation in subgroups, and during the discussion of the dilemmas provided. In general, it seemed that the participants set and brought forward the basic and most important issues of interest and they highlighted them from the early stages of deliberation. When the time of the discussion on the dilemmas came, the basic points had already been discussed.

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One participant mentioned that technology can help us further on how to inform patients and potential donors on their rights in a more automated way, following a digitalised procedure, without necessarily, for instance, the need to have specific employees informing all patients and donors every time they are having a medical test. People could log in a platform and be informed on their rights and possible use of their data, before proceeding with a medical test or the participation in a clinical trial etc.

More detailed analysis is provided in the section 3.2.3 on Dilemma 1.

3.2.2 Biobanks and governance

The matter of the use of personal data was raised in combination with the issue of access to the potential benefits of organoid research. There was an analogy made between insurance and access to new therapeutic methods. As in the case of private insurance policies that, for instance, smokers or patients with chronic diseases either cannot be insured or they are insured with high insurance premiums, it seems highly possible that there will be similar restrictions to the access of these types of end-users to therapies that are based on organoid research. This will probably result in the widening of the **healthcare-divide** by giving priority of access to those patients who can afford high costs for treatments or to those for whom there are foreseeable higher chances of successful treatment. In a participant's specific words:

> *"It is just like in the USA, as in private insurance, they tell you that you are risky for your life, so I do not offer you insurance. Respectively who has access there, to the organoids, to the use for transplantation, let's say? The one who has money, the one who has what, the one who will live for sure, let's say?"* (P2, general public)

The participants, both during the deliberation in subgroups and during the plenary discussion, expressed worries regarding possible **misuse of personal data** in various ways, and they put this disbelief in a broader scope that has to do with the general progress of science. As one of the participants put it:

> *"The more technology moves forward, [and we have] progress etc., the more our personal data are violated."* (P4, general public)

This attitude is combined with a stance of distrust towards the ways various unreliable bodies exploit personal data and derives from a sense that there is a lack of proper policies and governance on these matters. Moreover, this worry regarding the use of personal data is linked to a conception of **entanglement between**

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politics and science, meaning that science is subject to heteronomous determination by political interests and this may result in the disturbance of the public's trust to science. According to a participant's words:

> *"We are talking about politics involved in medical science, which (namely politics) I cannot trust for any reason, neither in political matters nor in anything else. And since I know that my data will end up there, that I cannot trust, this makes it very difficult for me!"* (P1, general public)

At this point another participant, also, expressed his/her worries:

> *"Whatever happens from now on it must be taken into account that a significant portion of the social body has identified and mixed the scientific world with the political world as the group that one must distrust from the beginning and react, whatever they say to react. This… is a serious problem that we do not know where it will lead. We have seen this with the pandemic in particular and we must take it into account for future… that is, around a strategy of properly informing the social body. That is, it is not enough to inform politicians and MPs, e.g. There is a portion of the social body, which by definition distrusts them, it is not enough to write some things in big newspapers, there is a portion of people who do not even read a newspaper. This is what I wanted to say, this is what worries me, I have no solution, but we are in a different era than 20 years ago, that is what I want to emphasize. The scientific reason is, by definition, considered suspicious by a large portion of the social body."* (P10, religious CSO)

Another issue is the distinction between **public/state and private use, possession and governance** of organoids and the related data. Many participants expressed worries about possible dangers, in the case of private interests being involved in this type of research to a great extent, without proper state governance. They seemed to agree on the idea that organoid research is sensitive and should not be fully left to the private sector for many reasons. It is important to have publicity and proper communication, regarding the relevant developments and results of the research. Furthermore, it is necessary to give proper governance in order to avoid or, at least, restrict cases of dual use and the development of organoid applications that do not serve right causes. Moreover, it is important, at least at the level of EU, to know the labs and institutes that are conducting organoid research, as previously quoted.

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3.2.3 Dilemma 1: Ownership, compensation, and patentability

Two major types of consent were discussed in particular during the deliberation on Dilemma 1, following the options of consent provided in the questionnaire: broad consent with some restrictions and continuous/dynamic consent which requires re-consent for new uses or purposes. Respectively, two were the main arguments:

- Broad consent with some restrictions: the participants who were in favor of this type of consent claimed that it is important to set some limitations in the use of donated biological samples; at least donors should be assured that there will be no misuse of their samples, and that they will be used for purposes of common good (treatments, drug discovery etc.) However, there is a practical purpose that this type of consent serves; namely, it covers the cases in which we have large-scale clinical trials and research projects that run for years and are conducted in stages. In such cases, it is both difficult to identify the initial donors and ask them again for their consent, and, at the same time, it affects a large number of patients who have tested certain therapeutic protocols and have invested their hopes and expectations on them. Any disruption in the advancement of related research, due to a potential withdrawal of donors' consent, would affect their health and the development of further therapeutic solutions.
- Continuous/dynamic consent which requires re-consent for new uses or purposes: the participants who were in favor of continuous consent that requires re-consent expressed worries regarding potential future misuse of the donated biological material and they considered more appropriate the initial donors to be asked again to consent in the case of new experiments or applications. Simultaneously, these participants considered the initial donors as the owners of the samples and for that reason they should be compensated in any case of commercial exploitation of the samples or the products of the related research (e.g. vaccines).

The issue of ownership of stem cells and other biological samples was discussed, also, separately within Dilemma 1 deliberation. It was linked to potential profits deriving from future products and applications, and the main idea was that whoever is the owner of the samples (whether the initial donor or the hospital/research institute/research group) should have a share in these profits.

Some relevant quotes from the discussion are the following:

> *"Regarding the first dilemma, we had two views. One is that the owner of the cells is Andrew and the second is that the owner is the scientists, after all, not Andrew. But also the same in relation to the profits; that part of the profits should be taken by Andrew or that Andrew should not have any share of the profits."* (P4, general public)

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> *"I tried to think with other similar examples. For example, one of the oldest, one of the oldest cases of biological material supply is the example of blood donation. Blood is provided by voluntary blood donors without it, without giving the blood donor the right to have a say in the progress beyond that. That is, to say that I want [my blood to be given] only to my relatives or, I know, only to Greeks, I only want to some who are not black, not gay, etc. This would open huge, let's say, huge moral issues, which would not be possible for society and the scientific community to allow. Also, the other example we have is the treatment with stem cells, where it is done today, for various diseases, where exactly they were given and received without being able to talk about further treatment and research. I want to say that, as Dilemma 1 describes it here, where this material is now the subject of research and after years it takes on extensions and there is a Nobel Prize. That is, behind all this there are hundreds, thousands of patients who received these treatments and the tests were done, etc. It is not possible for the one who originally gave the material to have a say in them. He is not knowledgeable, but neither, say, other ideological reasons, psychological prejudices, let him, say, allow him to intervene. So, I came to the conclusion that in the First Dilemma, in my opinion, two different philosophies collide: one is, let's say, whether individual rights must be considered very closely and all extreme extensions respected, and the other is whether common good prevails over individual rights, the good of humanity. And based on the examples I mentioned before the analogies I end up with the second. And that consent should be similar, let's say. It is not possible after years any donor to have a say, let's say he wants to know how this or that research in that part of the world is evolving and he can take back and cancel the research because he signs, something he does not like in research, without even knowing of course the scientific particularities. This was my position."* (P10, religious CSO)

3.2.4 Dilemma 2: Cerebral organoids

Regarding Dilemma 2, on cerebral organoids, participants spent less time deliberating during the discussion in subgroups, due to time restriction, but, also, because they found it more difficult to form clear opinions as they did not have a clear view on possible applications and uses of cerebral organoids, except for the use for treating patients with Alzheimer's disease. In this case they were, more or less, all positive in that perspective. As one participant put it:

> *"Obviously, possibly, thinking from the outside, realistically. That I have a patient who is a person, a normal entity… I try to answer here in the last question that says that 'we should weigh the interest of a patient with Alzheimer's in relation to the possibility of suffering of an entity that looks like a very simple form of life'. Thinking, then, I think I would probably end up saving the human, the Alzheimer's patient."* (P3, general public)

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The discussion was mostly around the notion of moral status and the conceptualization of consciousness. One of the participants posed the following question:

> *"What if, one day, it develops a brain, an entity which, anyway, I don't know, feels, walks, speaks, I don't know what of all these thing does. What is the problem? I mean, why not having organoids with the particular rights of organoids?"* (P2, general public)

And another participant replied:

> *"Yes, but such an entity, if it has self-consciousness, should be regarded as a legal subject, it should be treated as human being."* (P10, religious CSO)

To that comment the first participant responded:

> *"So be it! Why not be a legal entity, with responsibilities and rights?"* (P2, general public)

In general, the discussion, regarding the legal and ethical status of organoids, covered a significant part of the deliberation, both in subgroups and plenary, which derived from the acknowledgement that there are ontological, epistemological and regulatory uncertainties pertaining to organoid research.

3.2.5 Recommendations for future guidelines

The recommendations for future guidelines for organoid research are shown in Table 5 below. It includes recommendations grouped into three categories, following the corresponding structure followed by the Danish and Italian deliberative workshops' reports: communication, governance, and ethical implications.

Table 5. Recommendations for future guidelines.

Recommendations for future information and communication on organoids
All the participants agreed that more information on the potentialities of organoid research (stage of development, progress, potential applications) is necessary to be provided to the public, so as people to be able to contemplate on realistic scenarios, instead of imagining developments that actually could not be realised.

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Transparency regarding which stakeholders are involved in organoid research (RPOs, RFOs, policy-makers, public and private sector)
Informed consent procedures and forms, as well as all relevant information provided to patients and donors, should be clear, concise, simple and understandable. Some participants suggested that this kind of information can and should be fully digitalised and available in advance to all interested parties, at any given time.
Recommendations related to the governance of organoids
There was a consensus among the participants that there should be a list, a database of labs and research institutes that conduct organoid research, which will regularly updated. This database should, also, include the current state of research.
Regarding the guidelines, the participants suggested that it would be advisable to follow the examples of other, analogous types of research/technologies and procedures, already well-established, such as stem cell research, cloning, IVF, organ donation/transplantation, blood donation.
Regarding data collection, management and storage, the participants felt more comfortable with the perspective of these being governed by the state(s) and, in general, the public sector.
All participants expressed the demand organoid research to be strictly regulated in order to avoid misuse and maleficent applications, as those developed in other types of research.
Ethical implication to take into account
As organoid research and potential applications focus on the improvement of treatments, therapies and, in general, the quality of life, it should be made sure that there will be no exclusions to access -due to origin, sex, sexual orientation, religious orientation, economic status- to these benefits for the society at large. Organoid research should not broaden inequalities.
The extent to which intervention to the course of life is desirable is open to discussion. No participant expressed the desire to reach immortality.

3.3 Survey and Change of Attitudes towards Organoid Research

The results of the survey, as they were included in the questionnaires, were transferred to an excel file. Then, one of the members of the NTUA team produced the bar charts, in line with the guidelines sent by the Aarhus team. Following the guidelines, the survey results were reported to the Aarhus team in the form

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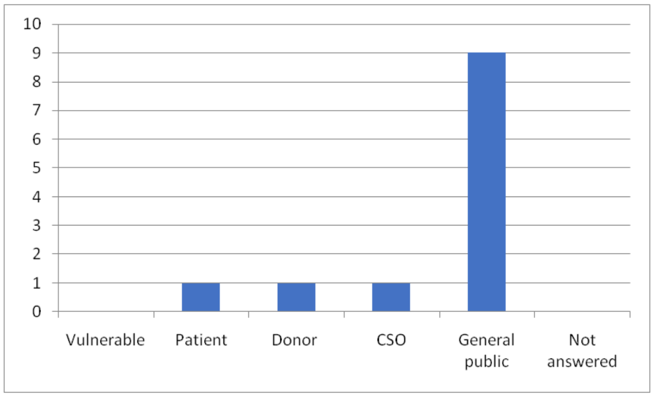
of bar charts and tables (in word and excel format). Following each diagram we present the responses/comments of the participants that were written in the questionnaires.

3.3.1 Distribution of answers

The Greek workshop had a total of 12 participants. Diagram 1 shows how they were distributed across the five participant categories based on their answers in the questionnaire, which may differ from the category they were recruited as. As seen in Diagram 1, nine out of the 12 participants place themselves in the category of general public.



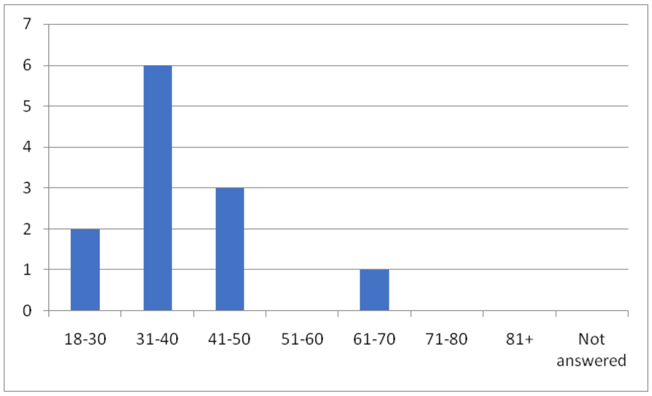
Participant category	
Vulnerable	*-*
Patient	*1*
Donor	*1*
CSO	*1*
General public	*9*
Not answered	*-*

sum	***12***

Diagram 1

Table 6

Diagram 2 shows the age distribution of the 12 participants at the deliberative workshop in Greece. All participants, except one, were at the age of 18-50. Half of them were at the age of 31-40.



18-30	*2*
31-40	*6*
41-50	*3*
51-60	*-*
61-70	*1*
71-80	*-*
81+	*-*
Not answered	*-*

sum	***12***

Diagram 2

Table 7

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Diagram 3 shows the gender distribution of the 12 participants at the deliberative workshop in Greece. Male participants were almost twice as much as women participants, while there was one participant that placed itself in the non-binary category.

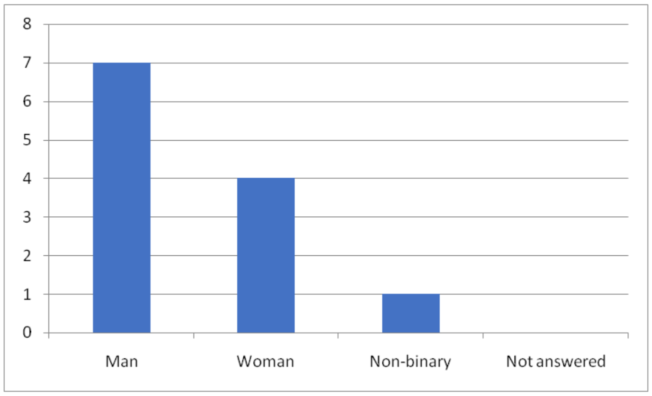

Diagram 3

Man	*7*
Woman	*4*
Non-binary	*1*
Not answered	*-*

sum	***12***

Table 8

Diagram 4 shows how the 12 participants are distributed related to whether they consider themselves being religious, and which religious orientation. From those participants that consider themselves being religious, only Orthodox Christians participated at the deliberative workshop. This is natural, since Greece is traditionally a Christian Orthodox country. However, what comes as a surprise is that only 25% of the participants declared of being religious, while more than half declared they are non-religious, while 2 participants did not respond to this question, for reasons that were not explained.

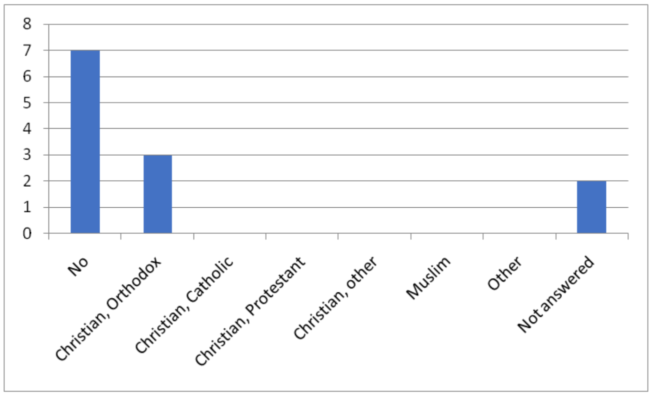

Diagram 4

No	*7*
Christian, Orthodox	*3*
Christian, Catholic	*-*
Christian, Protestant	*-*
Christian, other	*-*
Muslim	*-*
Other	*-*
Not answered	*2*

sum	***12***

Table 9

Diagram 5 shows how the participants were distributed regarding their relation to the job market/work force. Only one of the participants was unemployed, while the 75% of the participants declared a medium

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level of income was. However, it must be noted that, while their relation to the job market can be clearly described (i.e. being employed, unemployed or retired), the responses with regard to their level of income shows the participants' perception and not necessarily their true level of income.

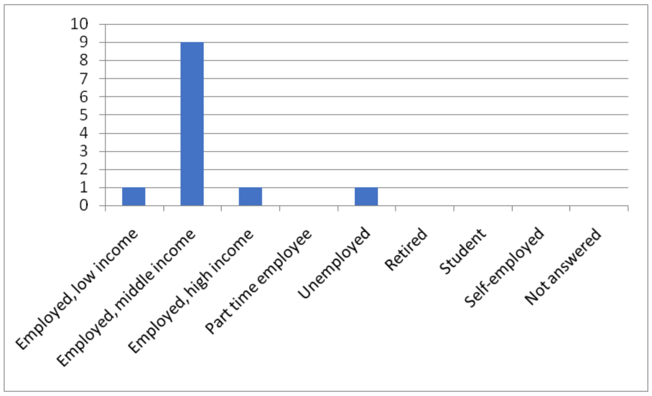

Diagram 5

Employed, low income	*1*
Employed, middle income	*9*
Employed, high income	*1*
Part time employee	
Unemployed	*1*
Retired	-
Student	-
Self-employed	-
Not answered	-

sum	***12***

Table 10

All participants at the Greek deliberative workshop declared that they were Greek citizens.

3.3.2 Analysis of potential changes in attitudes pre-and post the deliberative elements

The following diagrams shows which the 12 participants thought described organoids best, respectively, before (blue bars) and after (orange bars) the deliberative workshop.

Diagram 6 shows the chosen words for describing organoids before and after the workshop for all the participants combined. The categories not used by the participants neither before nor after the workshop were the following: Thing, Half thing/half person, Science fiction, Frankenstein-like, and Not answered. The two words that were selected by most participants, before the start of the deliberative workshop, were Artificial and Cell culture, while after the deliberative workshop the words that were selected by most participants were Artificial (with less votes) and Research tools. This shift of responses may be indicative of a shift of the participants' perception of what an organoid is. The prominence of the Research tool word could indicate that the participants created a more accurate perception on organoids. Also, it cannot be said that the perception shifted to a more "scientific" one, since the prominence of Cell culture before the delib-

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erative workshop is also related to research. Other noteworthy changes are the following: (a) Less participants chose the word "Living organism" after the deliberative workshop, while more participants chose the word Mini organ after the deliberative workshop.

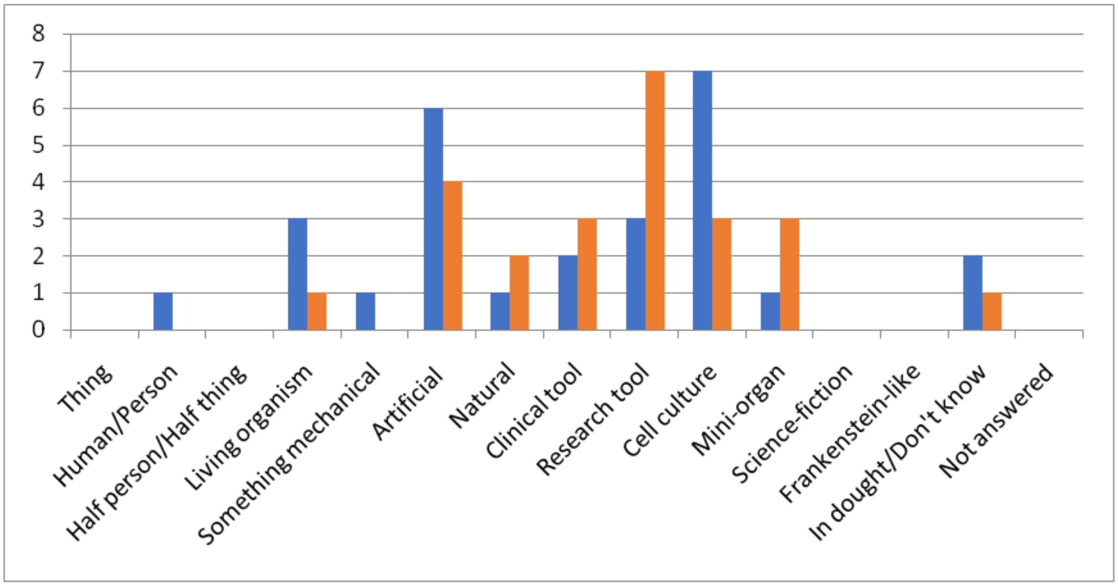

Diagram 6

Word to describe organoids	***Before***	***After***
Thing		
Human/Person	*1*	
Half person/Half thing		
Living organism	*3*	*1*
Something mechanical	*1*	
Artificial	*6*	*4*
Natural	*1*	*2*
Clinical tool	*2*	*3*
Research tool	*3*	*7*
Cell culture	*7*	*3*
Mini-organ	*1*	*3*
Science-fiction		
Frankenstein-like		
In doubt/Don't know	*2*	*1*
Not answered		

sum	***27***	***24***

Table 11

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As shown from Diagram 7, participants at the Greek deliberative workshop did not use Other feelings and Not answered responses. The feelings most of the participants selected before the deliberative workshop were Positive expectations and Hope, while after the deliberative workshop the most prominent response was Positive expectations. In addition, it seems that after the deliberative workshop the feelings the participants selected were less “extreme” or more moderate. For example, before the deliberative workshop 2 participants selected Fear and one Excitement, while after the deliberative workshop these feeling were not selected. It might be the case that Fear was replaced by Worries and Excitement by Positive expectations. However, this assumption has to be backed up by a case-by-case analysis.

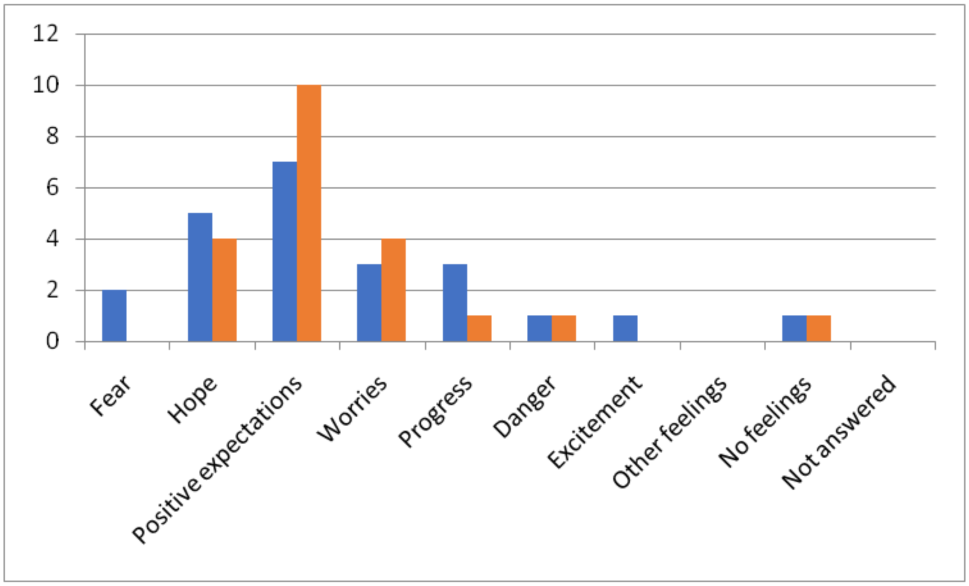

Diagram 7

Feeling related to organoids	*Before*	*After*
Fear	*2*	
Hope	*5*	*4*
Positive expectations	*7*	*10*
Worries	*3*	*4*
Progress	*3*	*1*
Danger	*1*	*1*
Excitement	*1*	
Other feelings		
No feelings	*1*	*1*
Not answered		

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sum	***23***	***21***

Table 12

Diagram 8 shows the responses of the participants on the ownership of organoids before and after the deliberative workshop. Before the deliberative workshop five out of the 12 participants were agnostic on the ownership issue, while 4 participants declared that organoids' ownership should be given to the cell donor. The changes after the deliberative workshop were significant – the most significant with respect to all other questions. Specifically, the cell donor response did not receive any vote, while the most prominent response (receiving 5 votes) was that the organoids are the ownership of the Hospital/Research institution/Company/Biobank. However, in this instance there were comments from the participants that are presented below. Also, fewer participants were agnostic on the ownership issue. It must be noted that the only response that did not receive any vote, before or after the deliberative workshop was the state.

Responses/comments of the participants: One participant erased the Company/Biobank from the ownership question (before and after the deliberative workshop). The same participant also added that organoids should be owned by society and that profit-making must be eradicated. Another participant left a comment on this question, before the deliberative workshop: "To whom organoid belong or to whom organoid should belong?" The same participant commented to this question, after the deliberative workshop in the following way: "Organoids should be public property, as research at large"

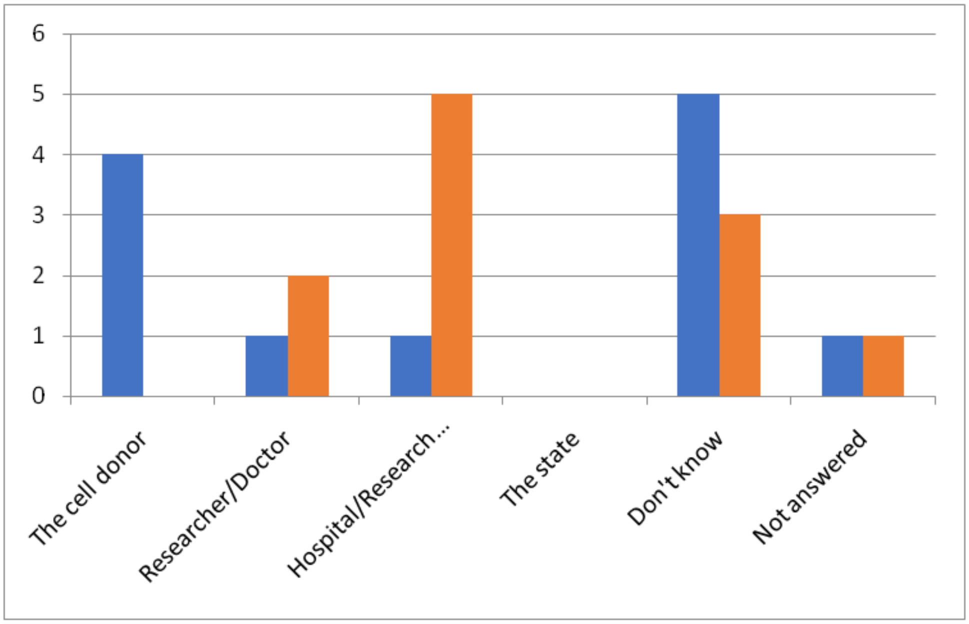

Diagram 8

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Organoid ownership	*Before*	*After*
The cell donor	*4*	
Researcher/Doctor	*1*	*2*
Hospital/Research center/Company/Biobank	*1*	*5*
The state		
Don't know	*5*	*3*
Not answered	*1*	*1*

sum	***12***	***11***

Table 13

Diagram 9 shows the responses of the participants on the type of consent that must be used in organoid research. No participant provided the Not answered response before or after the deliberative workshop. Before the deliberative workshop the response that received most of the votes was Ongoing consent, while 2 participants were agnostic. After the deliberative workshop the responses from the participants were more varied, without any type or response having a prominent representation. Perhaps the most interesting change is that no participant voted for the Don’t know response.

Responses/comments of the participants: One participant commented that a General consent could be applied, if commercial use of organoids did not exist, as long as anonymity was safeguarded. In current situation people should demand protection by the state and specific laws on the exploitation of organoids. Another participant commented that since organoids are a product of scientific research they should not be owned by the donor. However, in legal terms ownership depends on the type of consent. Another participant wrote the following comment: “*Patients should be briefed on the use of the organoids, before they consent. Briefing should be made in an easy-to-comprehend way. It must be also safeguarded that research will not be stopped.*”

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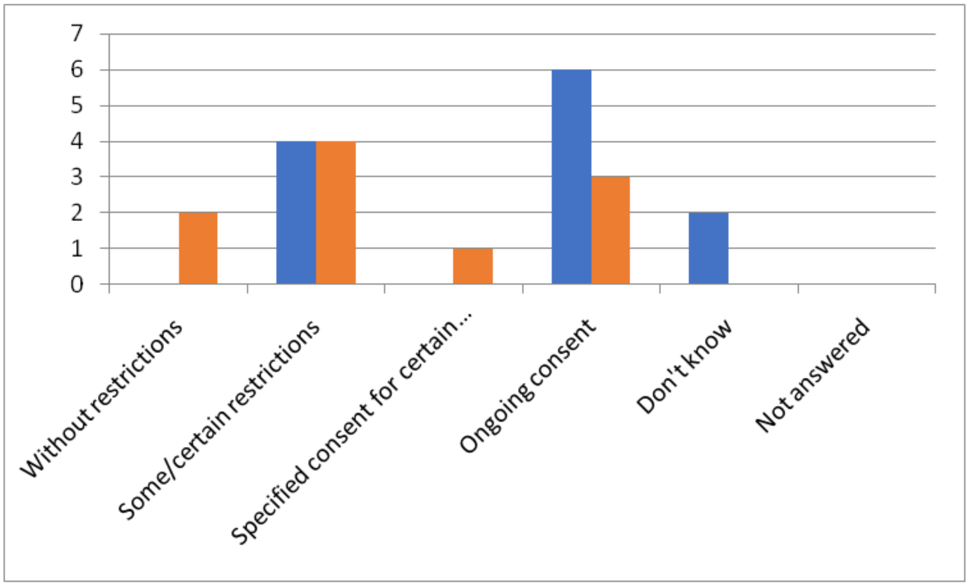

Diagram 9

Type of consent	***Before***	***After***
Without restrictions		*2*
Some/certain restrictions	*4*	*4*
Specified consent for certain areas or diseases		*1*
Ongoing consent	*6*	*3*
Don't know	*2*	
Not answered		

sum	***12***	***10***

Table 14

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3.4 Conclusion

The deliberative workshop in Athens, in addition to the acknowledged biases at the participant selection imposed by the pandemic situation that were described at Section 2.2, had the following two characteristics that were not obvious to the organizers before the commencement of the event. One was the underrepresentation of Orthodox Christians and another was the overrepresentation of people with a more-than-average background in Biology. These two characteristics must be taken into account, in order to avoid oversimplifications when trying to extrapolate the deliberative workshop's findings to the Greek society. The most persistent feature that permeated almost all discussions throughout the deliberative workshop was the skepticism of the participants towards commercial exploitation of organoids. The issue at stake was not profit making *per se* but that profit making was, according to most participants' views, directly related to breaches of ethical principles and legal provisions. Another feature was that after the end of the deliberative workshop overly pessimistic and optimistic views on organoid applications were turned into more moderate. This observation may have to do with the time given to the description of what can and cannot be currently done with organoids. So this might reflect a disappointment from the side of people that saw in organoids a "panacea" for drug development or transplantation or a relaxing of fears from the side of people that felt fear.

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Appendix C. National Report - Denmark

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HYBRIDA

Public attitudes, understandings and perspectives on organoid research

HYBRIDA

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

Report factsheet:

Project Title:	HYBRIDA
Title of Report:	Public attitudes, understandings and perspectives on organoid research
Author(s):	Louise Isgaard Saugstrup, Research Assistant Tine Ravn, Assistant Professor Mads P. Sørensen, Senior Researcher
Finalised on (date):	First version: 20.01.2022 Second version: 24.01.2022 Third version: 27.01.2022 Final version: 28.01.2022

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1 Introduction: Deliberative Workshops on Organoid Research

1.1 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[5].

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.

Following Roman times, all entities have been categorised 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 categorised as either persons or things? What *are* they? How do we *know* the characteristics of these entities called organoids?

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

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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. In order to develop ethically and socially robust ways of assessing the effects of organoid research and related technologies, there is a need to include these additional forms of uncertainty in the Health Technology Assessment (HTA).

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

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 the Deliberative Workshop in Denmark

This report focus on the deliberative workshop on organoid research that was conducted in Denmark in November 2021 as part of the HYBRIDA project.

Religion is known to influence attitudes towards emerging and controversial technologies (De Witt et al, 2015). Therefore, we chose to place the three deliberative workshops in this study in three different religious contexts in Europe. While the other countries in this study (Italy and Greece) represent cultures where Catholic and Orthodox Christianity, respectively, are the main religions, the dominating religion in Denmark is Protestant Christianity.

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The three countries' populations also represent differences when it comes to attitudes towards new technology. Denmark is categorised as an 'Innovation leader' on the European and Regional Innovation Scoreboards 2021, placing 4th of the 38 countries represented in the scoreboards (European Commission 2021a: https://ec.europa.eu/research-and-innovation/en/statistics/performance-indicators/european-innovation-scoreboard/eis). In comparison, both Italy and Greece fall under the 'Moderate innovator' category with Italy having the highest score and Greece the lowest score within this category. This means that the Danish citizens are generally more exposed to innovation, which might affect their approach and attitudes towards innovation and technological development. In the Eurobarometer Report on European citizens' knowledge and attitudes towards science and technology, it is concluded that Danish citizens are most likely to feel 'very well informed' about new medical discoveries, while, for example, citizens of Greece are among the least likely to feel 'very well informed' (European Commission 2021b: file:///Users/au456607/Downloads/ebs_516_science_and_technology_report_EN.pdf). Lastly, is it worth noticing that 54% of the Italian respondents in the same study and 53% of the Greek respondents either totally agree or tend to agree regarding the statement: 'Because of their knowledge, scientists have a power that makes them dangerous', while this only applies to 20% of the Danish respondents.

Based on this, it is therefore to be expected that the participants in the Danish deliberative workshop are more likely to be positive towards the development and use of organoids than the participants in the other two workshops.

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2 Methodology: Deliberative Workshops

This section outlines and details the methodological issues related to the design, planning and completion of the deliberative workshop, i.e. the particular research design, research questions, participant recruitment and data collection as well as the process of coding and analyzing the data and knowledge obtained from the workshop.

2.1 Design: Exploration of Public and Stakeholder Attitudes towards Organoids through Deliberative Workshops

Deliberative workshops can be characterized as "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). Great emphasis is placed on facilitating deliberation based on expert inputs and an examination of various issue positions with the objective to elicit a broad and diverse range of views on the topic in question (The Danish Board of Technology, 2014; O'Brien et al. 2020; Steel et al. 2020, for more details on the method of deliberative workshops, please see the research protocol for the study, Ravn and Sørensen, 2021).

The purpose of conducting three deliberative workshops is to explore and elicit different views on the use and derivation of organoids and organoid research to understand the public opinion (i.e. worries, concerns, fears, uncertainty and expectations) and key ethical issues and implications related to organoids from the point of view of citizens, vulnerable groups, patients, donors, and CSOs. More specifically, the deliberative workshop has been designed to answer the following research questions:

- *How do non-professional stakeholders and the lay public perceive organoids and organoid research?*
    - What are the participants' main worries, fears and expectations concerning organoid research?
    - How do participants conceptualise and understand organoids? (i.e. persons vs. things, moral status, mythological aspects)
    - What are the perceived current and future benefits of organoid research according to the participants?

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  - Which kind of ethical issues or research poses concern for the participants? (i.e. particular organoid types and uses; particular ethical issues such as informed consent, ownership and commercialisation)

The valuable public and stakeholder perspectives into these questions will provide key insights and unique knowledge into the continuous process of developing the four HYBRIDA project outputs, including operational guidelines and an ethics framework. The exploration of these questions was conducted in a two-phase deliberation where the first part explored the 'attitudes towards and conceptualisations of organoids' and the second part focused on 'perceived benefits and concerns in relation to the derivation and use of organoids' in terms of key ethical issues and implications to be taken into account in regard to organoid research.

2.1.1 Format and Setting in the Deliberative Workshop in Denmark

The deliberative workshop took place on a Saturday (November 27, 2021) as a one-day workshop with a duration of 9 hours including lunch, coffee breaks and dinner. The workshop took place at Munkebjerg Hotel near Vejle. The hotel is centrally located in Denmark, thus making it easily accessible for people from many parts of the country. Further, Munkebjerg is beautifully located at Vejle Fjord and is well-known for its high standard as a conference hotel. The workshop began at 11am to allow time for arrival and ended with a two-hour dinner at 18pm.

Before the participants arrived, the main room was set up with three big tables to facilitate the first group discussions. The research team had also divided the participants into three groups to ensure that all categories of participants were represented in each group. Upon arrival, each participant was provided with a folder and name tags. All folders contained paper, pens, and documents such as the programme, questionnaires, guiding questions for the deliberations, and dilemmas for group discussions.

Before the workshop all participants had been informed that the workshop would be conducted in a way that took the current national recommendations and restrictions related to the Covid-19 pandemic into account. For example, this meant that all participants had to show a valid Corona passport upon arrival.
The workshop was moderated by a professional moderator from the Danish Board of Technology. The Danish Board of Technology has extensive experience and expertise with public engagement activities, e.g. in relation to controversial technology. During the workshop the three members of the Danish HYBRIDA

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research team were present and divided amongst the participants to observe, assist on facilitation and answering questions. The research team also made a short introduction at the beginning of the workshop as well as a short summary of the day and the work ahead at the end of the workshop. The workshop language was Danish.

The programme started with a brief welcome and introduction by the research team. Hereafter, the moderator took over. He started with an icebreaker – a song accompanied by himself on violin. The song was a well-known Danish song with an additional, self-made organoid-themed verse. This icebreaker helped establish a casual environment where the participants felt comfortable. The rest of the activities in the programme were divided into two phases.

The 1st phase focused on the participants' attitudes towards and conceptualisation of organoids. This phase included:

- Filling out the first part of the questionnaire (Appendix A).
- Expert presentations by two researchers (Appendix D):
  - Thomas Lykke-Møller Sørensen, Associate Professor at the Department of Biological and Chemical Engineering, Aarhus University. This presentation was based on his experience with organoid research.
  - Morten Dige, Associate Professor at the School of Culture and Society, Aarhus University. The presentation focused on ethical and moral issues related to organoids and was based on his research in medical ethics and moral issues connected to questions on respect for human life, informed consent etc.
- Group discussions to make questions for the experts.
- Q&A session with the two experts.
- Group deliberation based on two guiding questions focusing on the perceptions and feelings regarding organoids. Each group presented their main points for the other participants.

The 2nd phase focused on the ethic perspective of organoid research, including hopes, fears, expectations, and worries related to it. During the second phase, the participants were divided into new groups. This phase included:

- An introduction to two dilemmas and time for the participants two reflect on them individually.

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- Group deliberation in two parts: First, they discussed the two presented dilemmas. Second, they had to discuss which ethical issues and recommendations for future guidelines they found most important.
- Group presentations of the main points from their discussions and a plenum discussion.
- Filling out the second part of the questionnaire.
- Conclusion and evaluation of the day.

After this and before dinner, all participants were provided with a small gift bag with chocolate and a reusable to-go cup. Participants were reimbursed for their travelling expenses, but apart from the small gift bag (which they did not know about beforehand), they did not receive any payment for their participating. Only small changes occurred in the programme. The expert presentations ended up taking a bit longer than planned, which resulted in less time for the participants to make questions and for the Q&A session with the experts. This did not appear to have any negative effect on the workshop, since all groups had time enough to come up with questions and the experts had time to answer most of them.

2.2 Sampling and Recruitment Procedures for Deliberative Workshops/mini-publics

As stated in deliverable 4.1. and 4.2, the sampled participants for the workshop had to represent a cross-section of relevant views. This led to a conscious oversampling of certain participant categories in order to obtain "(…) *information-rich cases* for in-depth study" (Patton, 2015, 265, emphasis in original). Because of this, the participants were not an approximation of the population distribution, based on an aim for a diverse set of perspectives. E.g. CSO's and patients were overrepresented in order to involve the perspectives from patients with different diseases and organizations with different focus areas.

The workshop participants were sampled from the following groups:

- The general public
- Vulnerable groups (e.g. relatives to patients with genetic diseases)
- Patients (e.g. with diseases such as Cystic Fibrosis, gastrointestinal diseases or cancer)
- Healthy donors
- Representatives from civil society organisations (CSOs), including religious organisations.

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Different approaches were used to contact different groups. Based on the assumption that patients and people from vulnerable groups would be the most difficult participants to recruit, we first focused on organizations such as The Danish Cancer Society, Parkinsonforeningen (The Danish Parkinson Association), etc. These were contacted directly either via email to their secretariat or other administrative personal, through management and internal board members, and the organization's Facebook page. The idea was to both recruit participants from the organizations as representatives of CSOs and to use them as gatekeepers to get in contact with patients or relatives. This approach was not a success, mainly because these organizations are contacted by many different people and organisations, making them busy and very strict in their selection on what to convey to their members. Based on these experiences, the strategy was adjusted. More individual people were contacted directly with a personal invitation to the workshop. This included representatives from the Protestant church, Muslim communities, and members of the boards in local associations connected to relevant diseases such as Cystic Fibrosis, different types of cancer, and gastrointestinal diseases. Parallel to this, posters and flyers with information were distributed and made available in waiting areas at relevant hospital departments. Further, a member of the research group spend time talking to donors and distributing flyers at the local plasma center. To recruit participants under the age of 35, we additionally contacted student associations, made posts on selected education programs' Facebook pages, and contacted the headmasters of different Folk High Schools with a focus on e.g. ethics or philosophy.

Lastly, a post was shared on different social media, e.g. Facebook, LinkedIn, and Twitter. It was noted in the post that people were encouraged to share the post with relevant people within their network. This led to the recruitment of several participants, especially patients with relevant diseases. Besides making aware of the event on social media and via gatekeepers, approximately 200 people were contacted directly with individual invitations.

Combined, these initiatives led to the recruitment of 23 participants. The goal was 15-20, but we decided to recruit three more based on the assumption that some participants most likely would be prevented from participating, for example due to Covid-19 or other forms of illness. Table 1 shows the intended distribution of the recruited participants compared to the actual distribution.

Table 1. Distribution of participants – planned and actual

	Planned distribution of participants	**Distribution of recruited participants before the workshop**
The general public	6	7

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Vulnerable groups	3	2
Patients	3	4
Donors	3	3
CSOs	5	7
Total	**20**	**23**

Two of the 23 recruited participants had to cancel their participation due to illness and one person didn't show up at the workshop. All in all, 20 people participated in the workshop. The final distribution of participants at the workshop is shown in Table 2.

Table 2. Final distribution of participants at the workshop

The general public	5
Vulnerable groups	2
Patients	4
Donors	2
CSOs	7

It is worth noting that several participants fitted into more than one of the mentioned categories, and some of them categorized themselves primarily as being part of another group than the one they were recruited from. One example was a participant recruited as a representative of a CSO, who categorized herself as a patient. Since the questionnaires were anonymous it has not been possible to transfer the information about how the participants categorized themselves, but some participants have identified as another category during the discussions.

Appendix C provides a further anonymized overview of the participants, and information on each individual. During the analysis, quotations will have an anonymous reference (e.g. P7, short for participant 7) followed by the participant category the individual is from. In relevant cases other information might be included, e.g. age, gender, or if a participant has expressed to identify with another participant category.

During the recruitment process there were a specific focus on the possible sensitivity of the subject. Consequently, we made sure to inform patients and people from vulnerable groups that the focus was not on their personal medical history and that they should not feel obligated to share any information they were not comfortable with.

2.3 Data analysis

The data from the workshop was collected through audio recordings from the workshop, posters made by the participants during group deliberations, potential field notes from the present researchers, and questionnaires filled out by the participants during the workshop.

Five Dictaphones were used to record all activities during the day. One per group and two additional Dictaphones placed near the moderator and in the centre of the room. Recordings from following parts of the programme were transcribed and coded.

- The group discussions on questions for the experts.
- The Q&A session with the experts.
- The group discussions regarding conceptions and feelings related to organoids, and the plenum presentation of each group's main points.
- The group deliberations based on the two dilemmas and their discussions while deciding which ethical issues they find most important.
- Plenum presentations from the groups and the subsequent plenum discussions.
- The conclusion and evaluation of the workshop.

The transcripts were made to reflect what was said as directly as possible, e.g. by making notes on the tone and mood, and making clear if specific words were emphasised.

The data from the transcripts was coded using the programme NVivo 12. The coding was mainly based on a deductive approach with predefined codes related to the research questions. When needed, new codes were added during the coding process, thus combining the main deductive approach with an inductive approach. Besides assigning relevant quotes to the codes, they were further assigned to a specific case. Each of the 20 participants has been registered as an individual case and assigned specific attributes under the same case clarification, thus making it possible to study codes based on specific characteristics such as gender, age, or participant category. Lastly, notes have been made during the coding whenever it was found relevant to remember certain thoughts or points during the coding. Further, the data from the questionnaires was sorted and registered in tables and diagrams[6].

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[6] These are presented in section 3.3 below.

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As stated in deliverable D4.1, the analytical strategy was aimed on:

- Reporting on in-depth descriptions on the attitudes, perceptions, and experiences of participants in relation to the derivation and use of organoids.
- Describing matters related to perceived benefits and concerns of organoids.
- Reporting on recommendations to show the breadth and depth of the ethical concerns amongst participants.

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3 Findings

This section presents the main results from the data collected during the deliberative workshop in Denmark. It is divided into subsections based on the different themes discussed during the two phases of the workshop and the data from the questionnaires, respectively. First, we make an analysis on the participants attitudes towards organoids, as well as their conceptualization of organoids. This is followed by a section on the ethical issues and implications related to organoids, including sub-sections covering themes such as informed consent, patient information, and governance. Further, the analysis include sub-sections focused on the discussions on ethical issues and implications related to the use of organoids based on the two dilemmas provided by the HYBRIDA research group (Appendix B), and lastly, an overview of the participants' recommendations for future guidelines for organoid research.

3.1 Attitudes towards and Conceptualisations of Organoids

The following section is based on the participants' discussions about their attitudes related to organoids. First, the focus will be on the positive attitudes. Second, the negative attitudes are described. In both cases, the account is based on the group discussions as well as the plenum presentations.

First of all, almost all of the participants expressed a positive attitude towards organoids in general. The participants especially mentioned hope, excitement, and positive expectations. This did not seem to be specific for any participant category, but was common regardless of age, gender, and whether the participant was from the general public, a CSO, a vulnerable group or was a patient or a donor. It is worth noting, though, that the conversations about the positive attitudes were often short and implicit, as shown in the quotes in Table 3. This was especially the case during the deliberation based on guiding questions related to the conceptualizations of and attitudes towards organoids. This means that the participants at this point had heard the expert presentations and had had the opportunity to get questions answered during the Q&A session. In this part of the workshop the participants had also been introduced to some of the ethical issues related to organoids but had not had time to discuss or reflect on them specifically.

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Table 3. Quotes expressing positive attitudes towards organoids.

(…) at the same time, they have this good purpose. (P6, general public)
Yes, you can always turn back to this thing, which I think all groups have talked about, that the basic feeling was hope or something positive, but at soon as we get to 'where to draw the line' it might turn a bit. (P20, donor)
I only feel excitement! (P10, CSO, identifies as patient)
Hope. (P10, CSO, identifies as patient)
I'm also primarily on hope. And we are already down the path, we have been for a while with stem cell research. It's already there. We haven't rejected it. (P8, religious CSO)
I mostly think development. And innovation (…) Maybe I'm thinking change the most. Change is the word I'm searching for. Change, excitement. Can it be moved forward? Is it going to work? (P17, patient, identifies as CSO)
I think it is really good, and I have many hopes for it! (P13, vulnerable group)
And it's not like I'm negative towards this, I'm actually very positive! (P9, CSO, identifies as vulnerable group)
Well, I'm sitting here with hopes for it, because it can cure some diseases and improve something (P11, religious CSO).
I want to say it gives me hope. Excitement! (P7, CSO, identifies as vulnerable group)
That was the first. Hope and something new, right? (P12, CSO)
I have positive expectations, progress, and excitement. (P5, general public)
It is always present when you are moving into unknown territory (ed: the worries) … but the hope is most dominant. (P14, vulnerable group)
Hope is straight-forward as a very important part of this. (P1, general public)
For the second part we wrote hope and excitement, because we discussed if there were any of us who was against this, since we are so excited, that we found it hard to see it from another perspective. (P7, CSO, identifies as vulnerable group)
We also discussed that there are worries, but the dominant feelings were without a doubt hope and excitement. (P14, vulnerable group)

While statements related to worries typically are followed by explanations (as discussed in section 3.1.1), the statements related to positive attitudes were generally not elaborated. The participants mention feelings such as hope and excitement, but most often without explaining what exactly makes them hopeful about organoids. They mainly use descriptions such as the "good purpose" and that organoid research can "cure

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some diseases and improve something". One way to interpret this could be that they consider the positive sides of organoid research to be self-explanatory, while worries and other negative attitudes need to be supported by further arguments. Yet, it should also be noticed that the positive attitudes were dominant, since they almost exclusively were the first attitudes to be mentioned when the participants told the other group members about their personal attitudes to organoids, during the first deliberation. Several participants also said that hope or excitement best represented how they saw organoids and organoid research. Lastly, none of the Danish participants mentioned that they were against organoid research or wished for it to be stopped. The overall agreement between participants was that organoids and organoid research has great potential and should be used – but in a proper, safe way (cf. section 3.2.5 on the participants' recommendations for future guidelines).

3.1.1 Commercialization, personal data, and misuse

As previously mentioned, discussions related to negative attitudes such as worries and fears were more explicit and elaborated. The participants also used more time on discussions about worries since it involved more descriptions, arguments, and different perspectives.

One of the main worries is related to commercialization – or over-commercialization – e.g. multiple participants were worried that the industry will end up dominating the field of organoid research, and that this can lead to increasing inequality and less people benefitting from organoid research and related technologies. For example, one participant said: "We might be able, in 10 or 20 years, to be able to help. But what if the price is too high? We already have this dilemma at this point." (P9, CSO). This is elaborated with an explanation about how there already exists medications and treatments we do not use, since the companies in the medical industry has set the price too high, thus making some treatments unavailable for patients. Another participant mentions a different risk related to commercialization and inequality:

> "But there's also an aspect of commercialization in it, right? It's like these "my heritage" DNA-sequencing private companies, who makes a lot of money on it, right? I could easily imagine a future, where you have this personalized medication and then it's private actors, where you pay. And the more money you have, the better and faster treatment you receive and all that."
>
> (P5, general public, 18-40)

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In both cases the participants argue that they worry that commercialization of organoids will lead to inequality. The first quote in relation to equality among different diseases, and in both quotes in relation to access to treatment based on financial status. The majority of the participants either agree or acknowledge this worry, but this is not the only perspective on the subject: “Well… I would say, I don’t care if anyone is making money on it. If it can help someone, that’s my priority.” (P7, CSO, identifies as vulnerable group). This participant is not necessarily disagreeing with the relevance of the other perspectives, but it is clear she is not sharing the worries on commercialization. Other arguments and perspectives related to worries on commercialization is provided in Table 4.

Table 4. Worries related to commercialization and social inequality.

Commercialization and social inequality
Since it’s so essential that society invests in basic research on this, I think it’s quite possible for it to develop in a way so the societies with most assets do the research that benefits exactly THEIR population. (P1, general public, 61+)
But if we take that perspective, it will mean that medical companies and others. The medical companies will focus their efforts on the big and broad diseases, while the specialized diseases don’t get anything. (P1, general public, 61+)
As I see it, the results from basic research should be available world-wide. Otherwise, I think it will become even more uneven. And then there’s of course the question on whether the applied research should be depending on the market forces? And what could an alternative be? (P1, general public, 61+)
But is this something for the economy to decide? It might be to some degree. They have some kind of power since they have the patent. Then something comes into play. I don’t want to earn anything from this, but others earning on it, others gaining power based on me delivering a good product? I don’t want that! (P18, patient, 41-60)
I think, one of the problematic things in this is this imbalance that might appear between those who can afford it, and those who can’t. Or the people worth taking a chance on, and those not worth it. If the technology is becoming more and more expensive because the way we do research keeps getting better and more elaborate, then the prices will grow as well. Then you end up having an A-team and all the other teams. (P19, donor, 41-60)
We are moving towards areas that are very sensitive regarding what human existence should be from now on. That’s why I don’t find it suitable that anyone think about the economics in it. That scares me. (P1, general public, 61+)

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Then there's this statement, that it's important (…) that it's not going to be reserved for the wealthy people. It could easily become something only the rich countries would have. We see the same with the Corona-vaccines. We're in the middle of people getting their third shot, while there're countries that haven't even got the first yet. (P4, general public, 61+)

Another worry is related to the possibility of organoids being misused. For example, several participants mention the risk of personal data being misused in different ways. Another worry related to misuse, that is only expressed by very few participants, is that the organoid technology might be used for biological warfare, e.g. development of super soldiers. Lastly, many participants express worries related to ethical implications. This includes themes such as lack of current guidelines, clarification about ownership, and the balance between offering the best possible treatment to patients and knowing when to stop[7]. Participants do make it clear, though, that they are not scared by organoids and related technologies: "So it is not fear, I'm not scared. I just think that we need to have the courage to stop and then do this properly." (P6, general public). This is supported by other participants, e.g. "I agree with you, I think this is really good and I have many hopes for it. If it is done in a way where we are having the discussions that we're currently having" (P13, vulnerable group).

The questionnaires show that there is an increase in the number of participants who feel worried after the workshop, but at the same time also an increase in the number of participants who express positive attitudes towards organoids[8]. Further, as previously discussed, the positive attitudes are also mentioned as being most prominent by the participants themselves during the deliberation. One likely explanation for the increase in worries during the workshop is that the participants via the expert presentations and deliberations got more informed about organoids and organoid research – and also about potential pitfalls. Through the deliberations, they got more aware of the complexity and ethical issues related to organoid research. However, it is important not to understand these worries as a general resistance against the use of organoids. The participants were still very positive towards organoids and organoid research. Therefore, the worries are most likely an expression of a more nuanced understanding of organoids and organoid research.

To summarize, the participants in the Danish workshop support the development and use of organoids and mainly express positive attitudes towards this. They are hopeful, exited, and have positive expectations to

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[7] These themes are further analyzed in section 3.2 and its sub-sections 3.2.1 through 3.2.5, which are focusing on ethical issues and implications including governance, ownership, etc.

[8] This is further elaborated in section 3.3, diagram 8.

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the potential of organoids, resulting in new treatments and increased knowledge and understanding of certain diseases. The participants' worries are mainly related to over-commercialization, social inequality, and the risk of misuse. One interpretation of this is that all the above-mentioned worries are built on uncertainties and current lack of knowledge, and/or clarification about ethical issues. For example, it is mentioned by some of the participants, that they do not know how organoids will develop, for example, if cerebral organoids will end up being conscious or being able to sense things (e.g. pain). Similarly, several participants expressed that both their hopes and worries are depending on how organoid research will be governed, monitored and how it will be communicated to the public. Since the guidelines for organoid research have yet to be made, this is also a cause for uncertainty. The participants express that they see it as a very positive thing, that they have been involved in the development of the guidelines by being invited to share their perspectives and thoughts in the workshop. Despite this, they are still uncertain about how the data will be used and what the result will be, when the guidelines are eventually made.

3.1.2 Conceptualisations of Organoids

The discussions regarding the conceptualisations of organoids took place after the expert presentations and the Q&A session with the experts. At this point the participants had been introduced to a 'vocabulary' to describe organoids through the first part of the questionnaire. Further, based on the expert presentations they had both been informed about the development and current state of organoid research, supported by pictures and videos of organoids shown during the first expert presentation on the development and current status of organoid research, and the second presentation on different ethical perspectives and information about moral status. Participants were given the two following questions to discuss in the three assigned groups:

1) How do you think of organoids? What are organoids? How can we best describe them? Do you think of them as human, as a thing, or as something in-between?
2) Discuss the feelings, organoids evoke in you. Which words come to mind when you think about organoids? Are organoids something to be feared – or do you see a hope in them? Which worries and/or positive expectations do you have regarding organoids?

While discussing these questions it was clear that the participants used the terminology from the guiding questions and the questionnaire as a shared vocabulary, e.g. by referring to which specific words they used to answer similar questions in the questionnaire. This can be seen as a positive thing since it gave the participants a shared common ground for the discussions, but it might also have limited the descriptions of

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the participants' conceptualisations, since they had already been provided with options in the questionnaire, which they could transfer to the later discussions. It was also pointed out by some participants that organoids are presented as something in development or non-static, which can be difficult to describe or define:" I'm sitting with a feeling that I'll never… it doesn't really stick, so I have two words, saying 'not static'" (P18, patient). The participants were introduced to many different perspectives and implications related to organoids, and further it had been emphasized by the experts that the development in methods and technologies like organoids typically happens very fast. This might have made some participants more focused on how the conceptions of organoids might also change very fast.

3.1.3 Human, thing, artificial, or natural?

Several participants expressed that they see organoids as something human. It is worth noticing, though, that the participants had different understandings of what makes something 'human'. Some participants define human as being able to sense, feel and/or think, while others use 'human' to describe things that are taken from the human body: "(…) as I see it, it looks like it starts with a stem cell that is human, right? And that it's not a hybrid, where we are building on it. Not as I understand it at least. I think it's a human, biological thing." (P12, CSO). It is also mentioned that human is understood as something living, thus making living organisms such as organoids human. Different arguments for seeing organoids as something human are displayed in Table 5.

Table 5. Quotes on human conceptualizations of organoids.

Organoids as human
And I think, some of the things I answered immediately are that it is some living, there is life in it. It is something living, and thereby something human. But it's also artificial because it has been created. (P11, religious CSO)
I see it as something human the same way as I would see a kidney or cornea or something else as human too. (P19, donor)
Yes, human, I will say… But how do we define words? I think 'human' is related to something being conscious. You know, something with thoughts and something with feelings, that the human part. (P12, CSO)
But if it is just some stem cells you have taken out, there is no need for that discussion. Then it's all human. (P15, patient)

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(…) it first becomes problematic if it's brain cells that developed, as someone said. Has it become more human when it reacts to light? And later might develop independent thoughts… At that point it can't be called a thing anymore. (P4, general public)
It's still a thing that can do something, but I wouldn't consider it being human. I think, that when something is human, it's part of something, then it should be something entering my body, then maybe it could be human. But as soon as it's in a petri dish I don't really see it. (P13, vulnerable group)

As shown in Table 5 the participants present various understandings of what 'human' means. Some participants define something as 'human' if it is alive, while others express the understanding, that being human is connected to the development of independent thoughts or consciousness. Another understanding is that organoids are human based on the fact that they are created from something human or can be seen as comparable to human organs.

Other participants argue that organoids are living organisms, living things, or that they are human made - but not human. A participant states that: "Well, it is an organism that would die if it didn't get help (…) It has no working functions. So, for me it is not a creature or organism as such, it's some pieces that are put together." (P14, vulnerable group). A similar perspective is, that for something to be living and human it must have a beating heart, thus excluding organoids as human: "Well, I'm just thinking that it doesn't have a heart. As long as there isn't a beating heart, I don't think you can't equate it with a human being" (P7, CSO, identifies as vulnerable group). This perspective started a new debate related to ethics, and human value and worth, since some people are kept alive by having machines that keeps their hearts beating.

Another argument is that organoids are things made from something human, that stopped being human when it was removed from the person and used for another purpose than as a part of the human body. In relation to this it is commented that this conception might be related to the fact that organoids are still very small and at an early stage – implying that the conception might change with future development of organoids. The participants also have different ways to categorize organoids as things. This is shown in Table 6. For example, one point of view is that organoids are a thing that can be used to research and the study of organs that are normally hard to study. Another perspective is seeing organoids as a form of early-stage spare parts.

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Table 6. Quotes on conceptualizations of organoids as things.

Organoids as a thing
My feeling it, that it's a thing created from something human. I wouldn't consider these, at least at this tiny size, I wouldn't consider it something human. I would rather see it as a thing that can be used for research or whatever. That was made om something human. (P13, vulnerable group)
It's just, it's just a feeling, but those who get a new hip, that is a piece of metal they put into the body. Or those who get one of those Hofmann rails or something, gets screws inside the body. That's nothing, it's just a way to fix things. (P6, general public: *implying organoids are also something used to fix things*)
I have a word. A precursor for spare part development. (P18, patient)
With an organoid, you create a special product. With an organoid, you get the opportunity to study the possibilities. (P15, patient)
Right until he showed that brain cell, that started moving. Before I also thought of it as just a spare part. It's a growth created for something else. Another way to do it. But when it starts moving and react because it has a nerval system. That moved a boundary. I don't know what exactly to call it. I'm still in the spare part terminology. (P6, general public)
I'm not following the belief that it is something you modify. It's more that it can be used like… well, I think of it as a microscopic opportunity to study an organ that would normally be difficult to study. (P12, CSO)

When discussing whether organoids are artificial or natural most people saw organoids as something artificial since they are made by people and would not appear/exist on their own. A few participants argued that organoids are natural since they are made of something human.

The discussions about conceptualizations were especially focused on the dualism between human and thing. This distinction was also used in later discussions regarding transparency and science communication (see section 3.2.2 on biobanks and governance).

3.1.4 Organoids' moral status

An important point made by a participant is that whether an organoid is perceived as something human or a thing does not necessarily affect if it is a good or bad thing to use organoids:

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> "As long as it is working, I think it is a good idea. And then it doesn't matter to me if I find it, the organ, as something that comes from something profound human. I don't think is has to be something negative if you think of it as being human when it is in these microscopic sizes."
>
> (P13, vulnerable group, young)

This perspective appears to be shared by many of the participants since there is no pattern in the data suggesting that the perception of organoids being human or a thing, respectively, is affecting whether a participant is either more or less positive about the use of organoids. On the contrary, the data implies a form of consensus regarding attitudes towards the moral status of organoids at their current state, where organoids are still very small and kept in petri dishes, thus making them harder to identify with. The overall expressed opinion amongst the participants is that they are prioritizing the development of treatments for patients over the well-being of organoids. They also argue that organoids are ranged very low in the hierarchy of living creatures' moral status: "I would rather have such small cells to give them (ed: researchers) than I want animals to suffer" (P9, CSO, identifies as vulnerable group). This is supported by statements placing organoids lower in the hierarchy than mosquitos and other small insects that most people don't like. It is pointed out that there is no doubt that those are living, feeling creatures, and that the participants find them to have a higher moral status than organoids as for now: "They can do all the experiments they want to. If they take something from me they can basically do everything with it if it can improve other peoples' health. (…) It is not something you have to respect in the same way as a person. Or an animal for that matter." (P13, vulnerable group).

The participants do recognize though, that this comparison is not as simple as such because organoids involve another level of complexity:

> "They kill animals in the nature, and that is much more violent than what we typically do (ed: when using animals for research). Simple lifeforms just have a lower priority than a human being. But I understand that there are some ethical and moral dilemmas that might come into play in case this lifeform can be misused."
>
> (P5, general public).

Some express that this view only applies at the current state of organoid research, and that it was uncomfortable or upsetting for them to watch a video showing an organoid reacting to light, a video shown to them by one of the experts. Further, a participant mentions: "Yes, I could also be… say, that there would be a difference. Without knowing enough about it. But maybe! The risk for it to become something more,

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the cognitive, the sensing, I think I can hear and read from this, it is there. Not just the risk, the possibility." (P11, religious CSO). Another participant explains why there can be different conceptualizations related to cerebral organoids: "And there is something completely different about moving into the brain, you know, it's the brain that moves into itself. It's not just an organ, it's US. So, changing other parts, but changing the brain, phew!" (P6, general public). Therefore, it is based on the data relevant to take into account that the moral status of organoids can – and based on the participants' statements are very likely to – change over time based on how they develop. Especially in relation to cerebral organoids if they become sensitive, conscious, or able to think.

The participants are hesitant when the conversations are related to where to draw the line and avoid expressing explicit opinions on what should be allowed. Instead, they are very clear that they want the organoid research and regulations to be monitored and adjusted regularly. This might be related to the fact that organoid research is still at an early stage, resulting in a lot of uncertainty and making it difficult to imagine how and how fast it will develop. The participants express different opinions about which type of monitoring and adjustments should be used for organoid research. This is further elaborated in sections 3.2.2 and 3.2.5 regarding biobanks and governance, and the recommendations for future guidelines.

3.1.5 Attitudes towards Organoids

As stated in section 3.1 the participants generally expressed positive feelings related to organoids. The participants mentioned hope, excitement, and positive expectations, mainly revolving around an unspecified believe that this could provide essential new knowledge about diseases and help patients. The patients among the participants and those who were next of kin to a patient were the ones, who were most specific when talking about their hopes; The possibility to give people back their sight or development of treatments for diseases that cannot be cured currently, such as Cystic Fibrosis. Another hope expressed was new possible treatments, e.g. for the patients that does not respond to the current cures for diseases such as colon cancer. It is also mentioned by participants from the patient group that some people are in a situation where they have nothing to lose on a personal level when it comes to organoid research. They do recognize the possible risks related to commercialization or misuse, but express that they do not worry about how samples would be used for medically relevant research. This attitude is partly shared by the youngest participants, who point out that they have never felt a form of ownership in relation to their blood or tissue, as soon as it is no longer a part of their body.

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In the Danish workshop there was a correlation between the participant's age and how much they worry in relation to organoids. The questionnaires show that the participants, who are 51 or above, became more worried during the workshop, while the participants under 50 years do not express the same increase in worries. During the workshop, older participants also to a larger degree than younger participants expressed worries of a more "extreme" or science fiction inspired character. This was especially applicable to the older participants from the general public. For example, some of them mentioned worries such as organoids being used to create armies of super soldiers or biological warfare, while the younger participants focused on the general worries related to commercialization, industry monopolizing the technology, and ethical concerns. It is important to notice, that these last mentioned, more general concerns were the most dominant regardless of the participants' age, while the more extreme, 'science fiction' like worries were only expressed by a few of the older participants. The overall impression was that all participants were open and considered all mentioned risks and worries, and the dialogue about all worries was respectful and constructive. The biggest difference was that the younger participants focused on the worries that seemed more current or likely to be relevant in the near future. These worries were also present for the older participants, and especially with the thought of over-commercialization, resulting in increased inequality both socially, internationally and in relation to different types of diseases. The worry related to inequality between different diseases was especially expressed by representatives of patient organizations. These worries were based on the existing trend, where some diseases (e.g. cancer) receive more awareness than other diseases. In Denmark, like in many other countries, cancer has an annual week with extra media exposure and fundraising. This is understood as a hierarchy among diseases, and one of the worries around organoids is that it will lead to even more attention, resources and energy going to the same diseases and patients. Either the patients with diseases dominating in developed countries with good economies or the diseases with most patients. The participants clearly states that they hope organoids can be administrated in a way which make organoids and future treatments accessible to as many as possible. Lastly, it is worth noting, that the participants were generally quick to address issues related to commercialization and financial interests in organoid research. This was also the theme of one of the first questions posed to the experts during the Q&A session; What economic interests are relevant in relation to this, and how is the industry involved? Therefore, it is no surprise that this became one of the main concerns during the following discussions at the workshop.

Another thing worth mentioning is, that participants with relation to the Danish church, e.g. a CSO representative from the Protestant church and members of a church council, expressed worries related to how organoids will affect how we perceive and value human beings and human life. Participants mention the

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risk that cerebral organoids can change the perceptions of life and its value if these organoids reach some degree of consciousness: "(…) it has something to do with how we perceive human beings, what are we going into? For me it is an extremely slippery slope. It can… it can turn into a landslide" (P11, religious CSO). These worries led to various discussions about how people want to live and the value of life. Further, it related to former discussions where some participants expressed the opinion that something cannot be human if it does not have a beating heart. Other participants argue against this with the fact that some human beings are kept alive with the help of machines, and that there are people in our society with diseases that limit their level of consciousness, and that these people are still human beings. The participants do not reach consensus on this issue. They appear to agree that there is a risk of organoid research affecting our perception of human beings and the value of life but do not reach a shared understanding on how to define something as 'human'.

Lastly, there are worries of misuse related to data storage, and the worry that the wrong people will gain access to their data if they have donated tissue for organoid research. As an example, it is mentioned that data based on individual tissues can be misused by insurance companies in order to avoid costumers that are particularly exposed to certain diseases.

Table 7 displays an overview over how the participants described their worries related to different subjects.

Table 7. Worries related to organoid research.

Misuse and data security
I guess there's a lot of information in an organoid. Could insurance companies use this to calculate the price of your life insurance? (P3, general public, 18-40).
That's where it gets dangerous. Because then it suddenly starts, that people with a chronic diagnosis now, they become secondary in the sense that there not much, what is it called, a will, you can't get the insurance, and you can't this and that. And that's why when you're sharing something, you don't want it to be used against yourself (P9, CSO, 41-60)
There is something with data, DNA, and… We have gone into something. You can link it directly to the internet, you know, the most valuable thing right now is data. Data about us. What we do, where we register it, what we're sharing on social media. And I see a parallel to this. A copy of people ending up in there (P6, general public, 41-60).
Well, I mean what you give to them. It can be used, and it can be misused. We're not talking about something that can only be used for good things. It can be misused (P1, general public, 61+)

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But is all research good? It's so positively charged for most of us, research. But it's also used for bad things. It can be misused. And we need to find those lines. It's so easy to say, well everything is going well, this is a nice story, and who is really losing in this? But we can't make the rules based on that, vi need to think about the scoundrels while making the rules (P1, general public, 61+)
And even if you don't have anything to lose personally, you still might lose something based on what consequences this might bring. Who can abuse it? (P11, religious CSO, 61+)
Changes in human value
What perception do we have on human life and which do we risk to get with this? Will it… Will we end up divided people into two groups? A group A and a group B of people, or two groups of life? (…) What about those among us with diseases, so they're mentally comparable to what you might end up developing here? They're sensing something, but in reality, they can't do much more than that. If we allow this, then will it also… What landslide will it bring on our perception of people living among us, who HAVE these diseases? (P11, religious CSO, 61+)
The scientist said that he could take this technology all the way to a point of eternal life. And that gets me thinking, what kind of human vision will that lead to? And it should… it was just to challenge the talk about ongoing development because there should be some cornerstones for this. And it should be our human vision that keeps the technology in place. To some degree at least. (P6, general public, 41-60).
'Extreme worries': Misuse for warfare
Many, many years ago I read this book (…) and the thing was, that they had some cells from Hitler which they used to copy Hitler. Big time! In South America. You can also use… Put cells into, at least they have done it in animal experiments, so the mother, the cow that will be feeding the calf, is not transferring the cells. And then they have made lots of copies. In that way, you could theoretically keep making copies of a person, if you have their stem cells. (P4, general public, 61+)
And essentially you can think, where the science fiction brain might be kicking in, that if South Korea, or that's not it, if North Korea thinks that they're not a million people enough for starting a war with USA, so they mass produce elite soldiers by using this technology. We know which ones are tough and maybe immortal, and then in a science fiction like manner, or Lord of the Rings technology. Making a lot of orcs, etc. There is something in this technology that can be used negatively. Evil. (P4, general public, 41-60)

I'm starting to consider that everything we can use in a good way can also be abused. There is biological warfare. There are people who knowingly use diseases that could kill us all. You can make conventions, etc. but some countries don't care about those conventions we make. So, you might imagine that somebody will use this for it. (P4, general public, 61+).
When they can make that small intestine. Can they also make the organ, that produces the eggs inside a woman? And could I live on in that way? (P19, donor, 41-60)
That's the problem, there only to be one maniac who says that in Belarus you can do research on whatever organs you might dream of. Then the rules we make doesn't matter. (P19, donor, 41-60).

Another interesting tendency is, that participants that are either recruited as or identify with patients and vulnerable groups are less engaged in discussions about worries. The impression based on the data is that the patients and people from vulnerable groups recognize the worries and consider the possible scenarios that courses these worries among the participants. However, they are not the ones expressing and describing the worries. This could be related to the previously mentioned feeling, that they do not have anything to lose. It could also be an expression of these participant categories being particularly focus on hopes and future possibilities.

3.1.6 Worries related to different types of organoids

It is noted that the participants' worries about misuse and ethical issues are primarily related to cerebral organoids and their potential for developing consciousness. For example, during the discussions based on the dilemmas in the second part of the workshop, some participants raise questions about how to be sure that cerebral organoids will not affect a patient's personality:

> "I'm thinking that if can contribute to e.g. stopping a disease or limit a disease, epilepsy, Parkinson's, then the research is okay. But also that you take it… take the personal things in it, then it becomes… For example, Alzheimer's, if you could adjust on it, how would you get your husband back? Would he be the same or would the personality be different?" (P10, CSO, identifies as patient)

A similar worry is expressed by another participant: "But what if they can develop nerve cells, brain cells. That they have received from, well let's say, P10's brain cells are put into another one of us. Where is it then… have we aquired anything from your personality then?" (P6, general public).

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The participants express worries both related to how cerebral organoids may develop and the potential side effects that may occur if we become able to use cerebral organoids to treat patients. For example, some participants mention being worried that it would be impossible to remove something that has been put into a person in the case it has unforeseen side effects. In such a case, the patient might have been better off without the treatment and the following side effects. Despite the worries, they clearly see the potential in research with cerebral organoids, for example, the opportunity to study diseases in living, human tissue instead of using animal models or human post-mortem tissue.

Another type of organoid that leads to worries among the participants is gonadal organoids. It is worth noticing, though, that these worries are expressed by a significantly smaller number of participants. One of the addressed ethical implications related to gonadal organoids is related to the question of who the parents of children brought into the world by the use of organoids would be, e.g. in a future scenario where a woman who has lost the ability to become pregnant after fighting cancer, and could regain the ability with the help of organoids. The question raised in relation to this is, whether the donor of stem cells used to develop the organoid that leads to the women becoming pregnant would somehow have parental rights or obligations, or if the donor in some sense is kept alive via the donated cells. Another concern is that organoids can be developed to the point where they become fetuses that can be used for research purposes:

> "We are talking about organoids, which are taken from a donor. A human, who have given some cells, but I think it could turn into an ethical dilemma, if you take it further and develop fetuses. Research on a fetus. That has been born. Or created to be used as spare parts. Then it will become an ethical dilemma."
>
> (P19, donor)

This scenario is currently prevented by the 14-days rule which makes it illegal to develop that type of cell further than 14 days.

3.2 Ethical Issues and Implications in relation to the Derivation and Use of Organoids

The current section is divided into five sub-sections, each focusing on different ethical issues and implications discussed by the participants during the workshop. The last of these sub-sections includes the themes, worries, and issues that, according to the participants, should be considered in future guidelines for organoid research and governance related to organoid research.

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3.2.1 Informed consent and patient information

Informed consent in regard to donations and the use of tissue for organoid research was one of the themes that were important to the participants during the workshop. It was not only mentioned in discussions directly related to consent but also several times by different participants in discussions focused on other issues or implications related to organoids. As an example, consent was mentioned in discussions about ownership and financial compensation, thus making it a very fundamental matter regarding organoid research and future guidelines.

The participants all found consent and patient information essential in relation to the use of and research with organoids. They stated that it should be communicated in a clear and simple way, so there is no doubt related to ownership, distribution of potential profit based on research with samples, what the sample can be used for, etc. Some participants explained that they prior to the workshop had allowed doctors to take a sample for research, but never knew how it was used or stored: "(…) I realize now, that I never consented to it. So, I have no clue what it was used for. But I would have liked to know how it was used. I live in a society where I trust the people doing this research, that they use it in a sensible way. But you can't be sure of that." (P11, religious CSO). The participant had explained that they consented for a sample to be taken from their newborn child's umbilical cord, but the only information they received was, that it was for research purposes and would be helpful. The participant concluded that she would have liked more information and for the consent to be more specific, so they knew how and what it was used for. One of the issues in this case is, that she had no information about her rights and ownership of the biopsy that was taken.

Another point discussed by the participants was the question of when a patient or donor can be considered as being informed. Several of them tell that they often consent to use or do something without reading the full description of what they are consenting to. E.g., a participant mentions that he signed the consent form for the workshop without reading it properly, while other mention to consent to the terms for the use of websites, smartphones, etc. Even though it is the individual's own responsibility to be receptive to the information, it is an important point that the information should be given as accessible, short, and clear as possible. A participant from the patient group tells that he consented to many things during the time he was treated: "Then they take out the tumor, and I'm busy trying to survive (…) After I survived, I take it up again, and they had found a genetic anomaly. And then I thought about the fact that I did not get to choose whether I wanted to know. The decision had been made for me." (P18, patient). While fighting diseases patients might be so focused on their illness that they are not capable of understanding the details of what

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they are consenting to. Based on these discussions and examples, the participants overall agree, that it is important that doctors and researchers take the patient or donors current situation into account, and further that information and consent forms must be simple and easy to understand.

This also raises the question related to how much a patient wants or needs to know. A participant mentions that it is normal for patients with gastrointestinal diseases to be treated with healthy faeces from a person with a healthy bowel, and that some people might be dismissive to specific types of treatments if they have too much information about it: “I learned, that there was a kind of protein, where they take it from guineapigs. Maybe, if I knew that before, I would have thought ‘ughhh’ But I’m so happy that they had some other material I could try” (P10, CSO, identifies as patient). This indicates a fine balance in relation to when a patient is properly informed, since they want to be informed, but on the other hand they can also be *too* informed. This creates a dilemma regarding how to best keep the patients’ interest and need of treatment in mind, while assuring they are able to give an informed consent.

Based on the deliberation during the workshop, the participants find consent essential – and critical – in relation to organoid research. During the deliberation, the majority of the participants in various ways expressed a wish for more restrictions. They prefer a type of consent either based on specific areas/diseases or an ongoing consent where doctors and researchers must get a new consent if they wish to use a patient or donor’s tissue to pursue new paths.

3.2.2 Biobanks and governance

Governance and storage of data are themes related to most of the participants’ concerns and worries related to organoids. These subjects were mentioned during multiple of the group deliberations both related to ownership, data security and communication between scientists and society.

When talking about the ownership of organoids the discussions were quickly linked to discussions about storage and biobanks. It included considerations related to how and where it should be stored, who should be responsible for the governance, and who should be able to access samples and data. One suggestion was that organoids should be owned by the state/society both to make sure the data would only be available for relevant researchers and medical professionals, and that it cannot be commercialized or misused:

> “(…) if it was the state alone who owned this biobank, and thereby the state who owns our DNA. From my point of view, it’s not a big challenge. As long as we are sharing the DNA in solidarity, as long as it is anonymous and can’t be traced. Of course you should be able to trace if you have some kind of uncurable diseases or something, and have given consent to

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> be informed. But in one way or another it's all about: Can we share it with each other, so it won't end… won't end in the hands of the industry? So, it is something we kind of share with each other as a society."
>
> (P9, CSO, identifies as vulnerable group).

The participants recognize that biobanks can be a necessity and useful but are concerned that data can be misused or that commercialization of organoids and related data and technologies will lead to an increase in inequality. Yet, there is no consensus of how organoid research and data should be governed. Some participants argue that if the consent is given to the doctor or researcher, it should be owned and governed by that person – or the hospital or research institution they represent. Other participants argue that the state should be responsible for the governance, e.g. as seen in the previous quote. Even though they do not fully agree on how it should be governed, a majority of the participants want organoid research to be managed in the public sector to avoid commercialization. However, several of them mention that commercialization and economic interest in many cases can be essential for the development in the medical industry:

> "I think that all this related to economy, who should be allowed to make money, how much will we allow that they profit? Against the fact that economy is a motivation for it and the development. It is a balance, which is connected to this thing, that we need to make sure it will benefit everyone. Because, we can say that it must be so cheap and so accessible for everyone, that it becomes uninteresting to research."
>
> (P19, donor, male)

It is also pointed out that it might be difficult to avoid commercialization and that we need this process in order for the research and technology to become broadly accessible. A conclusion related to this is that no matter, who ends up with the responsibility of governing organoid research and storage of data related to it, it is crucial that there is a high level of transparency, so it is transparent how it is handled. It is also stated that transparency can help to make people more open to the use of organoids and create more trust to the researchers and doctors using it. Further, the participants argue, that data in biobanks should be governed based on clear consent and agreements and only accessible to relevant people, e.g. they mention the worry that insurance companies could misuse information about citizens who have genetic anomalies, which could lead to discrimination.

3.2.3 Dilemma 1: Ownership, compensation, and patentability

The first dilemma is based on a case, where a biopsy is taken from a cancer patient in order to find the best possible treatment for him. A part of the biopsy is also used to produce cells for research, which eventually

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leads to the development of a new vaccine. The doctor who developed the vaccine further wins a Nobel prize. The dilemma raised ethical questions related to ownership, financial compensation, and patents.

While discussing the dilemma, only a few of the participants argued that the patient in the case should receive financial compensation. One argument supporting this opinion was based on the information, that the development of the vaccine was based on the patient's tissue. Another argument with a similar approach was that it could be considered as a form of copyright in the same way as musicians or artists have the copyright and are paid for the use of their music/art, even for several years after the musician/artist has passed away. Further, some participants pointed out that hospitals and research institutions are paid by the citizens through taxes, and therefore it seems wrong that researchers at these institutions as individuals can benefit financially from the research the population has funded. This issue is more complex as such since a lot of research taking place on public universities in Denmark is based on funding from private foundations. It could become difficult to distinguish where the money resulting in a discovery specifically came from, and further scientific discoveries can be based on research conducted over a duration of several years and involving knowledge from several projects with different funding.

Opposite to these arguments, most of the participants agree that the patient in the dilemma, Andrew, or his relatives should not be financially compensated since they were not actively involved in the research and discovery of the vaccine from the discussed dilemma. Participants did point out, though, that it depends on the type of consent given when the biopsy was taken. If the patient agreed to it being used for research, there is no basis for him to benefit from it financially, since he had given the researcher the right to use it. If he only consented for it to be used for studying his specific case and give him the best possible treatment, the doctor has crossed a line by using it for other purposes. In this case, the patient and/or his family should be compensated. Related to this, it is mentioned that there might be a distinction between consenting to doctors taking a sample and consenting to donating tissue, emphasizing the importance of clear communication and transparency.

Another argument in favour of the patient not benefiting financially from the discovery based on his biopsy, is that this is not the general practice (at least in a Danish context). When tissue is donated it should be seen as exactly that – a donation. This argument is, among other, based on the fact that donors do not get paid in other cases, whether it is blood, organs, stem cells, or other types of tissue. Several participants also point out that a donation should not be given based on hope of future financial benefits. In relation to this, it is also mentioned that we as a part of a society have an obligation to help each other. In the dilemma, the biopsy might help the patient specifically, though it is unclear whether the patient survives. Since there is no harm to the patient when the biopsy is used for research, and in the longer term, the discovery of a

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vaccine that can help many people, one could argue that he should be willing to let the biopsy be used for research because it is his social responsibility. This argument is not something the participants agree on, and the dominating approach is that it depends on the type of consent given when the biopsy was taken.

The previously mentioned argument that money can be an important motivation for research in new treatments is also mentioned related to this case. Again, it is stated that it should only be possible to benefit financially if it is a part of the consent given by the patient or donor, but it is further pointed out that: "It wouldn't hurt me that the researcher here is going out and gets a Nobel prize and something else, because she keeps researching and she is the one who discovers the medication and vaccine. I can't see a problem with that" (P11, religious CSO).

In conclusion, the discussions based on this dilemma was related to the ethical implications previously described in this report, e.g., commercialization and informed consent. The majority supports the opinion that prizes and financial gain from research is important to motivate doctors and researchers to keep doing their research, and states that one cannot expect to benefit from something one has consented to donate. An important point is that informed consent is essential in the discussion, and that consent has a clear effect on which conclusions the participants reach through the discussion. Further, it is worth noting that there appears to be different perspectives regarding financial gain. Here, participants find it problematic if private companies benefit financially from the research, while it seems to be more acceptable that researchers and doctors in the public sector benefit from it financially, because it will keep them motivated.

3.2.4 Dilemma 2: Cerebral organoids

The second dilemma is related to cerebral organoids and leads to discussions about moral status, worries for this specific type of organoids, and animal research. During the deliberative workshop, the participants express that they find cerebral organoids particularly challenging, because these organoids are more complex and involve the possibility – or risk – of developing consciousness. It is also mentioned by some of the participants that it might be relevant to have special regulation for this specific type of organoid. Participants explain that it is difficult to discuss these organoids since they it is unknown how cerebral organoids will develop and how conscious or sentient they will become in the future: "I actually find this one more difficult because it involves some kind of consciousness." (P20, donor). Most of the participants agree that morally an organoid is ranked below humans and animals, but this is based on the current state of organoids, where they can be perceived as cells in a petri dish. The uncertainty is based on the possible future development, e.g., questions whether especially cerebral organoids can be developed into something the average person find more recognizable as human:

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> "Will it become something similar to something living? Something living as we already know it? You know, people with diseases, people who are laying and can't do much more than breathe. And will it affect how we see those people, and the fact that it might be us lying like that someday. There is something about our fundamental perception of human life that is important to think about in this."
>
> (P11, religious CSO).

The concern is that the moral status of cerebral organoids made with human stem cells can affect how we perceive human life, e.g. related to brain dead people or persons with severe mental challenges that prevents them from contributing to society in a conventional way. The worry is that cerebral organoids eventually gain consciousness corresponding to that of a person in a coma, and it would result in people starting to find a brain-dead person more comparable with a conscious organoid, than a healthy human being, e.g. based on the distinction that a healthy person can actively contribute to society, while both a person in a coma and a conscious organoid cannot contribute actively. Some participants worry that this could affect the moral status of human beings in these positions, thus dividing human beings into categories of different worth.

As mentioned above the participants at the workshop in general agree that organoids – including cerebral organoids – have a very low moral status at their current state:

> "There was this thing about inherit value. It's hard for me to see this as long as it's a creature that can't exist or survive on its own. Then it's okay for it to react in a negative way if we can become smarter and help the global society. I'm almost more sorry about using a mouse to do it, than using organoids."
>
> (P9, CSO)

Several other participants also compare the moral status of organoids to the moral status of different animals. It is for example pointed out that they would rather have "some tiny cells" suffering than animals. Some also mention a hierarchy of different animals' moral status, based on the assumption that most people would agree, that it is more unethical to use monkeys or dogs for research than using a rat or mouse. This leads to some participants concluding that: "It's (ed: organoids) even lower than a mosquito. We all hate mosquitos, they're annoying, right? But for me mosquitos are at least some kind of feeling creature." (P9, CSO). This is also compared to the fact that plants and fungi can communicate through some kind of internal network, but a clear majority of the human population don't consider plants and fungi to be sentient or something that needs to be respected in the same way as humans or animals. It is worth noting that the

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participants do not discuss how developed an organoid must be for the moral status to change. They argue that the moral status can change based on the development, but it is not elaborated how much they must develop to reach the same moral status as a mouse, dog, or human.

Further, the participants are overall agreeing that helping patients is more important than cerebral organoids with a limited amount of nerval activity that makes them capable of reacting to light and other manipulation. At this developmental stage, they do not perceive organoids as creatures with feelings and experiences comparable to those of human beings or animals. They prioritize the possibility of developing new treatments and to obtain more knowledge about diseases such as Alzheimer's and Parkinson's. But just as with animals they find it difficult to discuss if or when this would change.

As previously stated in section 3.1.2 there are different worries specifically related to cerebral organoids, e.g. it is questioned whether people could change personalities if they are treated with something based on a cerebral organoid made with stem cells from another person's brain. Would the person be the same, and do we want to treat people to keep them alive if it means they will become another person after that? Another similar concern is regarding the responsibility if the use of treatment with cerebral organoids ends up affecting a person's personality, e.g. if the person getting treated becomes violent and hurts others afterwards.

To summarize, the discussions based on the second dilemma on cerebral organoids involves a lot of complexity and uncertainty. The participants over all agrees that organoids at their current state should be placed below both human beings and animals in the moral hierarchy, and that it should be prioritized to help patients. Further, it is expressed that this might change depending on how cerebral organoids develop. The participants do not reach a conclusion in this regard and point out that this should be discussed and regulated by others.

3.2.5. Recommendations for future guidelines

The recommendations for future guidelines for organoid research are shown in Table 8 below. They are based on the previous analysis and the posters made by the participants during the last deliberation at the workshop, where they discussed which subjects, they found most important to include in future guidelines.

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The recommendations are sorted into the following categories: Communication, governance, and ethical implications[9].

Table 8. Recommendations for future guidelines.

Recommendations for future information and communication on organoids
Transparency and focus on the dissemination of organoid research. Since the research has great potential and can possibly help a lot of patients in the future, it is important to the participants that it is conducted and governed in a transparent way. They argue this will result in the public feeling safe and more trusting. In relation to this they also emphasise the importance of how it is communicated, e.g. how organoids are described. If they are described as something human it might, according to the participants, result in fears and worries, while cell cultures or a thing similar to medication is more neutral.
The guidelines regarding informed consent and information to patients and citizens should be clear, and procedures for informing patients and getting consent should be simple and understandable for the patients. The participants suggest allocating funds for this specific purpose, e.g. to secure there is sufficient time for information.
Recommendations related to the governance of organoids
Clear rules for how organoid research and data related to it is governed. The participants do not reach consensus regarding how they think it should be governed and who should have the responsibility. Several mentions that the guidelines should be governed by the public sector, possibly a democratic body with members representing both medical or academic researchers, relevant stakeholders and the general public. Another suggestion is to involve the World Health Organization in the governance or monitoring of organoid research, e.g. by making them in charge of evaluating and monitoring the research and medical development based on organoid research, or having them participating in a council with various relevant stakeholders and citizens. It is also noted that the governance must avoid being *too* bureaucratic based on a worry that important decisions and actions will happen too late compared to how fast the development might be.
The majority of the participants are supporting the suggestion that the ethical guidelines should be evaluated regularly. There is no agreement on how often this should be done, since it is unknown how fast organoid research will develop. The recommendation is to stay ahead and as far as possible avoid addressing potential issues after they become problematic.

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[9] The recommendations are not mentioned in a prioritized order, though the listed recommendations are the ones the participants expressed as most important to them.

The participants recommend that the guidelines will use the experience we have from other fields such as cloning and donation of blood, organs, and sperm. The guidelines for organoid research should be inspired by the well-functioning parts of the guidelines in those fields.
Strict focus on data security and storage. It should only be accessible to relevant people such as medical professionals or researchers. This could be managed based on the consent given in the specific case.
Ethical implication to take into account
The guidelines should consider our current perception of human value, and how organoid research might affect and change this. The participants find it important that the guidelines are supporting a development that will not increase inequality, e.g. by avoiding monopolizing and commercialization resulting in treatments being too expensive or non-accessible to the general public.
It is recommended that the guidelines articulate the balance between how and when it is relevant to act and when it is time to “let life take its course”. It is expressed that death is a part of life and this should be used to improve and repair, but not to pursuit immortality.
The guidelines should include rules regarding responsibility in case something goes wrong, e.g. uninspected result from using organoid-based treatments.

3.3 Survey and Change of Attitudes towards Organoid Research

As previously stated, the participants had to fill out the first part of a questionnaire at the beginning of the workshop, before any deliberation had taken place, and a second part repeating some of the same questions at the end of the workshop. The answers from the questionnaire are displayed below in a number of tables and diagrams.

First of all, we have created basic diagrams on demographic information on the participants (Diagrams 1-6), on participant categories and distribution, age, gender, religiosity, relation to the job market, and ethnicity/nationality.

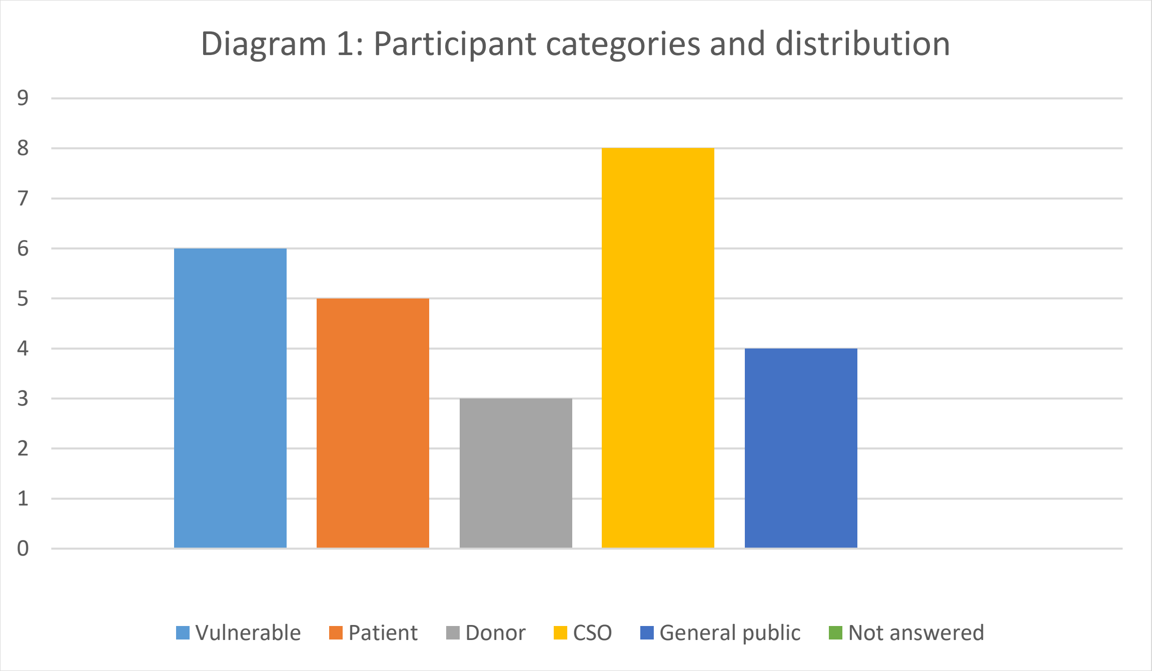

Diagram 1 shows how the participants in the workshop were distributed between the five recruitment categories, based on their own categorization in the questionnaire. As mentioned in section 2.2 the answers from the survey indicate a different distribution than the one from the recruitment process, because some of the participants identified themselves with other categories than the ones they were recruited on the basis of.

Table 9. Participant category distribution – Recruitment vs. questionnaire

Participant category	Distribution from recruitment	Distribution based on questionnaire at workshop
The general public	5	4
Vulnerable groups	2	6
Patients	4	5
Donors	2	3
CSOs	7	8
Total	**20**	**26**

Further, it is worth noting, that some participants identified themselves with more than one of the five categories. Therefore, the right side of Table 9 does not sum to 20, but to 26.

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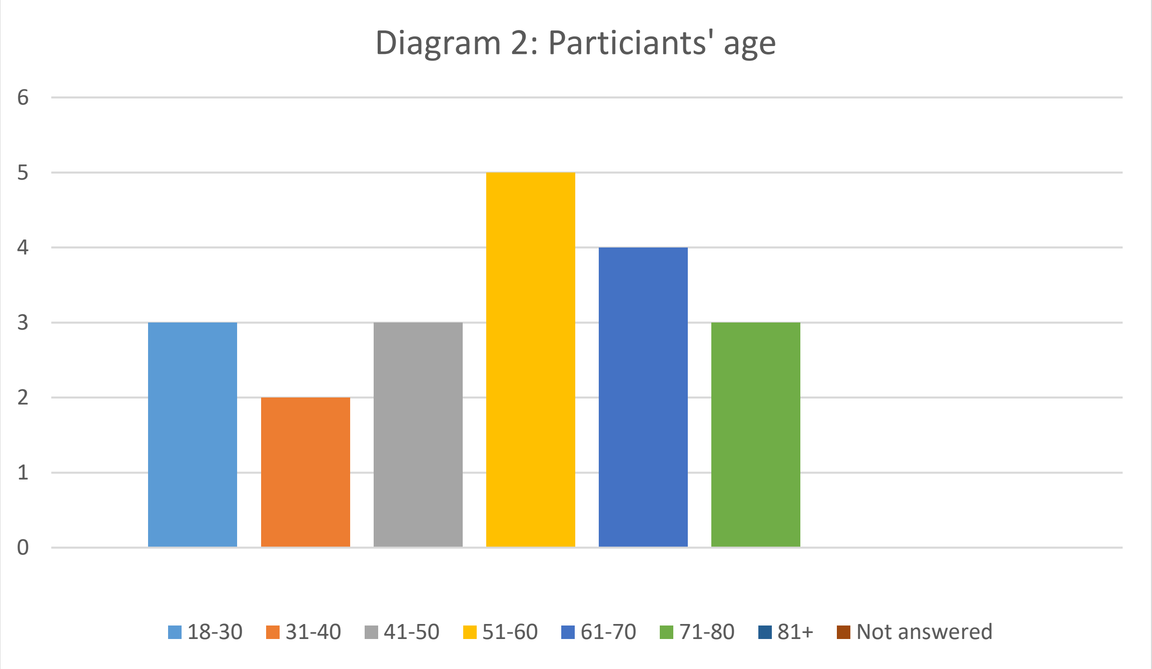

Diagram 2 shows the age distribution among the 20 participants in the Danish deliberative workshop. As the diagram shows, there was a fairly equal distribution of participants between the different age groups. 8 participants were under 51, 12 were 51 or above. The researcher, who was responsible for the recruitment of participants, experienced that young people more often than older people declined the invitation to participate, e.g., because they had young children and therefore found it difficult to spend a Saturday away from home.

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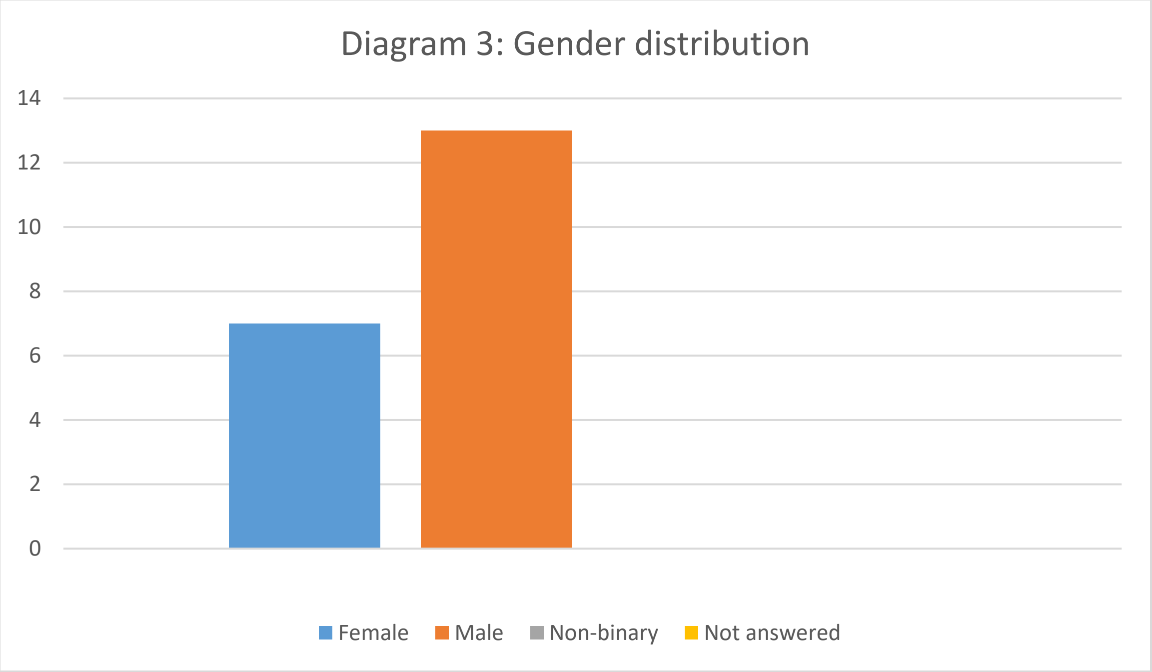
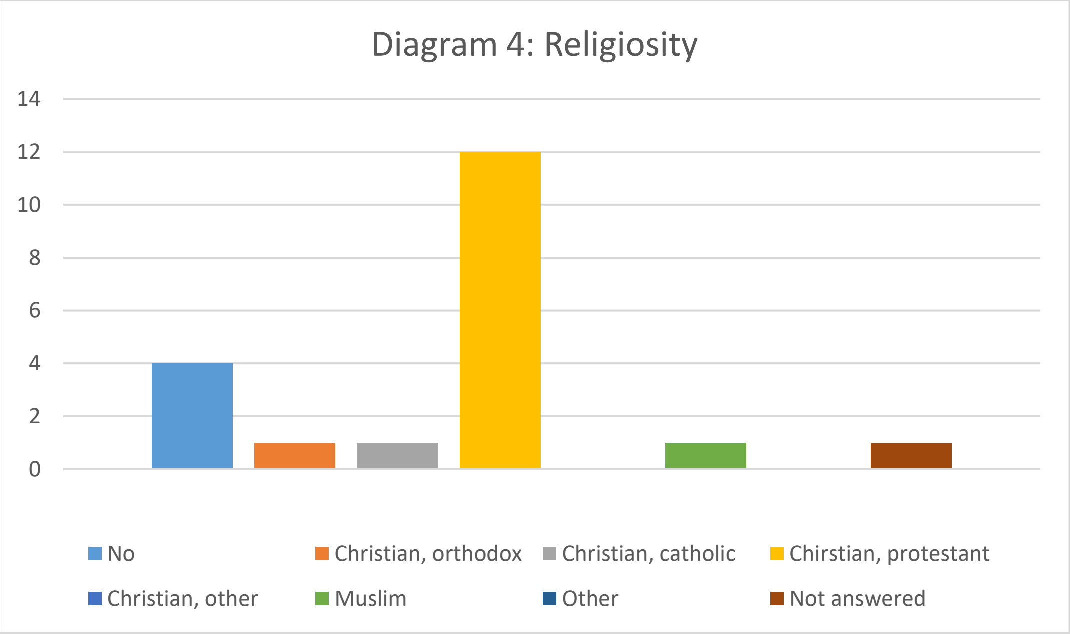


The diagram shows the gender distribution among the participants. Seven women and 13 men participated in the workshop.



As diagram 4 shows, most of the Danish participants described themselves as Christians (Protestants).

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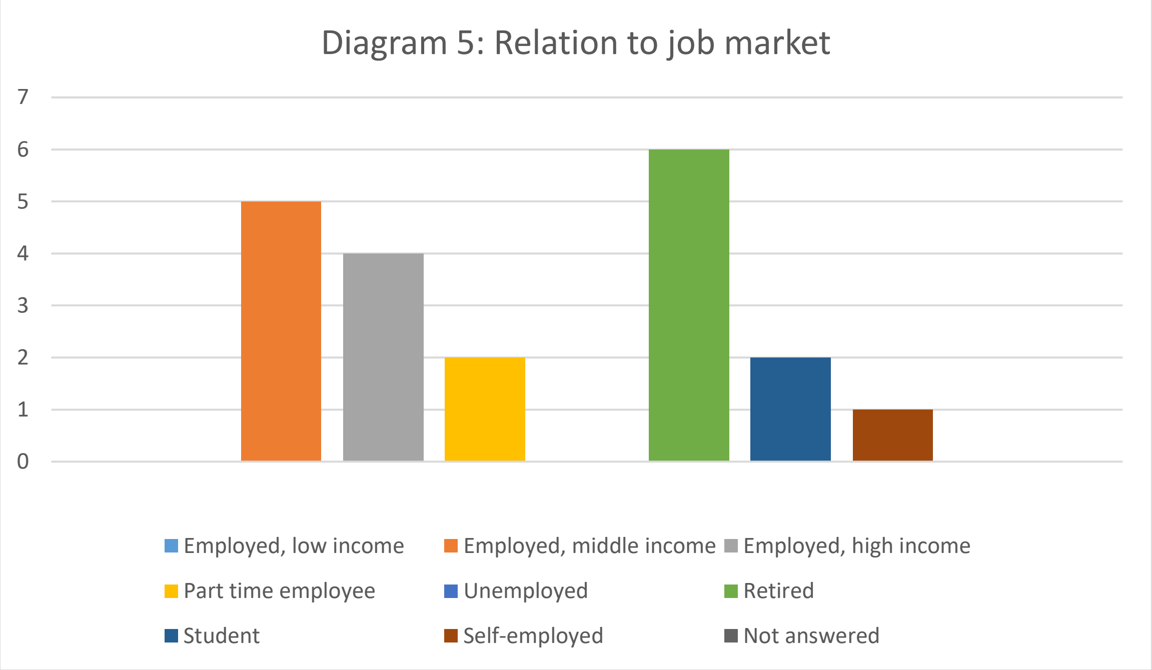
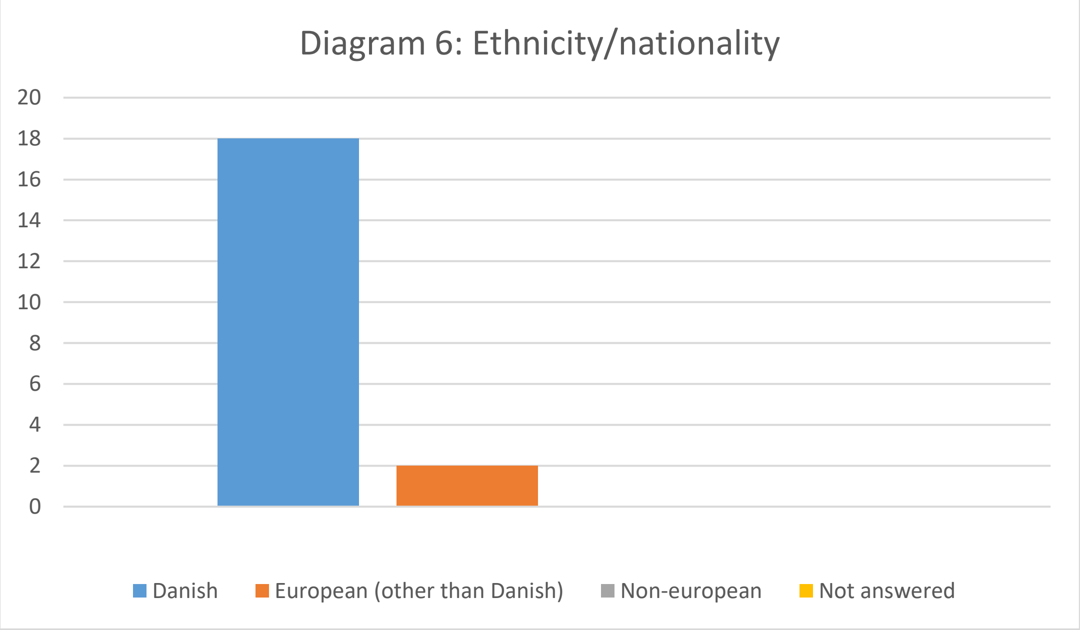


In this part of the survey, the participants were asked to indicate their relationship to the job market. The biggest group was ‘retired’ (6 participants). Many of them had been recruited from voluntary organization (e.g. related to the church), where this group is traditionally very active and engaged in voluntary work.



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The majority of participants consider themselves to be Danish. This is not surprising given the fact that all the recruitment material was in Danish and that the workshop language was Danish.

3.3.1 Potential changes in attitudes

Besides using the survey for sociodemographic background information on the participants, we also wanted to use it to capture changes in attitudes towards organoids and organoid research as a result of the expert knowledge and deliberations at the workshop. Diagram 7-10 show the participants' answers from the beginning as well as the end of the workshop. The results are shown as side-by-side bars for easier comparison.

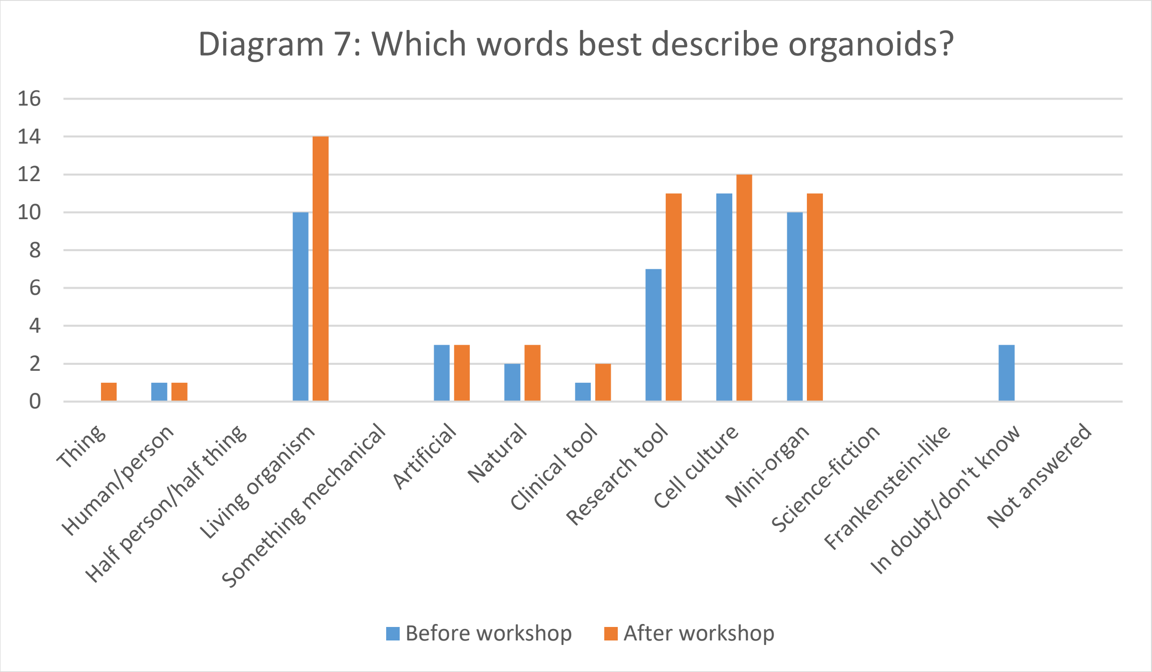

Diagram 7 shows which words the participants found to be the best words to describe organoids – before and after the deliberations at the workshop. They could choose up to three words. We see the biggest changes in the words 'living organism' and 'research tool'. After the workshop, 14 participants considered organoids to be a 'living organism' as opposed to 10 at the beginning of the day. For 'research tool', the figures shifted from 7 to 11. It is also worth noticing that none of the participants chose 'in doubt/don't know' after the workshop. This indicate that the workshop has helped inform the participants, who were in

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doubt. But the workshop also seems to have helped participants get a more nuanced understanding of organoids, as indicated by the increased number of words they used at the end of the workshop (n=58) to describe organoids compared to the number used at the beginning of the workshop (n=48) (see Table 10).

Table 10. Words describing organoids – Before and after the workshop

	Before workshop	After workshop
Thing	0	1
Human/person	1	1
Half person/half thing	0	0
Living organism	10	14
Something mechanical	0	0
Artificial	3	3
Natural	2	3
Clinical tool	1	2
Research tool	7	11
Cell culture	11	12
Mini-organ	10	11
Science-fiction	0	0
Frankenstein-like	0	0
In doubt/don't know	3	0
Not answered	0	0
Total	**48**	**58**

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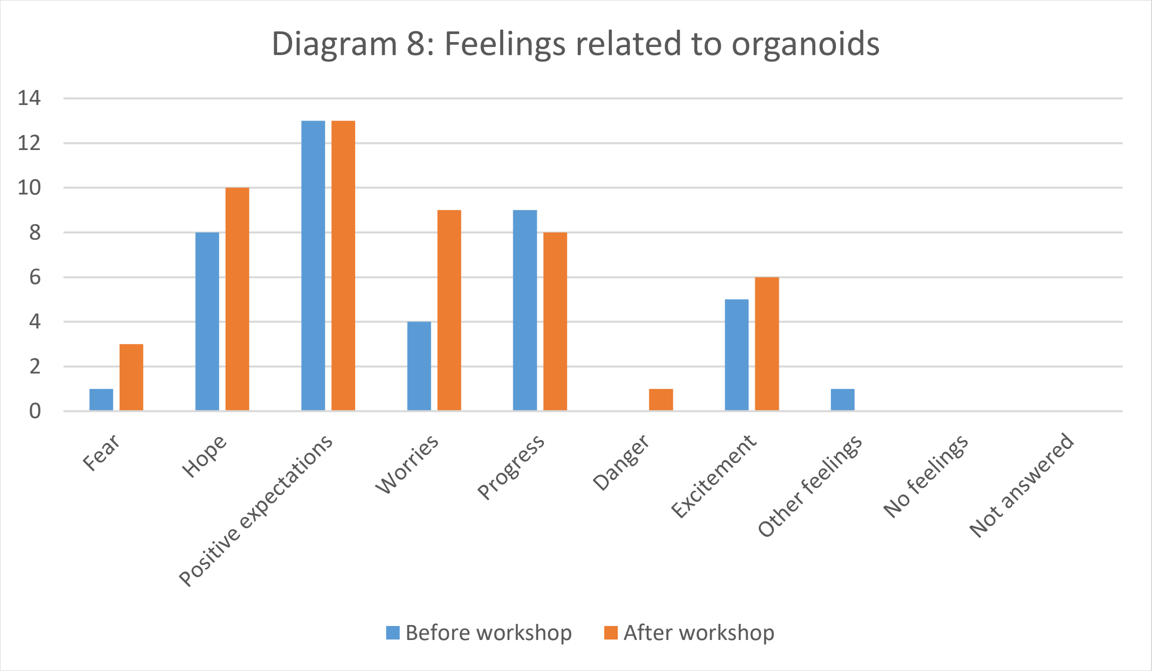

Diagram 8: Feelings related to organoids

Diagram 8 shows the distribution of the participants' answers on the feelings they had in relation to organoids before and after the workshop. Both before and after the workshop, positive feelings such as 'hope', 'positive expectations' and 'excitement' are dominating. However, there is a noticeable increase in the number of participants, who are 'worried' after the workshop (from 4 to 9). 3 express 'fear' (it was 1 before) and 1 see 'danger' in organoids. There were 8 participants who after the workshop used 'living organism' to describe organoids and also answered they felt worried in relation to organoids. Out of these 8 people, three of them had also answered to feel worried before the beginning of the workshop. The input from the experts as well as the deliberations thus seem to have increased the awareness of the possibilities in organoid research - both the positive ways it in the future can be used to help patients, but also the potential problems related to this technology, as discussed above.

As Table 11 shows, the participants have also in this case used more words to answer the question at the end of the workshop than at the beginning of it.

Table 11. Feelings related to organoids before and after the workshop

	Before workshop	After workshop
Fear	1	3
Hope	8	10
Positive expectations	13	13
Worries	4	9
Progress	9	8
Danger	0	1
Excitement	5	6
Other feelings	1	0
No feelings	0	0
Not answered	0	0
Total	**41**	**50**

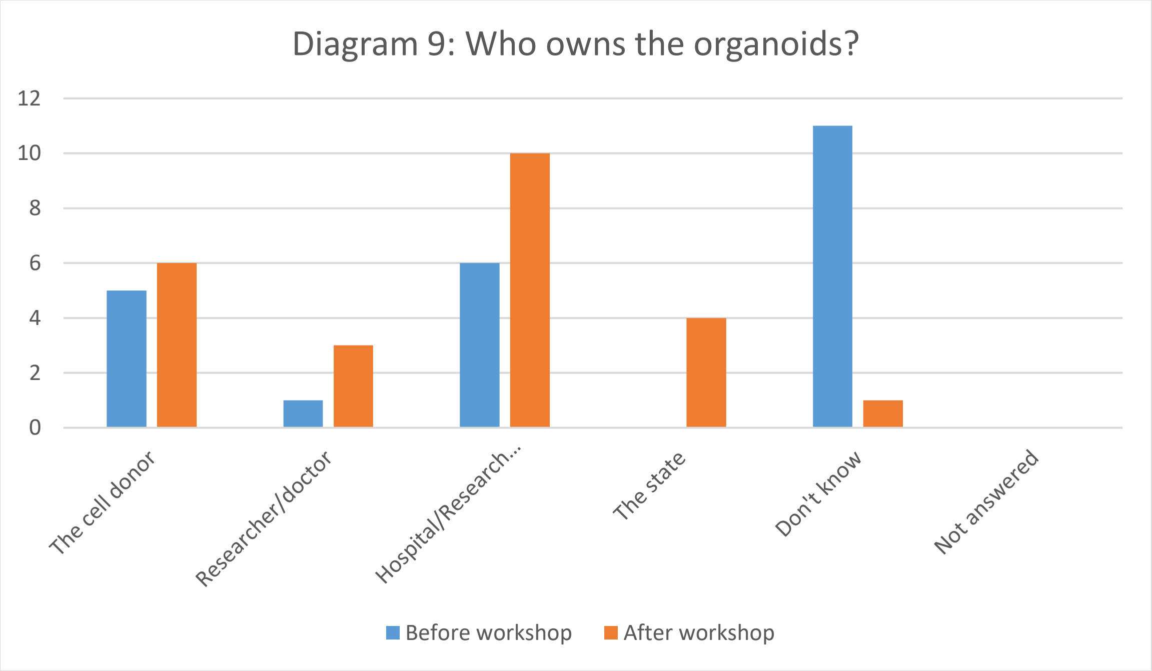

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Diagram 9 shows that at the beginning of the day, more than half the participants did not know, who should own the organoids that are produced at research institutions, whereas the rest of the answers were mainly distributed between the cell donor and the hospital/research institution. After the workshop, only one participant did not know, who to consider the owner whereas half of the participants felt that the hospital/research institution owned the organoids. After the deliberations, four people felt that the state should own the organoids, which can be explained by some of the concerns expressed in the deliberations about making sure that the befits of this technology are equally distributed between poor and rich populations. However, at the end of the workshop, a relatively big minority (n=6) expressed the view that the donors should own the organoids.

In relation to this question, multiple participants at the end of the workshop wrote in the survey, that the ownership depends on the type of consent given by the donor or that the hospital or state is the owner after the donor has given their consent.

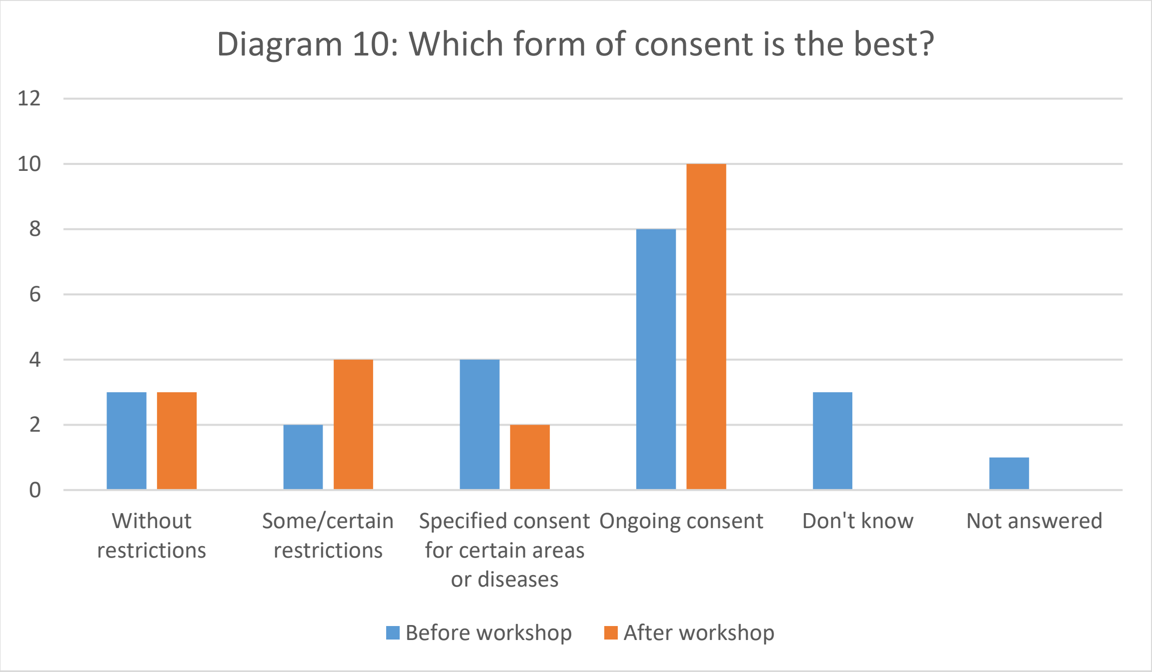

Diagram 10 shows the distribution of answers from the participants - before and after the deliberations - on the question of which form of consent they prefer. The diagram shows a clear decrease in the number of participants, who after the deliberation do not know or do not wish to answer the question. After the workshop neither of those categories are used. Here, half of the participants prefer ‘ongoing consent’ and the

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rest of the answers are distributed between the other consent forms, with ‘specified consent for certain areas or diseases’ as the second most popular answer (n=4).

3.4 Conclusion

The Danish deliberative workshop has clearly shown that there are several issues to consider when developing an ethical framework for future organoid research. First, it is important to notice that the participants were mainly positive and hopeful regarding research with organoids and the ways it can contribute to important knowledge about diseases and development of new treatments and medications. This is expressed several times during the workshop and can be seen in the survey as well. However, during the workshop the participants also became aware of the complexity and dilemmas related to organoid research, which also seems to have resulted in an increased number of worries. The analysis showed that these worries are connected to the many uncertainties and unknows in the research and future development of the research field. The worries are especially related to cerebral organoids and the possibility for them to develop consciousness, but participants also express worries related to misuse of data and the risk of the technology leading to an increase in inequality and access to treatment. The participants were particularly occupied with questions related to consent, transparency, governance, and data security. This can be seen in their recommendations in section 3.2.5, where they ask for clear rules and governance to avoid over-commercialization and misuse.

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Appendix D. Invitation to participate

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.

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 E. Information letter

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.

What is a mini-public/deliberative workshop?

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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[10]). 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.

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

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

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.

Appendix F. Consent form

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 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).

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

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

Appendix G. AU processing of personal data

How Aarhus University, Università Degli Studi Dell'Insubria, and National Technical University of Athens process your personal data

In connection with your participation in a research project at Aarhus University, Università Degli Studi Dell'Insubria, and National Technical University of Athens pursuant to the General Data Protection Regulation, we are required to inform you about how your personal data will be processed. As joint controllers we also provide you with information about our arrangement concerning the processing of personal data.

The data controllers	Aarhus University (data controller 1) Nordre Ringgade 1 DK-8000 Aarhus C Denmark CVR no.: 31119103 and Università Degli Studi Dell'Insubria (data controller 2) VAT 02481820120 Via Ravasi 2 21100 Varese Italy and National Technical University of Athens – NTUA (data controller 3) Heroon Polytechniou 9, Zografou Campus VAT EL099793475 15780 Athens Greece are the data controllers responsible for the processing of personal data in the research project. The research project is headed by senior researcher Mads P. Sørensen from Aarhus University, who can be contacted at Department of Political Sciences, Aarhus University, mps@ps.au.dk and phone +45 87165897.
The arrangement between the joint controllers	Aarhus University (data controller 1) is responsible for: Leading the work packages, the analysis of the data, and is responsible for storing the data. To be able to analyse the mini-publics/deliberative workshops, the single workshops will be audio recorded by the data controllers. On the basis of the recordings, transcription of the discussions will be made by data controller 1, 2 and 3. Hereafter, 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 by data controller 2 and 3. Data controller 1 will store informed consent forms for participation separately from the recordings and transcripts. The findings from the mini-publics will be analysed and published in collaboration with the other data controllers. No personal identifiable information will be mentioned or disclosed at any point in these publications.

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	Università Degli Studi Dell'Insubria (Data Controller 2)'s overall responsibility is to collect data from the deliberative workshop in Italy. Data Controller 2 will recruit participants, collect consent forms and data about the participants, audio record the workshop, transcribe the audio recordings, and make a study protocol for the workshop. Hereafter, all data will be transferred to Data Controller 1 (Aarhus University) and all locally stored data will be deleted. National Technical University of Athens (Data Controller 3)'s overall responsibility is to collect data from the deliberative workshop in Greece. Data Controller 3 will recruit participants, collect consent forms and data about the participants, audio record the workshop, transcribe the audio recordings, and make a study protocol for the workshop. Hereafter, all data will be transferred to Data Controller 1 (Aarhus University) and all locally stored data will be deleted.
Data protection officer at Aarhus University, Università Degli Studi Dell'Insubria, and National Technical University of Athens	Aarhus University Søren Broberg Nielsen Data protection officer/DPO dpo@au.dk Università degli Studi dell'Insubria Data protection officer/DPO privacy@uninsubria.it National Technical University of Athens Data protection officer/DPO elke_dpo@mail.ntua.gr
Title of the research project	HYBRIDA (Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies)
The purpose of the project and of processing your personal data	HYBRIDA will use personal data to better understand the general public, vulnerable groups (e.g., parents to children with genetic diseases), patients (e.g., with diseases such as cystic fibrosis, cancer, neurologic diseases, gastrointestinal disease, macular generation among others), donors, and civil society organisations, including religious organisations, views on organoids. 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 any ethical "blind spots" of current practices. This will help the project describe known, as well as hitherto unrecognised, ethical challenges, and start developing possible ways to deal with them.
Which personal data will be processed in the project?	The project will process the following information about you as a participant: ☒Name ☒Age ☒Gender ☒E-mail address ☒Race and ethnic origin ☒Political opinions, religious or philosophical beliefs ☒Organizational memberships

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	☒Data concerning health ☒Sex life or sexual orientation
Use of automated processing (profiling)	Profiling is the automated processing of your personal data. For example, processing determined by an algorithm. See below whether processing of your personal data will involve automated processing. ☐Your personal data will be subject to automated processing. ☒ Your personal data will <u>not</u> be subject to automated processing.
For how long do we store your other personal data?	At present, we cannot say for how long we will be processing your personal data. Your personal data will be processed by Aarhus University, Università Degli Studi Dell'Insubria, and National Technical University of Athens in a personally identifiable form for as long as required by the research purpose and the rules on storage according to responsible conduct of research. When we no longer need your personal data for processing, the data will be anonymised, transferred to the Danish National Archives or erased.
Will personal data be made available or disclosed to others, e.g. researchers at other universities?	Your personal data collected for the project will only be disclosed to the other joint controllers.
The personal data has been obtained:	☐From you ☒From you and others* ☐From others* [*In some cases, we have obtained your name and email address from an organisation that you are a member of, e.g., through the public webpage of the organisation. All other personal data we only have if you have given them to us.]
We are entitled to process your personal data pursuant to the rules of the General Data Protection Regulation and the Danish Data Protection Act. We are obligated to inform you about the rules that apply to our work with your personal data.	☒Article 6(1)(e) entitles the data controllers to process non-sensitive personal data about you without your consent, because the research project is a task carried out in the public interest and because processing of personal data is necessary for the performance of the research project. ☒Article 6(1)(e) of the General Data Protection Regulation and section 10(1) of the Danish Data Protection Act entitle Aarhus University to process your sensitive personal data and/or data on criminal offences for scientific research purposes without your consent.
Your rights under the General Data Protection Regulation	You have the following rights if Aarhus University, Università Degli Studi Dell'Insubria, and National Technical University of Athens process your personal data as part of a research project carried out in the public interest: • Right to erasure or the "right to be forgotten". • Right to data portability - in some cases, you have the right to receive your personal data and to request that the personal data be transferred from one data controller to another. • Right not to be subject to an automatic decision based solely on automated processing, including profiling.

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	Note that your rights may be limited by other legislation or be subject to exemptions, e.g., in relation to research and the exercising of public authority.
Complaints	If you wish to complain about the processing of your personal data, you can do so by contacting the supervisory authority: **The Danish Data Protection Agency** **Carl Jacobsens Vej 35** **DK-2500 Valby**

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Appendix H. Questionnaire

Questionnaire to participants in HYBRIDA's deliberative workshops on organoids

QUESTIONS FOR THE MORNING

1. WHICH PARTICIPANT CATEGORY BEST DESCRIBES YOU?

   a. VULNERABLE GROUPS (E.G. PARENTS TO CHILDREN WITH GENETIC DISEASES)
   b. PATIENT (E.G. PATIENTS WITH GENETIC DISEASES SUCH AS CYSTIC FIBROSIS, CANCER, NEUROLOGIC DISEASES, GASTROINTESTINAL DISEASE, MACULAR GENERATION AMONG OTHERS).
   c. DONORS (HEALTHY DONORS DONATING DIFFERENT TYPES OF BIOLOGICAL MATERIAL)
   d. CIVIL SOCIETY ORGANISATIONS, INCLUDING RELIGIOUS ORGANISATIONS
   e. GENERAL PUBLIC
   f. PREFER NOT TO ANSWER THIS QUESTION

2. WHICH AGE GROUP DO YOU BELONG TO?

   a. 18-30 YEARS OLD
   b. 31-40 YEARS OLD
   c. 41-50 YEARS OLD
   d. 51-60 YEARS OLD
   e. 61-70 YEARS OLD
   f. 71-80 YEARS OLD
   g. 81+ YEARS OLD
   h. PREFER NOT TO ANSWER THIS QUESTION

3. WHICH GENDER CATEGORY BEST DESCRIBES YOU?

   a. FEMALE
   b. MALE
   c. NON-BINARY

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d. PREFER NOT TO ANSWER THIS QUESTION

4. DO YOU CONSIDER YOURSELF RELIGIOUS?

a. NO
b. YES, CHRISTIAN (ORTHODOX)
c. YES, CHRISTIAN (CATHOLIC)
d. YES, CHRISTIAN (PROTESTANT)
e. YES, CHRISTIAN (OTHER)
f. YES, MUSLIM (ALL TYPES)
g. YES, OTHER (THAN MUSLIM OR CHRISTIAN)
h. PREFER NOT TO ANSWER THIS QUESTION

5. WHICH WORK MARKET CATEGORY BEST DESCRIBES YOU?

a. EMPLOYEE, LOW INCOME
b. EMPLOYEE, MIDDLE INCOME
c. EMPLOYEE, HIGH INCOME
d. EMPLOYEE, PART-TIME
e. UNEMPLOYED
f. RETIRED
g. STUDENT
h. PREFER NOT TO ANSWER THIS QUESTION

6. WHAT IS YOUR ETHNIC/NATIONAL BACKGROUND?

a. DANISH
b. GREEK
c. ITALIAN
d. EUROPEAN (OTHER THAN DANISH/GREEK/ITALIAN)
e. NON-EUROPEAN
f. PREFER NOT TO ANSWER THIS QUESTION

7. WHICH WORDS BEST DESCRIBE AN ORGANOID? PLEASE CHOOSE UP TO THREE ANSWERS

a. THING
b. HUMAN
c. HALF HUMAN, HALF THING
d. LIVING ORGANISM
e. SOMETHING MECHANICAL

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f. ARTIFICIAL
g. NATURAL
h. CLINICAL TOOL
i. RESEARCH TOOL
j. CELL CULTURE
k. MINI-ORGAN
l. SCIENCE FICTION
m. FRANKENSTEIN-LIKE
n. IN DOUBT/DON'T KNOW
o. PREFER NOT TO ANSWER THIS QUESTION

8. WHICH OF THE FOLLOWING WORDS (OR WORD COMBINATIONS) BEST DESCRIBE HOW YOU FEEL ABOUT ORGANOIDS? PLEASE CHOOSE TWO WORDS.

a. FEAR
b. HOPE
c. POSITIVE EXPECTATION
d. WORRIES
e. PROGRESS
f. DANGER
g. EXCITEMENT
h. OTHER FEELINGS
i. DOES NOT EVOKE ANY FEELINGS
j. PREFER NOT TO ANSWER THIS QUESTION

9. WHO OWNS THE ORGANOIDS?

a. THE DONOR OF THE CELLS
b. THE RESEARCHER/DOCTOR
c. THE HOSPITAL/RESEARCH INSTITUTION/COMPANY/BIOBANK
d. THE STATE
e. DON'T KNOW
f. PREFER NOT TO ANSWER THIS QUESTION

10. WHICH TYPE OF CONSENT SHOULD DONORS GIVE FOR THE USE OF THEIR CELLS FOR ORGANOID RESEARCH?

a. BLANKET CONSENT (I.E. MATERIAL IS DONATED WITHOUT ANY RESTRICTIONS)
b. DYNAMIC CONSENT (I.E. ON-GOING ENGAGEMENT AND COMMUNICATION BETWEEN DONORS AND USERS)
c. DON'T KNOW
d. PREFER NOT TO ANSWER THIS QUESTION

QUESTIONS FOR THE AFTERNOON

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11. WHICH WORDS BEST DESCRIBE AN ORGANOID? PLEASE CHOOSE UP TO THREE ANSWERS

    a. THING
    b. HUMAN
    c. HALF HUMAN, HALF THING
    d. LIVING ORGANISM
    e. SOMETHING MECHANICAL
    f. ARTIFICIAL
    g. NATURAL
    h. CLINICAL TOOL
    i. RESEARCH TOOL
    j. CELL CULTURE
    k. MINI-ORGAN
    l. SCIENCE FICTION
    m. FRANKENSTEIN-LIKE
    n. IN DOUBT/DON'T KNOW
    o. PREFER NOT TO ANSWER THIS QUESTION

12. WHICH OF THE FOLLOWING WORDS (OR WORD COMBINATIONS) BEST DESCRIBE HOW YOU FEEL ABOUT ORGANOIDS? PLEASE CHOOSE TWO WORDS.

    a. FEAR
    b. HOPE
    c. POSITIVE EXPECTATION
    d. WORRIES
    e. PROGRESS
    f. DANGER
    g. EXCITEMENT
    h. OTHER FEELINGS
    i. DOES NOT EVOKE ANY FEELINGS
    j. PREFER NOT TO ANSWER THIS QUESTION

13. WHO OWNS THE ORGANOIDS?

    a. THE DONOR OF THE CELLS
    b. THE RESEARCHER/DOCTOR
    c. THE HOSPITAL/RESEARCH INSTITUTION/COMPANY/BIOBANK
    d. THE STATE
    e. DON'T KNOW
    f. PREFER NOT TO ANSWER THIS QUESTION

14. WHICH TYPE OF CONSENT SHOULD DONORS GIVE FOR THE USE OF THEIR CELLS FOR ORGANOID RESEARCH?

a. BLANKET CONSENT (I.E. MATERIAL IS DONATED WITHOUT ANY RESTRICTIONS)
b. DYNAMIC CONSENT (I.E. ON-GOING ENGAGEMENT AND COMMUNICATION BETWEEN DONORS AND USERS)
c. DON'T KNOW
d. PREFER NOT TO ANSWER THIS QUESTION

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Appendix I. Guiding questions and dilemmas

Two guiding questions for the discussion starting at 13:00

1) How do you think of organoids? What are organoids? How can we best describe them? Do you think of them as human, as a thing, or as something in-between?

2) Discuss the feelings, organoids evoke in you. Which words come to mind when you think about organoids? Are organoids something to be feared – or do you see a hope in them? Which worries and/or positive expectations do you have regarding organoids?

Dilemma 1

Consent, Ownership, and Compensation

Andrew is sick with cancer and hospitalised. His doctor suggests that they make a biopsy of his tumour, so they can grow an organoid in the lab to better understand his form of cancer and see how he (the tumour) reacts to different forms of medicine. Only some of the material from the biopsy is used for the organoid, the rest is stored at the hospital to be used for research. When they start using Andrew's cells for research, they find out that they are especially robust and easy to use in the lab. Therefore, the hospital starts mass producing these cells and use them for general research deceases that are different from Andrew's form of cancer. Years after, a young female researcher at the hospital develops a vaccine for a deadly disease by using cells stemming from the original cells that were taken from Andrew. This is a real scientific breakthrough! The female researcher and the hospital also take out a patent for the vaccine and teams up with a renowned pharmaceutical company that can mass produce the vaccine and sell it world-

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wide. The vaccine is selling fantastically well, and earning are sky high. The female researcher is also awarded a Nobel prize for her pathbreaking research.

- Who owns the cells from the biopsy of Andrew?
- How should the money earned on the vaccine be distributed? Should Andrew (/Andrew's relatives) have a part of it?
- What kind of consent should Andrew and other donors – healthy as well as sick – give when donating cell-material to organoid research?

Dilemma 2

Cerebral Organoids and the issue of consciousness

Dr. Davis is a scientist, who currently develops 'brain organoids' or 'cerebral organoids' to study Alzheimer's disease. Through animal models, it is very difficult to study how the brain develops and to study diseases, which affects the brain. Alzheimer's disease cannot currently be cured, and it is very difficult to evaluate the effect of Alzheimer's medicine with existing research models. The use of cerebral organoids is seen as very promising and as a very big step forward in biomedical research; for Alzheimer's disease, cerebral organoids are likely to help researchers understand why and how the disease develops – an understanding that may further help in the advancement of effective treatments. Currently, Dr. Davis and her colleagues are able to develop cerebral organoids from a human skin biopsy or embryonic tissue. These organoids can resemble parts of the brain. They are around the size of a few millimetres and can be as developed as a few-months-old fetus. The cerebral organoids currently being developed are too primitive to be conscious or sentient (be able to feel pleasure and pain) but they have been shown to exhibit some electrical activity. While Dr. Davis and her team have no interest in developing sentient organoids or organoids with cognitive functions, this may be a research consequence of their future research. Dr. Davis and other brain organoid scientists argue that it is important to start thinking about and developing an ethical framework for how brain organoids are made and used. Some of the major ethical issues relate to whether brain organoids to some degree will be able to exhibit characteristics akin to human sentience or some kind of consciousness. If this is the case, it is argued that it is very important to clarify the moral status of the cerebral organoids as to whether they should be given some human moral status and special protection. How should we, for instance, balance and go about the interest of a patient

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with Alzheimer's disease compared to the potential suffering of an entity that is similar to a very simple lifeform?

- What do you think about these questions?
- If possible, how do you think cerebral organoids can be used in a socially acceptable and morally justifiable way?

Guiding question for afternoon exercise

What are the most important ethical issues that need to be addressed in a regulatory framework for organoid research?

Please write down your answers on a poster.

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Appendix J. Overview of participants

Overview of participants in the Italian deliberative workshop

Participant reference	Participant category	Gender	Age
P1	General public	Male	18-40
P2	General public	Male	18-40
P3	General public	Male	61+
P4	General public	Female	18-40 (absent)
P5	General public	Male	18-40
P6	General public	Female	41-60
P7	CSO	Female	18-40
P8	CSO	Male	18-40
P9	CSO	Male	18-40
P10	CSO	Male	61+
P11	CSO	Male	41-60
P12	Vulnerable group	Male	41-60
P13	Vulnerable group	Female	61+
P14	Vulnerable group	Female	41-60
P15	Patient	Female	61+
P16	Patient	Male	18-40
P17	Patient	Male	41-60
P18	Donor	Male	41-60
P19	Donor	Female	41-60
P20	Donor	Female	61+

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Overview of participants in the Danish deliberative workshop

Participant reference	Participant category	Gender	Age
P1	General public	Male	61+
P2	General public	Male	61+
P3	General public	Male	18-40
P4	General public	Male	61+
P5	General public	Male	18-40
P6	General public	Male	41-60
P7	CSO	Female	61+
P8	CSO	Female	41-60
P9	CSO	Female	41-60
P10	CSO	Female	41-60
P11	CSO	Female	61+
P12	CSO	Male	41-60
P13	Vulnerable group	Male	18-40
P14	Vulnerable group	Female	41-60
P15	Patient	Male	61+
P16	Patient	Male	61+
P17	Patient	Male	18-40
P18	Patient	Male	41-60
P19	Donor	Male	41-60
P20	Donor	Female	18-40

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Overview of participants in the Greek deliberative workshop

Participant reference	Participant category	Gender	Age
P1	General public	Female	18-30
P2	General public	Non-binary	31-40
P3	General public	Female	31-40
P4	General public	Male	31-40
P5	General public	Male	41-50
P6	General public	Female	41-50
P7	General public	Male	31-40
P8	General public	Male	31-40
P9	General public	Male	18-30
P10	CSO	Male	61+
P11	Patient	Female	31-40
P12	Donor	Male	41-50

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Appendix K. Overview of expert presentations

Expert presentations in the Italian deliberation

1. Teresa Rinaldi, a graduate in biological sciences, currently works at the Department of Biology and Biotechnology "Charles Darwin" of the Sapienza University of Rome, where she teaches pharmacogenomics, fermentation biotechnology and applied geosciences and bio conservation laboratory.
The presentation entitled "Organoids" introduced the topic in general terms, explaining what organoids are, by which cells and how they are produced and the various types of organoids that exist today. The expert illustrated the possible applications of this new biotechnology and the ethical questions it raises. Possible fields of application include developmental biology, regenerative medicine and personalized medicine. In particular, the expert illustrated how organoids can be used as a model for the study of genetic diseases, infectious diseases and for the study of tumors. Finally, some ethical issues raised by the use of organoids were pointed out, for example: the moral and legal status of organoids, the use of gene editing, the creation of chimeras, marketing and storage in biobanks.

2. Andrea Lavazza is Senior Research Fellow in Neuroethics at the Centro Universitario Internazionale di Arezzo and Adjunct Professor at the University of Pavia. He is also a lecturer at the Master of Forensic Psychopathology and Neuropsychology at the Faculty of Psychology, University of Padua.
The presentation with the title "Cerebral organoids and ethical questions" focused on a particular type of organoid: brain organoids. The expert outlined a number of ethical issues, some relating to organoids in general (such as issues relating to informed consent and ownership of the cells used) and some specifically relating to brain organoids (e.g. the transfer of brain organoids into animal models chimeric.). After an overview of the various issues raised by brain organoids, the professor explored the question of whether organoids can develop a form of consciousness and how this possibility affects their moral status.

Expert presentations in the Greek deliberation

1. Dr Olga Tzortzatou-Nanopoulou, Legal counselor and President of the Intellectual Property Committee of the Biomedical Research Foundation of the Academy of Athens (BRFAA), European Commission Expert, specialised in GDPR/informed consent issues and IP/patents:

The presentation with the title "Information Society and the current role of bioethics: Personal Data and Informed consent" focused on the existing regulation on biomedical research, regarding, particularly to informed consent. The expert referred to the International Chapter of Principles for Sharing Data and Biospecimen, to the GDPR regulation and crucial bioethical questions. She, also, presented relevant ELSI issues, as well as the role of Bioethics Committees. Finally, she, presented some cases of breach of the aforementioned regulations.

2. Dr Miltos Ladikas, senior researcher at the Institute of Technology Assessment and Systems Analysis, Karlsruhe Institute of Technology, Germany, adviser to the European Commission, the European Research Council, the European & Developing Countries Clinical Countries Partnership, and a number of National Research Organisations, on social-ethical issues in Science & Technology developments, specialised in Global aspects of Technology Assessment, Responsible Innovation, Ethics in Science and Technology Policy, as well as, Science Diplomacy:

The presentation with the title "Technology Assessment and Policy making" was relevant to the connection of Technology Assessment with policy making. The expert explained the procedure of policy making on a new technology and how the public opinion is introduced into this procedure. He proceeded to the description of policy making system of some European countries and he notified the importance of the public participation to the technology assessment and policy making.

Expert presentations in the Danish deliberation

Presentation 1. Thomas Lykke-Møller Sørensen, Associate Professor at the Department of Biological and Chemical Engineering, Aarhus University.

The presentation was based on his experience in working with organoids. During the presentation the participants was introduced to information about the development in organoid technology, and how organoids are grown and used in laboratories. The expert introduced different kinds of organoids (for example bowel, brain, and cancer), and gave different examples on how organoids are used, e.g. for research in disease development based on studies with healthy and sick tissue, drug development. Further, it included pictures of organoids during the development, and a video of a bowel organoid made with a mix of different cells, which were able to react with movement when stimulated.

Presentation 2. Morten Dige, Associate Professor at the School of Culture and Society, Aarhus University. This presentation focused on different ethical questions related to organoid research. The main focus was

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questions on moral status, informed consent related to the use of human tissue, and whether it is problematic to make artificial human organoids in general. The presentation included information on what moral status is, and how the attitudes on who/what has a moral status has changed over time.

The participants were also introduced to different types of consent, and how consent is related to governance in organoid research, and the relevance of commercialization, patents, and consent as issues in relation to the handling, distributing, and storing peoples' stem cells.

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