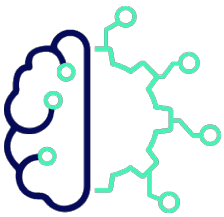
HYBRIDA



HYBRIDA

D3.1: Map report of Normative, Research Ethics and Research Integrity frameworks

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Reviewer: Charles Pence
Editors: Costas A. Charitidis, Jan Helge Solbakk

Project title: Embedding a comprehensive ethical dimension to organoid-based research and relating technologies

Project acronym: HYBRIDA

HYBRIDA

Coordination and Support Action
H2020-SwafS-28-2020

Project full title

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

Project acronym

HYBRIDA

Grant Agreement no.

101006012

D3.1: Map of Normative, Research Ethics and Research Integrity frameworks

Deliverable factsheet:

Project Title:	HYBRIDA
Title of Deliverable:	Map of Normative, Research ethics and Research Integrity frameworks
Work Package:	3
Due date according to contract:	M6
Editors:	Costas A. Charitidis, Jan Helge Solbakk
Authors:	Panagiotis Kavouras, Eleni Spyrakou, Vana Stavridi, Anastasia Deligiaouri
Reviewer (*of the July 2021 version*):	Charles Pence

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

ABSTRACT:	The nature of organoids, as entities that can be categorized neither as objects nor as things, is a source of uncertainty on their ethical and legal dimensions and on the efficiency of the current research ethics, legal and research integrity frameworks that regulate organoid research. This report presents the findings of a systematic scoping review study, with the aim tocollect and elaborate on the ongoing debates, regarding the ethical,legal/normative and research integrity-related dimensions of organoid research and compare them with the debates that have occurred in the past with regard to similar technologies (i.e. induced pluripotent stem cells, embryonic stem cell, gene editing and cloning technologies). The findings indicate that the majority of ethical issues pertaining to these similar fields of research and technologies converge in organoid research and more acutely in the research on cerebroids and gastruloids. Open issues are related to the moral status of a gastruloid, the consciousness of a cerebroid, and the naturalness and artificialness of all types of organoids. In addition, all issues related to harvesting, storing and using for research purposes human-derived materials emerge. These last issues relate to both research ethics, like debates on the appropriate type of informed consent, and return of results/handling incidental findings, as well as research integrity, like how to strike the right balance between openess and privacy of data, FAIRification of data, harmonisation of data and metadata across biobanks, i.e. issues that fall under the umbrella of research data management. The main issue of the existing legal framework is that there is still uncertainty on the potential applications of organoids. Legislation is expected to provide protection and set the rules for scientific research. Legal provisions are general and abstract but, at the same time, very specific on the level of protection they provide. In general, new advancements in health research should be examined under the prism of existing legislation by taking into consideration the rapid growing scientific evidence while ensuring the protection of human life and human dignity as their main priority.

Keyword List:	Organoid, Gene-editing, Cloning, induced Pluriponent Stem Cells(iPCS), embryonic Pluripotent Stem Cells (PSC), Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), Chimera,Precision medicine, Personalised medicine, Drug development, Ethics, Bioethics, Research Integrity, Responsible research, Responsible science, Moral status, Regulatory,Biobank, Operational guidelines, Legal, Regulatory, Regulation, Code of conduct, Ethical framework.

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Revision history:

VERSION	DATE	Revised by	Reason
0.1	11June 2021	Vana Stavridi, Eleni Spyrakou, Panagiotis Kavouras	1st draft
0.2	25 June 2021	Anastasia Deligiaouri, Vana Stavridi, Eleni Spyrakou	2nd draft
0.3	30 June 2021	Panagiotis Kavouras	3rd draft
0.4	05 July 2021	Vana Stavridi, Eleni Spyrakou	4rd draft
0.5	12 July 2021	Anastasia Deligiaouri	5th draft
0.6	14 July 2021	Panagiotis Kavouras	6th draft
0.7	16 July 2021	Costas A. Charitidis, Jan Helge Solbakk	Comments on the content
0.8	23 July 2021	Anastasia Deligiaouri, Vana Stavridi, Eleni Spyrakou, Panagiotis Kavouras	7th draft
0.9	27 July 2021	Charles Pence	Review of the 7th draft
1.1	28 July 2021	Vana Stavridi, Eleni Spyrakou, Anastasia Deligiaouri, Panagiotis Kavouras	8th draft
1.2	29 July 2021	Panagiotis Kavouras	Pre-final version
1.3	30 July 2021	Costas Charitidis	Final version for the coordinator
1.0	31 July 2021	Jan Helge Solbakk	Final version
1.1	18 July 2022	Panagiotis Kavouras	Addition to Part 3 – Section 14
1.2	19 July 2022	Vana Stavridi, Eleni Spyrakou	Review of Part 3 – Section 14
1.3	20 July 2022	Costas Charitidis	Final version for the coordinator
2.0	19 August 2022	Jan Helge Solbakk	Final version

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Part 1: INTRODUCTION

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1 The HYBRIDA project

An organoid is a self-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, especially, the functional properties of different organs, both human and non-human such as the retina, heart, brain, intestine, kidney, pancreas, liver, inner ear and skin.

Since Roman 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 disruptive research and innovation – that challenge this conceptual, epistemological and regulatory dualism. More precisely, the dualistic normative framework pertaining to health and life science research are disrupted by three different kinds of uncertainty (Figure 1).

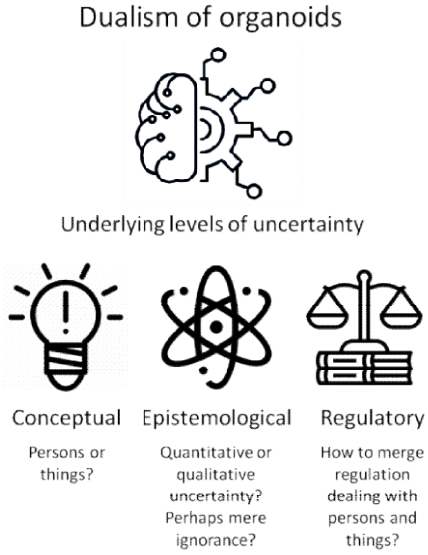

Figure 1: Levels of uncertainty stemming from the dual nature of organoids.

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

Second, ***epistemological and methodological uncertainty*****:** How do we address forms of uncertainty that cannot be evaluated through the use of statistical methods, i.e. risk assessment? This is particularly pertinent where organoids are intended for personalized or precision medicine, where the number of research subjects with a certain characteristic 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. Epistemological uncertainty comes in two kinds, which can be categorized as qualitative, or strict, uncertainty and ignorance or non-knowledge. Qualitative or strict uncertainty is a form of uncertainty where possible positive and negative outcomes can be identified in advance but, 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).

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

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

2 Executive summary

The yet vague nature of organoids is a source of uncertainty with regard to their ethical and legal dimensions, as well as with regard to the efficiency of the current ethical, legal and research integrity frameworks that regulate organoid research. Starting from this regulatory ambiguity, the authors of this report have conducted a systematic scoping review, with the aim to collect and elaborate on the ongoing debates regarding the ethical, legal and research integrity-related dimensions of organoid research and compare them with the debates that have occurred in the past with regard to relevant technologies, i.e. induced pluripotent stem cells, embryonic stem cell technologies, gene editing and cloning.

The findings of the systematic scoping review indicate that virtually all ethical issues pertaining to these pre-existing fields of research converge in organoid research and more acutely in the research on cerebroids (brain organoids), and gastruloids (cell clusters imitating the human embryo during the initial stages of embryonic development). These are questions about the moral status of a gastruloid, the consciousness of a cerebroid, and the naturalness and artificialness of all types of organoids. In addition, the fact that the "seed" of an organoid is a human stem cell gives rise to issues related to harvesting, storage and use for research purposes of human-derived materials. These relate to both research ethics, like debates on the appropriate type of informed consent, and return of results/handling of incidental findings, as well as research integrity and research data management issues.

The dilemmas and ambiguities in relation to organoid research refer to their nature and their potential applications and not to legal provisions that set specific rules and principles to be respected on relevant issues as these are described in a strict manner in legal texts. The main problem is that there is still uncertainty and doubt on what to anticipate with regard to the development of such forms of research and developments. Legislation is expected to provide protection and set the rules for scientific research. Legal provisions are general and abstract but, at the same time, very specific with regard to the level or protection they provide. In general, new advancements in health research should be examined under the prism of existing legislation by taking into consideration the rapid growth of such research while ensuring the protection of human life and human dignity as their main priority.

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3 How to read this report

The aim of D3.1 is to present a map of ethical, legal and research integrity frameworks and an outline of the ongoing ethical, legal and research integrity-related debates. This report is structured into four parts: 1. Introduction, 2. Methodology, 3. Results and 4. Annexes. The reading of this report can be comprehensive, by going through all parts, but can also be made in a modular fashion, according to the interests of the reader. In addition, Part 3 has a modular character in itself; sections 11, 12 and 13 can be read in isolation from one another, depending on the specific interests of the reader. Section 14 that contains the preliminary results of the expert interviews (see disclaimer in section 14) can be more closely paired with section 11 that treats the research ethics frameworks and ethics-related debates. Below there is a table in lieu of a suggestive short guide on how to read this report.

Table 3.1: Reading guide in relation to the reader's interests

Reader's interests	What to read
An outline of the context and the most important results	Sections 1, 2, 11.6, 12.6, 13.4 and 15
The context of this report and comprehensive view of the results	Parts 1 and 3
The context of this report, detailed information on the methodology followed and comprehensive view of the results	Parts 1 – 3
The context of this report and comprehensive view of the research ethics-related content	Part 1 and Sections 11 and 14
The context of this report and comprehensive view of the legal/normative content	Part 1 and Section 12
The context of this report and comprehensive view of the research integrity-related content	Part 1 and Section 13
Documentation of GDPR compliance of the experts' interview study	Part 4

4 Outputs to other work packages

WP3 is one of the three HYBRIDA WPs, together with WP1 and WP2 that is bound to provide its findings quite early in the project's timeline. The following outputs per WP (the flow of information from WP3 is depicted in Figure 2) are foreseen by HYBRIDA's Description of Action (DoA):

- **To WP4:** Responses from the interviewees that will aid the engagement processes (NTUA has received input from the AU team during the planning phase of WP3)
- **To WP5:** Overview of existing Research Integrity guidelines, Operational guidelines, and Codes of Conduct that are relevant to research on organoids and related technologies (gene-editing, cloning technologies and IPS technologies, and embryonic stem cell technologies) – i.e. elements from the WP3 repository

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- **To WP6:** Overview of existing Ethical and Normative frameworks that are relevant to research on organoids and related technologies (gene-editing, cloning technologies and IPS technologies, and embryonic stem cell technologies) – i.e. elements from the WP3 repository

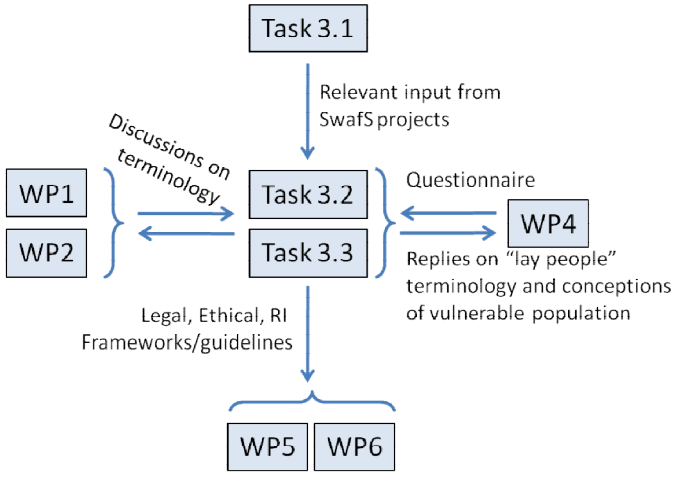

Figure 2: A flowchart depicting the flow of information from and to WP3.

NTUA, acting proactively, held a series of meetings with all HYBRIDA beneficiaries in order:

- To define in detail their needs from WP3
- Whether these needs could be fulfilled by solely adhering to the DoA
- Whether any additional "*ad hoc*" inputs were needed from WP3

The meetings that took place, the composition of the attendees and the points that were discussed are listed in Table 4.1.

Table 4.1: Overview of WP3 preparatory meetings

Date	Attendees	Aims
27 November 2020	All HYBRIDA partners	Set a rough plan for WP3
28January 2021	WP4 partners	Action points for the smooth cooperation between WP3 and WP4. Specifically: • Elements that have to be collected through the expert interviews (WP3) that would help designing the engagement processes of WP4. • Discussion on the methodology for the Scoping Review
1 February 2021	All WP3 partners	Agree on the detailed plan for WP3 activities and review the questionnaire
12 February 2021	All WP3 partners	Presentation of the pre-final version of the

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		Scoping review protocol

The agreed additional, with respect to the DoA, activities requested from NTUA in order for the cooperation with other WPs to be facilitated were the following:

- ✓ WP4 leaders received the responses from the expert interviews with regard to their notion of "vulnerable groups" well in advance of the D3.1 deadline
- ✓ WP6 leader received the collection of peer-reviewed articles (in *.bib format) well in advance of the D3.1 deadline.

5 Timeline of work package 3 activities

WP3 had to streamline a significant amount of different tasks in a relatively short time (6 months) from the initiation of HYBRIDA. This is the reason why WP3 leaders started to plan all activities foreseen by the DoA before the official initiation of the project. In Figure 3, the timeline of WP3 activities is depicted. The NTUA team initiated a survey at the beginning of December 2020 with the aim to find the most appropriate review methodology for Tasks 3.2 and 3.3 (red bar at Figure 3). In parallel, all necessary documentation describing the protocol of the conduct of the expert interviews was prepared and submitted on 15 December 2020 to the Research Ethics and Deontology Committee of NTUA. The protocol was approved on 14 January 2021 (Green bar at Figure 3).

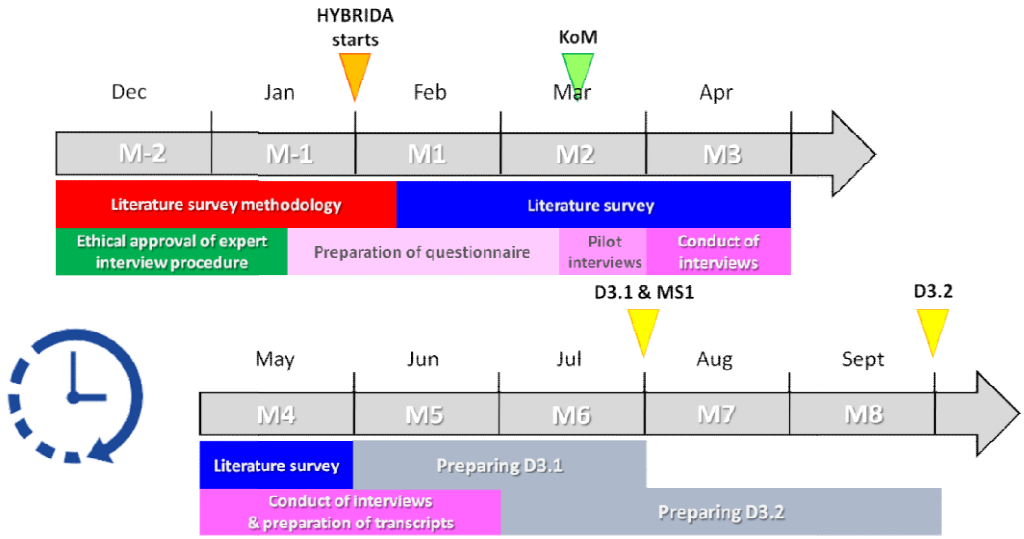

Figure 3: Timeline of WP3 activities. Orange arrow indicates the official starting date of HYBRIDA, the green arrow indicates the date of the kick off meeting and yellow arrows indicate the delivery dates of D3.1 and D3.2, as well as the only WP3 milestone.

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The preparation of the questionnaire was initiated in mid January 2021 and was concluded at the end of March 2021, i.e. at M1 of the project (light and dark pink bar at Figure 3). The light pink bar corresponds to the stage where NTUA prepared the first drafts of the questionnaire with the help of WP3 partners and the dark pink bar corresponds to the stage where the pilot interviews were conducted with two members of the HYBRIDA Advisory Board. The literature survey was initiated at the beginning of February 2021 and ended at the end of May 2021 (blue bar at Figure 3) and the conduct of interviews was foreseen to start at the beginning of April and end at the end of June (magenta bar at Figure 3). However, due to the difficulties encountered in finding interviewees the interview phase will last until the end of August 2021. The preparation of D3.1 was mainly done in June and July 2021 (grey bar at Figure 3).

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Part 2: METHODOLOGY

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6 Underlying methodology

Deliverable 3.1 has been drafted to present the outcomes of a wide survey, i.e. a map of Normative, Research ethics and Research Integrity frameworks. The type of survey used for D3.1 was a **Systematic Scoping Review**. This type of review is a relatively new approach to evidence synthesis and differs from systematic reviews in its purpose and aims. The purpose of a scoping review is to provide an overview of available research evidence without producing a summary answer to a discrete research question. The reasons for choosing a Systematic Scoping Review are the following:

- A mixed-methods study was necessary, where, in addition to bibliographic research, a series of expert interviews were carried out. Methodologically, this approach falls into the Scoping Review type of study.[1,2]
- An iterative method was followed, where the initial protocol was fine-tuned according to the efficiency of the progress of the review process (*see section 7.5.5 for details*).[3,4]
- The resources planned to be reviewed were of a complex and heterogeneous nature:
    - peer reviewed publications
    - grey literature (openly available resources like deliverables, policy briefs, and guidelines from relevant Science with and for Society (SwafS) projects) that were mapped within Task 3.1
    - ethical/legal guidelines from international and European organisations, and selected countries
    - primary/secondary legislation, treaties, international conventions (*see sections 6.1 and 6.3 for details*)
- The aims of Task 3.2 (that informs D3.1) as specified in the DoA was to map ethical dimensions and elaborate on the debates on regulatory, ethical and integrity-related dimensions. In other words, it was not meant to provide a comprehensive synopsis of specific qualitative or quantitative results (e.g. to provide feedback for a meta-analysis or meta-research).

7 Systematic scoping review protocol

The protocol for the systematic scoping review was drafted by following the comprehensive guidelines described in Peters *et al*. (2015) and through consultation with the WP3 partners (see section 3).Below there is a detailed description of the elements that comprise the protocol.

[1] M.J. Grant, A. Booth "A typology of reviews: an analysis of 14 review types and associated methodologies" *Health Information and Libraries Journal* 26 (2009) 91–108.
[2] A.C. Tricco, J. Antony, W. Zarin, L. Strifler, M. Ghassemi, J. Ivory, L. Perrier, B. Hutton, D. Moher, S.E. Straus "A scoping review of rapid review methods" RMC Medicine 13 (2015) 224.
[3] D. Levac, H. Colquhoun, K.K. O'Brien "Scoping studies: advancing the methodology" *Implementation Science*5 (2010) 69.
[4] M.D.J. Peters, C.M. Godfrey, H. Khalil, P. McInerney, D. Parker, C.B. Soares "Guidance for conducting systematic scoping reviews" *International Journal of Evidence-Based Healthcare* 13 (2015) 141-146.

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7.1 Set the objective of Task 3.2

Mapping ethical dimensions and elaborating on the debates that have occurred in the past, and are still ongoing, regarding the regulatory, ethical and integrity-related dimensions in organoid and similar technologies.[5]The above aims were accomplished by the following two main studies:

a. By conducting a Systematic Scoping Review of existing (and emerging, where possible) regulatory, RE and RI frameworks regarding organoid research and similar technologies, having a global perspective (i.e. EC, Germany, Great Britain, USA, Israel, Russia, China, Japan, and Australia)
b. By conducting 10 interviews with experts that work in Europe.

Note: The Systematic Scoping Review protocol was also used for the study of Task 3.3, namely the identification and comparison of relevant regulatory environments and cultures that deal with the selected technologies and will gather knowledge on existing (and emerging) Codes of Conduct, Standard Operating Procedures and Guidelines in organoid and similar technologies.While the underlying Scoping Review protocol was the same as for Task 3.2, the research questions, inclusion criteria, and selection of interviewees was adapted to the needs of Task 3.3. More information will be included in D3.2 that will be informed by the work conducted within Task 3.3.

7.2 Review questions and objectives

The research questions were drafted by following the description of Task 3.2. The research questions are the following:

- What are the **ethical dimensions** (i.e. ethical issues) in organoid and similar technologies?
- Which **debates** have occurred in the past, and are still ongoing, regarding the *regulatory* dimensions in organoid and similar technologies?
- Which **debates** have occurred in the past, and are still ongoing, regarding the *ethical* dimensions in organoid and similar technologies?
- Which **debates** have occurred in the past, and are still ongoing, regarding the *integrity-related* dimensions in organoid and similar technologies?

7.3 Inclusion and exclusion criteria

As with systematic reviews, inclusion criteria provide a guide to understanding what is proposed by the scoping review and, more importantly, a guide for the researchers themselves to base decisions on the sources to be included in the scoping review. The rationale or justification for each of the inclusion criteria are explained in detail in the following points, taking into account the type of input needed, as presented at section 7.2.

- **Ethics and RI frameworks**

[5] Gene-editing, cloning technologies, induced pluripotent stem cell technologies, and embryonic stem cell technologies. These technologies were recognized as the most relevant to organoid research, by the consortium's biomedical experts, and have been listed at the proposal document, as well as at the Grant Agreement.

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Inclusion criteria:

- Policy documents from UN, UNESCO, WHO, EC, USA, Japan, China, Israel, Russia, Australia (Databases: Google search)
- Peer reviewed publications (Database: Hellenic Academic Libraries Link – HEALlink: https://www.heal-link.gr/en/bibliographic-full-text-databases/)

Exclusion criteria:

- Conference papers
- Pre-prints
- Non-English texts.

- **Legal frameworks**

While the same steps can be followed for the mapping of regulatory and legal framework, apart from Google search, targeted search in legal databases was also carried out in order to retrieve legal documents. The main online repository for EU legislation is EUR Lex (https://eur-lex.europa.eu/homepage.html?locale=en). Documents retrieved from relevant bioethics committees or institutions and agencies involved in the relevant field were also consulted. Thus, the legal framework will be analyzed essentially by following two steps.

a. Delineating the legal/regulatory framework as this accrues from legal texts. The results for this stage will come from legal texts from law repositories
b. Provide, wherever needed, clarifications on how legal terms are being understood or being implemented by referring to judicial decisions.
c. Wherever there is a good analysis we cite 'grey literature' from studies or relevant publications that highlight the main points of contestation.

For the legal framework the following critical variables were considered:

1. International Conventions that apply in and beyond the European area and constitute the International legal framework. We also examine regional legislation such as Council of Europe legislation.
2. For EU legislation. First, relevant articles in Treaties were examined. Then, European legislation which applies to all member statesas it is issued (*regulations)* and *directives* that need to be ratified by Member States' internal legislative procedures or adjust their legislation to meet the objectives to gain power. Then, soft law such as recommendations that are not binding for Member States and suggest an action but do not impose a legal obligation, and *opinions* which are a non-binding instrument, were consulted.
3. In this study there was not conducted an analysis of national regulatory frameworks, but just a reference to some of their sources if they were considered appropriate.
4. Relevant opinions from established committees or professional bodies also clarify legal issues occasionally.
5. Medical Ethics (codes of conduct in health-related professions) are also important in designating the limits of health practice.

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Based on the aforementioned below the main inclusion and exclusion criteria used to identify relevant material for the legal analysis are described.

Inclusion criteria: Type of resources to be included in the review, as they are differentiated with regard to the type of input needed.

Inclusion criteria:

- International Conventions
- EU legislation (Treaties, Regulations, Directives, Recommendations, Opinions)
- Wherever there is a specific interest or a case of importance we will also expand our research and include national perspectives from Germany, Great Britain, USA, Israel, Russia, China, Japan, and Australia (the rationale below gives some glimpses into the differentiation we have to make with regard to the different sources in the various national settings)

Exclusion criteria:

- Non-English texts.
- Texts that are outdated as new legislation come into force.

7.4 Context (geographical, cultural, disciplinary factors)

Task 3.2 had a global perspective with regard to the resources retrieved. As a result, the scoping review was inclusive with regard to geographical and cultural factors. The disciplinary factors were those described in the DoA and focus on biomedical research and, more specifically, on research on organoids, gene-editing, cloning technologies, induced pluripotent stem cell technologies, and embryonic stem cell technologies, as described in section 6.1.

7.5 Searching

7.5.1 Initial limited search

Apilotstudy was applied with an initial set of keywords. This set included keywords that straightforwardly reflected the technologies under study (organoids, gene-editing, cloning technologies, induced pluripotent stem cell technologies, and embryonic stem cell technologies), the fields or areas of debates (normative/legal, research ethics, research integrity), and the forms of target documents (guidelines, standard operating procedures, framework), as described in section 6.2. According to the results of this pilot study the authors included additional keywords/search terms that were extracted from the Titles, Keywords, and Abstracts of the retrieved resources.

7.5.2 Categorised search terms

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The search terms that were used for the full-scale search are listedin Table 7.1. The search strategy followed was the following:

- For an article to be includedin the Scoping Review results it had to combine at least one term from at least two of the three different search term categories
- These terms had to be found inthe Article Title or Author Keywords or in the Abstract.

There were cases, like "Drug development", in which an overwhelming number of publications was returned from the system. In those cases (marked in the table below with red text) the authors opted for including the specific search terms only int the Article Title or in the Author Keywords.

Table 7.1: Keyword list used for the search of articles.

Category	Search key
Technology	*Organoids, Gene-editing, Cloning, IPs, iPCS, iPSC, iPC, PSC, embryonic PSC, ESC, EPSC, CRISPR, Embryonic stem cell (technologies), Chimeric entities, Chimeras, In vitro tissues, Primary tissues, Hybrid, Synthetic biology, Cell biology, In vitro testing, Organ culture, Genetic engineering, Genetic modification, Genetic manipulation, Genomics, Human genetic intervention, Animal testing, Precision medicine, Personalised medicine, Drug development (only title and only keywords), Organ-on-a-chip, Mini-organ, Transplantation.*
Fields of interest (related to the non-biomedical fields)	*Ethics, Bioethics, Research Integrity, Responsible research, Responsible science, Moral status, regulatory, (Organoid) Biobanking*
Form	*Operational guidelines, Legal, Regulatory, Regulation, Code of conduct, Ethical framework*
Other	*Cultural, Cultural environment, Debate*

7.5.3 Full-scale search

a. Peer reviewed articles

The full-scale search was composed of the following steps:

1. Full-scale search was performed from the search functionality of the HEALlink system. The metadata of the retrieved articles, i.e. full bibliographic data and abstracts, were collected in txt format. Then the authors went through the information gathered and performed an initial screening (**SCREEN_01**) of the retrieved articles. The full procedure is illustrated in the flow diagrams of the scoping review process that are presented separately for each one of the three different sub-surveys, in Sections 10, 11 and 12.

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2. All remaining articles were imported in the Mendeley desktop software; usually the authors included only the title and all bibliographic data were retrieved automatically from Mendeley. In some exceptional cases, where the title was not indicative and Mendeley retrieved the wrong resource, the authors used the DOI of the article that was retrieved from the previous step of the full-scale search. If the use of DOI also did not retrieve the correct document the specific item was removed from the Scoping Review results.

3. Removal of duplicates (**SCREEN_02**).

4. The authors worked in pairs and categorized all articles in three basic categories: Research Ethics, Law and Research Integrity. Each article could belong to more than one category. In practical terms, the categorization was made in Mendeley by assigning Tags to each retrieved article.

5. The NTUA team split in three groups, reflecting the three broad categories, downloaded all PDF files and initiated the process of reading through the downloaded documents. There were a few cases, where the document could not be downloaded; these items were removed from the Scoping Review results (**SCREEN_03**).

6. Reading through the articles revealed that a number of them were not relevant to the Scoping Review study. The non-relevance of these articles stemmed from the following characteristics:
    a. Articles that were totally irrelevant to our study
    b. They were of generic character, so the input they would provide was redundant
    c. The connection to the study proved to be superficial, as in case (a) the input they would provide was redundant
    d. Articles that fell outside the geographical scope defined (see 6.3)
    e. Articles that were relevant with regard to the technology under study (e.g. Gene editing), but not specifically relevant to the applications of this technology (e.g. Gene editing in plants or animals)

    These articles were also removed from the Scoping Review results (**SCREEN_03**).

While searching backwards in time for articles and especially before 2000 we have implemented more strict exclusion criteria as there is a great likelihood for legislation or any relevant legal issues mentioned in these articled to be outdated.

7. As soon as all retrieved articles were read, they were saved in a new folder that comprised the “WP3 repository”. The title of the article was put as the name of the PDF file; this collection of articles is the final result of the Scoping Review for the peer reviewed documents.

b. Grey literature

Grey literature was retrieved by searching through the internet via Google Search. The search terms used were those reported in section 6.5.2.

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7.5.4Search among references of the resources found from the full-scale research

One additional step was needed for the Research Integrity-related part of the Scoping Review. Since the full-scale search, until step 7, did not result in as many documents as in the other two broad categories, the NTUA team decided to scan the references of the retrieved peer reviewed articles and of the Research Integrity-related Scoping Review results.

8. The group assigned to Research Integrity-related documents went through all references of the retrieved documents of step 7, in order to expand the results for this broad category. According to their title the references were categorized as irrelevant, possibly relevant and relevant. The second and third categories of references were downloaded and the procedure of steps 6 and 7 was repeated.

7.5.5 Critical review of the protocol and revision (if needed), also in view of the results of the pilot interviews

The original protocol of the Systematic Scoping Review study was revised as soon as the pilot expert interviews were conducted and the initial test search was concluded (see Section 8). The element of the systematic scoping review study that was revised was the exclusion criteria. Specifically:

- The geographic context was narrowed down
- Articles relevant to plant and animal research were removed
- Articles relevant to the legal/normative part of this study that were published before 2000 were removed, with the exception of the ones referring to Cloning technologies.

In section 6.5.3 there is a detailed description of the final set of inclusion/exclusion criteria.

7.5.6Feed all resources retrieved from Task 3.1

A final step was to include the findings of Task 3.1. The projects scanned for relevant results (deliverables, policy briefs) are listed in Table 7.2.

Table 7.2: SwafS projects scanned for relevant results.

Project acronym	Relevant to HYBRIDA area
SIENNA	• Frameworks to help develop RE protocols, professional ethical codes and better legal frameworks, for AI, Robotics and Human Genomics & Enhancement
PANELFIT	• Operational standards and practical guidelines able to reduce the ethical and legal issues posed by ICT technologies • Concrete improvements to the current regulatory and governance framework

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SHERPA	• Workbook on responsible development of Smart Information Systems • Technical and regulatory proposals for Smart Information Systems related technologies
PRINTEGER	• Develop improving integrity policies of national and international research organisations, but also by providing better tools for research leaders and managers
PRO-RES	• Develop a RE and RI framework devised cooperatively with, and seen as acceptable by, the full range of relevant stakeholders • Foster informed policy making
SOPs4RI	• Developing Standard Operating Procedures for RPOs to adhere to the highest standards of RI
EnTIRE	• Rendering compliance with EU, national and discipline-specific RE+RI standards and legislation easy to find and understand
TRUST	• Counteract the practice of "Ethics dumping" in research • Co-developing with vulnerable populations tools and mechanisms for the improvement of research governance structures
i-CONSENT	• Improve the information received by patients from clinical studies • Develop guidelines to improve Informed Consent process, including vulnerable populations, under a gender perspective
PRO-Ethics	• Develop an ethics framework for involvement of populations in desired change or innovation in people's lives and environments
TRESCA	• How to foster public trust in science communication
GRACE	• Spreading and embedding RRI in the European Research Area
NEWSERA	• Analyse and evaluate the complex and multidirectional science communication strategies, including digital and non-digital ones
EU-Citizen.Science	• Promote interdisciplinary, cross-border, cross-sector collaboration

Despite the anticipated relation of HYBRIDA with the projects listed above, the ones that had publicly available outputs (i.e. deliverables, policy briefs, brochures) with a meaningful relevance were i-CONSENT, PRINTEGER, GRACE and TRUST. The only project that contributed, in a substantive manner, to

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the knowledge base of WP3 of HYBRIDA was the SIENNA project. The deliverables that were used to inform D3.1 and are going to be used to inform D3.2 are listed in Annex 5.

8 Expert interviews

The interviews relevant to Task 3.2 that were to be obtained until the middle of July 2021 were targeting experts in Organoid (and similar technologies) research, Research Ethics, Law and Research Integrity who work in Europe. This was initially decided taking into account the focus of the Task 3.2 study, i.e. to map the normative, Research Ethics and Integrity framework of organoid and similar technologies with a main interest in the European Research Area. This interest was based on the fact that HYBRIDA's main outcomes (i.e. Code of Conduct, supplement to the European Code of Conduct for Research Integrity) will be implemented mainly in European Research Performing Organisations.

The initial intention of the authors was to feed the study of Task 3.2 only with the interview outcomes of experts who work in Europe and to feed the study of Task 3.3 (on cultural differences and their effect of governance of organoid research) only with the interview outcomes of experts who work outside Europe. However, the pilot interviews with HYBRIDA's Advisory Board members who work in European and non-Europe countries proved that their input was also relevant for the studies of both Tasks 3.2 and 3.3. This was because experts working in Europe had personal experience either from working outside Europe, for a period of time, or cooperating with non-European experts. Similarly, non-European experts had personal experience of either working in Europe, for a period of time, or cooperating with European experts. So both European and non-European experts had direct or indirect experience of the normative, Research Ethics and Research Integrity frameworks, the debates and the cultural factors that shape their field of research both inside and outside Europe.

This led to the conclusion that the division of the interviewees working in European and non-European settings did not serve the initial purpose. As a result, the authors decided that the outcomes of all twenty interviews were going to feed both D3.1 and D3.2. To achieve this, the questionnaire for all expert interviews was the same. Specifically, it was differentiated taking into account the expertise of the interviewee but not the country/continent of her/his affiliated occupation.

8.1 Context of interviews

- Geographical context: HYBRIDA is mostly concerned with the ethical implications of organoid research in the European context, but as described above there is an interest to gain insights from experts who work all over the world. As a result, half of the experts interviewed or bound to be interviewed work in Europe and the other half works in the rest of the world. All interviews are going to be analysed in the context of Tasks 3.2 and 3.3. For the context of Task 3.2 the interviews will provide input that will mostly target the upcoming/foreseeable RE/RI/legislative frameworks and describing ethical debates.
- Disciplinary context: The expertise of the interviewees was chosen in order to reflect the different types of outcomes desired (legal and ethical framework, RI guidelines, operational guidelines). So

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our interviewees are experts in organoid research or similar technologies, bioethicists, legal experts, and research integrity experts.

8.2 Drafting procedure of the questionnaires

The questionnaires were drafted via an elaborate procedure that was initiated via two teleconferences on the 28th of January and 1st of February 2021, with WP4 leaders and all WP3 members respectively. During these two teleconferences it was decided that 3 different questionnaires must be prepared that would be targeting experts in Organoid research, Research Ethics & Integrity, and Law. The NTUA team prepared a matrix with the three different types of questionnaires with probes and comments on the aim of each question (the final version of it can be found at Annex 3). This matrix was discussed during a teleconference with all WP3 members on the 12th of February, when the pre-final Scoping Review protocol was discussed.

The pre-final question matrix was sent to two Advisory Board members, namely Dr. Miltos Ladikas of Karlsruhe Institute of Technology (expert in Technology assessment) and Professor Megan Munsie of the University of Melbourne (expert in organoid research). These two experts were involved in two one-hour pilot interviews, where the interview questions were addressed in in-depth discussion. Both experts provided valuable feedback and based on that the NTUA team finalized the question matrix (see Annex 3).

8.3 Recruitment of interviewees

The NTUA team prepared a list of potential interviewees that was discussed and revised during the 12th of February teleconference. There were no actual experts suggested at this initial phase but WP3 partners agreed on the geographicalspread, their expertise and the type of organizations in which they worked (i.e. Research Performing Organisations, Supranational entities/networks,Policy making bodies etc). Table 8.1 lists the final agreed composition with respect to the three abovementioned parameters of potential interviewees, as well as with regard to which WP3 partner was bound to conduct it. The specific number of expert interviews assigned to each WP3 partner was based on the person months they had in WP3. Colored in red are the experts that work outside Europe.

Table 8.1: Disciplinary and geographical composition of expert interviewees.

No.	Expertise	Country	Responsible WP3 partner
1	Organoid research	Austria	**UiO**
2	Biobank	UK	
3 (1)	Bioethics	Latin America	
4	Bioethics	Netherland	**UCL**
5	Bioethics	Europe (tbd)	
6 (2)	Bioethics	USA	
7	Legal expert	EGE	**INSERM**

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8 (3)	Organoid/similar technologies	WHO /UNESCO	
9	Organoid research	Germany	**LUMC**
10	Organoid research	Netherland	
11 (4)	Bioethics	Israel	**UNINS**
12 (5)	Legal expert	WHO/ UNESCO	
13 (6)	Bioethics	Africa	**NTUA**
14 (7)	Bioethics, Governance	China	
15 (8)	Organoid/similar technologies	Russia	
16	Technology Assessment	Germany	
17 (9)	Organoid research	Australia	
18 (10)	Organoid research	Japan	
19	RI/RE expert	Luxembourg	
20	Ethics and innovation	UK	

The recruitment of interviewees began with an **invitation e-mail** together with a **one-page information sheet**. The e-mails of all potential interviewees were either retrieved from the internet, i.e. they were freely available, or provided by HYBRIDA consortium partners or Advisory Board members who have established cooperation and acted as liaison. In the latter case an e-mail was sent from the liaison to the potential interviewee in order for the liaison to ask permission to send to WP3 partners her/his e-mail, so that the initial invitation letter could be sent. The invitation e-mail and the information sheet can be found in Annex 1.

As soon as the potential interviewee accepted to participate in the interview the interviewer sent, as attached files, the **Privacy Policy document** that describes the safeguards set by WP3 leaders, so as to preserve the anonymity of the interviewee and her/his right to step out of the interview at any time without providing justification, and the **Informed Consent form**. The informed consent form was already signed by the interviewer and also contained the date of the interview. Both documents are provided below. In addition the interviewee was provided with the **Questionnaire**, according to her/his expertise. The Privacy Policy document and the Informed Consent form can be found in Annex 2; the three types of questionnaires can be found in Annex 3.

9 Combined steps

Task 3.2 required the gathering and analysis of a large amount of bibliographic and empirical evidence during a relatively short amount of time, i.e. six months. Taking this into account the NTUA team started the planning and application of the initial steps of Task 3.2 even before the official start date of HYBRIDA. The work within Task 3.2 was divided into four subtasks (see Figure 4), three of which had to be applied simultaneously:

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- **Preparation:** Setting of the objectives and research questions for the Task 3.2 study, deciding the methodological framework and applying the initial methodological steps.
- **Search and retrieve:** Gathering of the resources (peer reviewed articles and grey literature)
- **Extracting and charting:** Study of the gathered resources and initiation of D3.1 drafting
- **Interviews:** Conduct of interviews with the experts who work in Europe

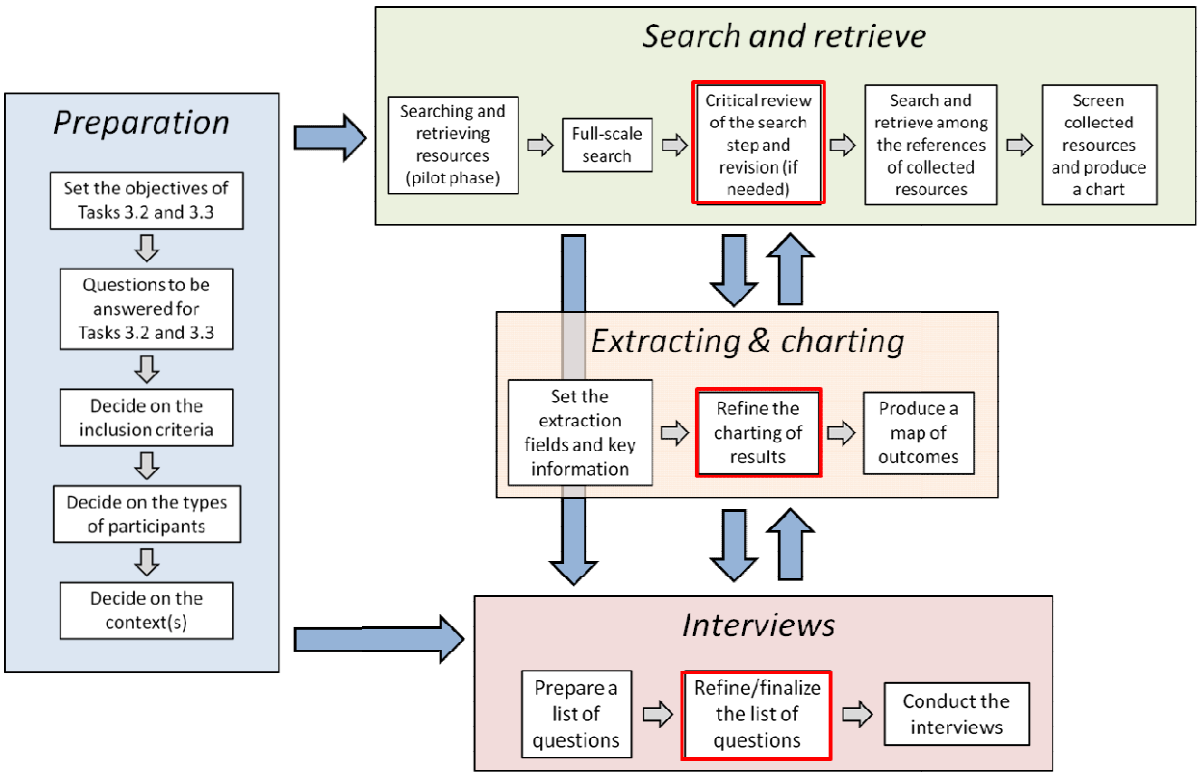

Figure 4: Schematic diagram of the four subtasks and their mutual interaction (blue arrows) within the context of Task 3.2.

These four subtasks were carried out at the same time and they interacted substantially. The Preparation subtask set the basis for the Scoping Review study and the experts' interviews. The three other subtasks interacted deeply, since there was a need to adapt/refine their search strategy, to base the extracting and charting procedure on the early/preliminary findings of the Scoping Review, as well as to adapt the questionnaires for the expert interviews based on the pilot interviews with HYBRIDA's Advisory Board members. These critical steps are marked with a red square in Figure 4 and they ensued within the second half of March 2021.

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10 Approval for the expert interview study

The NTUA team prepared all required documentation and applied for approval of the expert interview study to NTUA's Research Ethics and Deontology Committee (REDC) on the 9th of December 2020. In addition to the required application form REDC received the documents included in Annexes 1 and 2. Ethical approval of the study was granted on the 14th of January 2021; the original document of the ethical approval is included in Annex 4, together with the translation in English. In Figure 5 there is a flow chart that depicts the procedure of data handling, starting from the initial contact with the potential interviewee until the foreseen storage of the anonymised transcripts in the Open Science Framework platform.

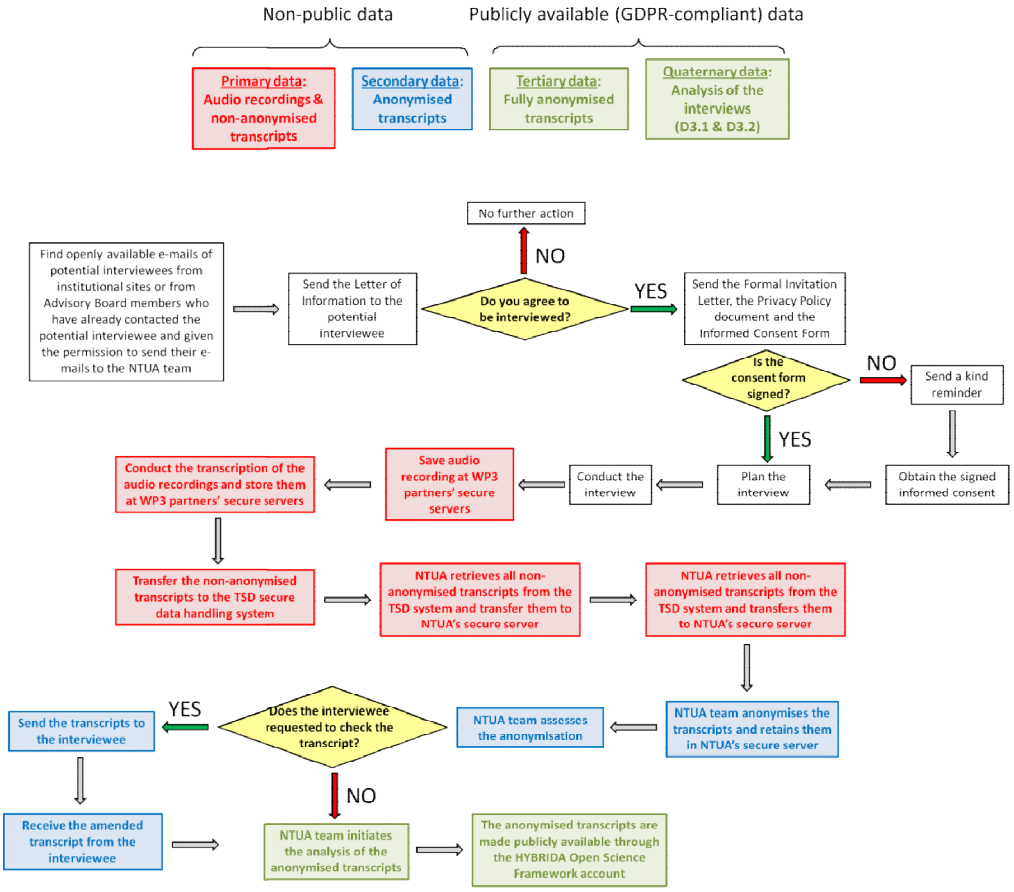

Figure 5: The procedure of data handling, starting from the initial contact with the potential interviewee until the storage of the anonymised transcripts in the Open Science Framework platform.

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Part 3: RESULTS

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11 Research Ethics frameworks mapping

In mapping the RE framework regarding organoid research and similar technologies (gene editing, cloning technologies, ESC technologies and iPSC technologies), we did an extensive search on the *Scopus* abstract and citation database by applying a variety of keywords and combinations of them, as already described in the protocol of our scoping review. After compiling the list of relevant articles, we used the Mendeley repository. Within the Mendeley lists, we applied specific inclusion and exclusion criteria, in order to compile the final version of the reading list. Regarding the inclusion criteria we proceeded to map the knowledge/available information about organoids research, based on what is described in WP3 on similar technologies. Thus we included articles that discuss the ethical dimensions that technologies such as gene editing, cloning, ESC and iPSC raise in the geographical contexts of Europe, USA, Canada, Australia, China, Japan and Israel. However, we have also included articles on other related technologies, broader families of technologies/techniques or sub-fields, such as genetic manipulation, genetic modification, genetic engineering, genomics, recombinant DNA, genetic Enhancement, research on chimeras, as described more thoroughly in the Methodology section. The methodological decision to include articles referring to the above-mentioned technologies derived from the consideration that such technologies are shared and constitute applications of the general concept of Genetic Intervention. This concept is common in the discussion of technologies such as gene editing and others aimed at altering the information in the genetic code. Genetic intervention seems to be fundamental conceptually, and thus more general in that sense, but, also, it is actually discussed in many papers included in our reviewed literature. In addition, we have observed that these additional technologies raise ethical issues like human dignity, issues related to consciousness, identity etc. that are also encountered in the discussion on organoids research.

The criteria by which some articles were excluded were related to the geographical context to which they refer, articles which capture the debate on Research Ethics for countries which are not included in our scope of the review. In addition, we excluded articles that are not related to technologies, such as those mentioned above and in description of work in WP3, and/or related to them but applied to plants or animals. They were excluded as they did not raise ethical issues encountered in research on organoids and similar technologies. It is, also, important to note that articles found to be relevant with regard to data management and biobanks have been considered as more related to Research Integrity and legal frameworks, however we make some references to these issues for the sake of the completeness of the argument related to Research Ethics.

11.1 Introduction

Technologies such as gene editing, cloning or involving the use of ESCs and iPSCs have brought revolutionary changes and have activated many potentialities both in the field of research and that of clinical application. In the same context, organoid research and technology is leading to further

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advances in medicine and biology.[6] And while the aforementioned biotechnologies, in their transition from the realm of possibility to the realm of realization, demonstrate potential for the well-being of living beings, they create, simultaneously, social phobias, visions and expectations of all kinds, the possibility of unfulfilled promises of treatments or cures,[7] as well as new utopias and dystopias. Undoubtedly, apart from the exaggerations that often characterize the social reception of new technological developments, there are questions about the changes to human beings and the future of human species, which require prudent, responsible and scientifically informed thinking. Some of these questions are ethical ones and require, also, philosophical, sociological and anthropological reflection.

In this review, we focus on organoid research and on the ethical issues that it raises through a comparative analysis with similar technologies, like gene editing, cloning, ESC and iPSCs research. The similarity between organoid technology and these technologies is drawn on the intervention on gene, cell or tissue level, offering new strategies for drug discovery and testing. These technologies, also, have the potential to provide new transplantation therapies for the treatment of a wide variety of human diseases.[8] However, with organoids we have a further advantage related to animal research ethics, as "*organoids enable the development of alternative methods that are used upstream of or in parallel to animal testing. This represents a potentially substantial contribution to the 3Rs.*"[9] The comparative analysis suggested here is not a new one. It is often found in the literature,[10] not only because all the aforementioned technologies hold a common great promise, but also because of the common ethical concerns they raise.Through this systematic scoping review, we aim at providing a comprehensive view of ethical issues raised and, also, a reasonable justification and consideration of the risks posed by the use of the technologies in question.

Additionally, at this point, it should be mentioned that throughout our research and literature review and our interaction with experts, we observed that a common debate among researchers specialized in organoid and related technologies research and scholars from other fields (bioethicists, sociologists, legal experts, philosophers) has to do with whether or not it is valid to examine organoids as a single field of research raising shared ethical challenges, or if each type of organoid instead raises

[6] A.L. Bredenoord, H. Clevers, J.A. Knoblich (2017). Human tissues in a dish: The research and ethical implications of organoid technology. Science, 355(6322), eaaf9414. https://doi.org/10.1126/science.aaf9414.

[7] B. Baertschi, H. Atlan, M. Botbol-Baum, B. Bed'hom, H. Combrisson, et al. Organoids Research: What are the ethical issues? 2020. ffinserm-03117706.

[8] T. Heinonen (2015). Better Science with Human Cell-based Organ and Tissue Models. Alternatives to Laboratory Animals, 43(1), 29–38. https://doi.org/10.1177/026119291504300107. See also Tsai, D. F. C. (2005). Human embryonic stem cell research debates: A Confucian argument. Journal of Medical Ethics, 31(11), 635–640.https://doi.org/10.1136/jme.2005.011924, F. Memi, A. Ntokou, I. Papangeli (2018). CRISPR/Cas9 gene-editing: Research technologies, clinical applications and ethical considerations. Seminars in Perinatology, 42(8), 487–500. https://doi.org/10.1053/j.semperi.2018.09.003, Wilson, J. F. (2003). How Cloning Could Change Medicine. Annals of Internal Medicine, 139(6), 535–538. https://doi.org/10.7326/0003-4819-139-6-200309160-00036.

[9] B. Baertschi, H. Atlan, M. Botbol-Baum, B. Bed'hom, H. Combrisson, et al (2020).Organoids Research: What are the ethical issues?. ffinserm-03117706, A.L. Bredenoord, H. Clevers, J.A. Knoblich, (2017), ibid, p.2.

[10] M. Munsie, C. Gyngell (2018). Ethical issues in genetic modification and why application matters. Current Opinion in Genetics and Development, 52, 7–12. https://doi.org/10.1016/j.gde.2018.05.002 See also K.R. Jongsma, A.L. Bredenoord (2020). Ethics parallel research: an approach for (early) ethical guidance of biomedical innovation. BMC Medical Ethics, 21(1), 81. https://doi.org/10.1186/s12910-020-00524-z.

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particular issues, with most prominent those related to cerebroids and gastruloids. In other words, this is the right time to decide whether we need a further taxonomy discussion, since it is widely accepted that not all types of organoids raise ethical concerns and challenges. However, there seems to be something in common that all types of organoids share which has given rise to the concept of the "ethics of organoids" as a single field. What does 'organoid' as a term entail? Can it be considered as a 'generic' term? These are issues identified within the development of the work of other WPs of the HYBRIDA project,[11] as well as addressed by our expert interviewees. For the purpose of clarity of our analysis and in order to present the full range of particularities, in the following sections we refer to both ethical issues pertaining to human organoids as a collective field and particular ethical issues related to cerebroids and gastruloids.

11.2 Mapping of ethical issues in organoid research and similar technologies

11.2.1 Gene editing

The discovery and optimisation of new technologies like CRISPR-Cas9 make the processing of the human genome easier and more likely, both in somatic cells and in germline cells. Gene editing with the use of CRISPR-Cas9 technology, can be used both in the human genome, in order to avoid or treat genetic diseases, as well as in other species, with the aim of creating organisms with specific properties for research purposes. The relative ease with which these genome modification methods can be applied in the laboratory and their precision, combined with their relatively low costs, makes them important tools for Genetic Engineering, raising at the same time intense reflection on their ethical and responsible use.[12]

An argument against gene editing which is related to the issue of naturalness, is the attempt to transcend nature and interrupt natural selection and the natural process of evolution. Natural versus artificial selection is one of the most important and controversial issues in bioethics, additionally, the issue about naturalness accompanied by another issue concerning the biodiversity reductionand the randomness of the physical process. The way the natural recombination of chromosomes and genes works during the reduction of germ cells, creates the conditions for a huge number of possible genetic combinations, which are almost impossible to repeat again.[13] 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 humanness/humanity. This argument combination is stated in the following claim:

[11] See, for instance, WP1 D1.2 (forthcoming) including a comprehensive list of conceptual distinctions pertaining to the ontological status of organoids.
[12] J. Sugarman (2015). Ethics and germline gene editing. EMBO Reports, 16(8), 879–880. https://doi.org/10.15252/embr.201540879 See also M.Baumann, CRISPR-Cas9 genome editing – new and old ethical issues arising from a revolutionary technology.
[13] European Group on Ethics in Science and New Technologies (2021), Opinion on Ethics of Genome Editing European Group on Ethics in Science and New Technologies, Directorate-General for Research and Innovation.See, also, J. Habermas (2003) *The future of human nature*, Cambridge: Polity Press, p.16.

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"The starting-point of every evaluation must be that the humanity of human beings rests at its core on natural development, not on technical production and not on a social act of recognition. The dignity of human beings is based essentially on their being born and on the naturalness of their origins, which all humans share with each other."[14]

Following the issue of naturalness, the question of unforeseen genetic modifications to future generations and to the whole of humanity arises. Gene editing can take place in somatic cells, where only desirable tissues or systems are affected, without hereditary transfer of changes to offspring. However, there is another type of gene editing which is applied in germlines[15] and its possible changes might be inherited to future generations.[16]The editing of the human genome, while aimed at eliminating particular disease-causing traits, is likely to lead to long-term changes in the future frequencies of other, correlated genetic traits as well. This phenomenon is sometimes considered to be a version of genetic drift, and it affects the evolution of species, including humans, with consequences that are not easy to predict. Genome editing in other types of organisms will undoubtedly lead to genetic engineering and potentially, if these modified organisms are released in the wild-to disruption of biodiversity, endangering species populations and the balance of ecosystems. The value of biodiversity and the "*rights of future generations*"[17] are a moral obligation, which might not be guaranteed by editing plant and animal genomes, causing changes that are inherited by future generations and altering the gene pool of species.[18]

Another important issue concerns eugenics.[19] This issue is directly related to the application of gene editing to embryos. On the one hand, some argue that the application of such technologies to embryos could eventually eliminate serious and fatal human diseases. On the other hand, others believe that the fact that future generations inherit these changes in the genome is not permissible and crosses

[14] West Germany. Enquete Commission. (1988). A REPORT FROM GERMANY. Bioethics, 2(3), 254–263. https://doi.org/10.1111/j.1467-8519.1988.tb00051.x

[15] N.H. Evitt, S. Mascharak, R.B. Altman (2015). Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework. American Journal of Bioethics, 15(12), 25–29. https://doi.org/10.1080/15265161.2015.1104160.

[16] K.R. Smith, S. Chan, J. Harris (2012). Human Germline Genetic Modification: Scientific and Bioethical Perspectives. Archives of Medical Research, 43(7), 491–513. https://doi.org/10.1016/j.arcmed.2012.09.003
Brokowski, C., & Adli, M. (2019). CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool. Journal of Molecular Biology, 431(1),p.97. https://doi.org/10.1016/j.jmb.2018.05.044

[17] A. Caplan (2019). Getting serious about the challenge of regulating germline gene therapy. PLOS Biology, 17(4)

[18] See ibid. p. 4

[19] Modern genetic technology has enabled the following options. On the one hand, prenatal screening and therapeutic or non-abortion reject the unwanted offspring. The same happens with preimplantation diagnosis, where the fetus is rejected. On the other hand, the technology of gene editing makes possible the correction of genetic defects and the introduction of desired characteristics. These two options of gene editing are considered as a path towards eugenics which violates the autonomy, freedom and dignity of the offspring. This argument is strengthened by the fact that the choices in both forms of modern eugenics are made by the parents, without the possible consent of the unborn fetus. See, F. Memi, A. Ntokou, I. Papangeli (2018). CRISPR/Cas9 gene-editing: Research technologies, clinical applications and ethical considerations. Seminars in Perinatology, 42(8), 487–500. https://doi.org/10.1053/j.semperi.2018.09.003, M. Baumann (2016). CRISPR/Cas9 genome editing – new and old ethical issues arising from a revolutionary technology. NanoEthics, 10(2), p.143-144. https://doi.org/10.1007/s11569-016-0259-0, V.L. Raposo (2019). CRISPR-Cas9 and the Promise of a Better Future. European Journal of Health Law, 26(4), p.316. https://doi.org/10.1163/15718093-12264438.

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ethical boundaries. According to this view, if the genome of embryos is allowed to be edited then there is a risk of eugenics and the creation of designer babies.[20]

Closing this review of the ethical issues raised by gene editing technology, we find it appropriate to mention that in the relevant literature there is an interest in the combination of gene editing and organoids mainly through the CRISPR method. It is considered that their combination will be a powerful tool for rapid screening of modified genes and will be a significant contribution in making decisions which might prove critical to clinical practice.[21]

11.2.2. Cloning

Another technology that reproduces to some extent the ethical issues raised in relation to gene editing and which, as will be seen, are included in the various debates about organoid research is cloning. Regarding cloning we should begin with a distinction between therapeutic cloning[22] and reproductive cloning. Although therapeutic cloning, in the sense of creating embryos for the production of stem cells for therapeutic purposes (without any intention to bring them to term), is widely considered to be acceptable, we cannot claim the same for reproductive cloning,[23] which aims at the reproduction of genetically identical beings. The questions and inquiries that arise regarding the permissible limits of cloning research usually refer to reproductive cloning as a punishable act. Those who, from a critical point of view, oppose these uses of cloning, broach a main argument which pertains to human dignity and its inextricable relation to the formation of the personality of an individual.

This argument is, also, related to the issue of naturalness and the question of the moral value of clones. A clone is the copy of its 'ancestor', raising the concern about loss of individuality and identity as far as the natural characteristics are concerned. This concern rests on an assumption that uniqueness and individual identity require a unique genome. However, this argument is weakened by the example of identical twins which are, in fact, genetic clones and do not seem to lack uniqueness, as they develop into completely distinct individuals with their own unique personalities.[24] The formation of personality is not only attributed to the genetic material but also to the environment. For example two humans might share a common genetic material, but this does not mean that they have the same personalities.

Another view of those opposed to both reproductive and therapeutic cloning, relates to the moral value of the clone itself, particularly, to whether it is merely a means to an end; a challenge similar to

[20] R. Dresser (2004), Designing Babies. Human Research Issues. IRB. Ethics and Human Research.
[21] A. Ivonne Vazquez-Armendariz, S. Herold (2021). *From Clones to Buds and Branches: The Use of Lung Organoids to Model Branching Morphogenesis Ex Vivo,* Front. Cell Dev. Biol., https://doi.org/10.3389/fcell.2021.631579.
[22] S. Manzoor, M. Elahi (2005). Embryonic stem cell biotechnology research and the ethics of derivation: Safe step towards therapeutic cloning [1]. Journal of the College of Physicians and Surgeons Pakistan, 15(8), 517.
[23] D. Bruce (2001). Human embryonic cloning. Human Reproduction and Genetic Ethics, 7(1), 3–7. https://doi.org/10.1179/hrge.7.1.kq10365373hp6561.
[24] Standing Committee on Legal and Constitutional Affairs. (2001). Human cloning: scientific, ethical andregulatory aspects of human cloning and stem cell research.http://wopared.parl.net/house/committee/laca/humancloning/report.pdf
M. Sandel (2005), "The Ethical Implications of Human Cloning", *Perspectives in Biology and Medicine,* Volume 48, No. 2, Spring, pp. 241-2.

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

the case of the use of cloned embryos for the production of tissues and organs.[25] The fetus resulting from this method is not created for its own benefit, but for someone else's. In this way, it is argued, human existence is devalued and the conditions are built for the violation of the rights of the clone in the future, as they are the means for another purpose.

11.2.3 Embryonic Stem Cell (ESC) research

Following the examination of these two key technologies (gene editing, cloning) and the general ethical issues they raise, we will proceed with the examination of the ethical issues raised by research in ESCs and iPSCs. Since these two cell types are basic for a major part of gene editing applications, cloning and organoid technologies, we will try, through the presentation of the ethical issues that research on these two cell types has raised, to show the new meaning that their use acquires within specific technologies and mainly within the context of organoid research.

The use of human embryos in ESC research is an area of controversy among various stakeholders and has raised many ethical issues. And while it promises a treatment for many diseases, the debate over whether and to what extent its use should be allowed has raised the interest of researchers. The key element of the controversy concerns their origin, namely that they are derived from human pre-implantation embryos, i. e. embryos that were intended for IVF.[26] In that context today there is a strong debate about creating embryos only for the purposes of ESC research.

The key ethical issue that permeates the debate on ESC research is the destruction of embryos or the creation of embryos for instrumental use. ESC are cells derived from human pre-implantation embryos and have the ability to divide and form cells and tissues of adult organisms (pluripotent).[27] As in the case of organoid research, the emergence of ethical issues is related to the status of the objects of this kind of research. In this case the object is the embryonic stem cells. To the extent that they have the intrinsic potentiality to develop into an embryo, the ethical issues revolve around the status of the embryonic cells and the embryo and especially the question whether ESCs should be considered to be equivalent to an embryo.[28]

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[25] D. Bruce, D. (2001). Human embryonic cloning. Human Reproduction and Genetic Ethics, 7(1), 3–7.https://doi.org/10.1179/hrge.7.1.kq10365373hp6561. See also P.R. Henon (2003). Human embryonic or adult stem cells: An overview on ethics and perspectives for tissue engineering. Advances in Experimental Medicine and Biology, 534, 27–45. https://doi.org/10.1007/978-1-4615-0063-6_3.

[26] R. Porz, P. Bürkli, G. Barazzetti, J.L. Scully, C. Rehmann-Sutter (2008). A challenged choice: Donating spare embryos to stem cell research in Switzerland. *Swiss Medical Weekly*, *138*(37–38), 551–556. https://doi.org/2008/37/smw-12420.

[27] I. Klimanskaya (2011). Embryonic stem cells from blastomeres maintaining embryo viability. Stem Cells in Reproductive Medicine: Basic Science and Therapeutic Potential,84–92. https://doi.org/10.1017/CBO9781139540742.009. K. George (2007) What about the women? Ethical and policy aspects of egg supply for cloning research, Reproductive BioMedicine Online, Volume 15, Issue 2, pp. 127-133, https://doi.org/10.1016/S1472-6483(10)60700-6.

[28] M. Bobbert (2006). Ethical questions concerning research on human embryos, embryonic stem cells and chimeras. Biotechnology Journal, 1(12), 1352–1369. https://doi.org/10.1002/biot.200600179, See also J. Pugh (2014). Embryos, the principle of proportionality, and the shaky ground of moral respect. Bioethics, 28(8), 420–426. https://doi.org/10.1111/bioe.12013, Hanson, S. S. (2006). "More on Respect for Embryos and Potentiality: Does Respect for Embryos Entail Respect for In Vitro Embryos?" Theoretical Medicine and Bioethics, 27(3), 215–226. https://doi.org/10.1007/s11017-006-9001-1.

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Some researchers argue that because ESCs are derived from embryos, they therefore carry the status of an embryo. Even though they cannot develop into human beings on their own,[29] they have the potential to do so under certain conditions and in special circumstances.[30] This view reproduces the potentiality argument[31] according to which if the embryo has the potential to develop into a person, it ought to be considered as a person. On the other hand, there are researchers who argue that the isolated cells of an organism do not constitute the organism itself but a part of it which, although it carries the information needed to produce an organism, cannot become an independent entity, as such an entity would require the use of a technology. This distinction of part – whole which appears here is central, also, for the debates on the ethical dimensions of organoid research and other similar technologies. In other words, it is implicated both in arguments that claim that the part has the same ethical value as the whole to the extent that it is a component of it and from the other side, which argues, for instance, that the cell or the tissue itself does not have the same value as a whole organism, even if their use can lead to in vitro constructions that mimic the organs that derived from this specific cells (case of organoid technology) or in the case of cloning.[32]

In addition to the instrumental use of ESCs and embryos, emerges the issue of instrumental use of women. In order for embryos to be created for research, should the woman undergo hormone therapy, with no benefit to her or even with the risk of a detrimental effect to her health? From a feminist perspective,[33] creating embryos for research could make women tools, that is, means to an end. However, there is a different view that the body can be seen as a gift to advance research and achieve the well-being of humanity. Relevant assessments relate to whether the research serves an important purpose or not, whether the burdens and risks to individuals are proportionate and whether valid consent is provided after the research subject / donor has been informed.

11.2.4 Induced Pluripotent Stem Cells (iPSCs) research:

iPSCs have been seen as a more ethical alternative to ESCs, because iPSCs present the same potentialities for research and clinical activity as ESCs without duplicating the ethical problems that the

[29] K. Elliott (2007). An ironic reductio for a “pro-life” argument: Hurlbut’s proposal for stem cell research. Bioethics,21(2), 98110.http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L46046383%5Cnhttp://dx.doi.org/10.1111/j.14678519.2007.00530.x%5Cnhttp://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=02699702&id=doi:10.1111%2Fj.1467-8519.2007.00530.x&atitle=An+ironi

[30] A. McLaren (2002). Human embryonic stem cell lines: Socio-legal concerns and therapeutic promise. ComptesRendus - Biologies, 325(10), 1009–1012. https://doi.org/10.1016/S1631-0691(02)01528-7

[31] G.D. Wert (2003). Human embryonic stem cells: research, ethics and policy. Human Reproduction, 18(4), 672–682. https://doi.org/10.1093/humrep/deg143 See also K. Devolder (2005). Human embryonic stem cell research: Why the discarded-created-distinction cannot be based on the potentiality argument. Bioethics, 19(2), 167–186. https://doi.org/10.1111/j.1467-8519.2005.00432.x

[32] G.Q. Daley (2003). Cloning and Stem Cells — Handicapping the Political and Scientific Debates. New England Journal of Medicine, 349(3), 211–212. https://doi.org/10.1056/nejmp030088.

[33] D. Dickenson (2002). Commodification of human tissue: Implications for feminist a development ethics. *Developing World Bioethics*, *2*(1), 55–63. https://doi.org/10.1111/1471-8847.00035.

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use of the latter brings.[34] The main ethical concern that iPSC technology seems to be able to overcome is the destruction of embryos and, therefore, all the ethical issues and controversies about the status and moral value of embryos. Given that iPSCs have shown research and clinical similarities to ESCs,[35] the debates around this technology mainly concern the basis of its ethical advantages over ESC technology.

The first ethical issue that could be avoided by the use of iPSCs is the instrumentalization of the female body and all the ethical issues raised by feminist ethics. Because no egg is needed for the derivation of iPSCs, the woman is not burdened with the production of cells necessary for the technology. As we have mentioned when examining the issues of ESC research, egg donation is a procedure that can put women's health at risk. Following the issues raised by feminist ethics, iPSCs technology also comes to resolve ethical disputes regarding the commercializationof women's eggs.

While iPSCs eliminate significant risks to women's health and restrict the issues which concern to the instrumental use of embryos and women, it seems that there remains debate around the ethical issues related not to what iPSCs are and their current use, but to their ability to create a human embryo.

The question that is usually asked is: to what extent would the "humanity" of an embryo be changed if it were created from iPSCs, and what legal protection against this kind of research is to be required? Therefore, while iPSCs and their use to date transcend the ethical issues related to the status of the embryo and its moral value, it seems that to the extent that their potentiality to create embryos is proven, this raises anew the same issues present in ESC research.[36] In addition, and again in relation to the future potential of this technology, the issue of cloning, genetically engineered human embryos and human-animal chimeras, is also resurfacing.[37] If researchers reveal full embryonic potential in IPSCs, the cloning controversy would also enter the mix, as the resulting cells would be exact genetic matches of human donors. Once again, regarding the creation of chimeras from iPSCs through gene editing, ethical issues arise anew related to e.g. human dignity.

The development of human / animal chimeras for organ transplantation may offer hope to many who would have to wait for a long time for an available human organ donor. However, the creation of chimeras has raised moral concerns about the risk and violence of nature, causing moral concerns with regard to the way the organism is handled, i.e. as an animal or as a human.[38] On theone side, some scholars claim that chimeric creations provide the ability to grow organisms with human-derived cells or

[34] W. Malcolm Byrnes, & Edward J. Furton. (2009). Comments on "Moral Complicity in Induced Pluripotent Stem Cell Research." Kennedy Institute of Ethics Journal, 19(2), 202–205. https://doi.org/10.1353/ken.0.0286. Morady *et al*. Stem Cell Research & Therapy (2019) 10:341 https://doi.org/10.1186/s13287-019-1455-y.
[35] H.W. Denker (2009). Induced pluripotent stem cells: How to deal with the developmental potential. Reproductive BioMedicine Online, 19(SUPPL. 1), 34–37. https://doi.org/10.1016/S1472-6483(10)60062-4
[36]X. Zhang, Z. Li, Y. Liu, Z. Gai (2020). Great expectations: Induced pluripotent stem cell technologies in neurodevelopmental impairments. *International Journal of Medical Sciences*, *18*(2), 459–473. https://doi.org/10.7150/ijms.51842
[37] R. Streiffer (2005). At the edge of humanity: Human stem cells, chimeras, and moral status. Kennedy Institute of EthicsJournal,15(4),347370.http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L43052058%0Ahttp://dx.doi.org/10.1353/ken.2005.0030.
[38] G. Hermerén (2015). Ethical considerations in chimera research. Development (Cambridge), 142(1), 3–5. https://doi.org/10.1242/dev.119024.

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tissue, which may affect the identity of the human species, hence affecting its dignity.[39] On the other side, scholars point out that an organism which contains human cellsis not transformed into a human, and in this sense human dignity remains intact. The human-like feature associated with the chimera is only biological in nature, and in no way affects the animal's moral condition (since, for example, they do not attain consciousness).

The fact that iPSCs are versatile and their range of possible uses is constantly increasing raises ethical issues in relation to donor consent. The donation of tissue samples for research on iPSCs, in the current state of research, is no different from research involving other stem cells or human biospecimens and genetic/genetic analyses. However, the development that is foreseen because of the potential of these cells is likely to raise new ethical issues in relation to donor consent.[40] They are likely to undergo genomic analyses for intensive characterization and disease control, coupling these cells with the ethical concerns of genomics. Furthermore, because these cells can be derived from almost any sample type and can be used for potentially unlimited rounds of production and differentiation pathways, there is the potential for unprecedented flexibility in production, sharing and banking. The scientific potential of iPSCs and the future therapies[41] they make possible are extraordinary. However, it is precisely because of these potentials and, in addition, because the donors are adults and living that researchers are calling for informed consent[42] that will be dynamically structured to inform donors about the current and potential future use of the cells.

Additionally, further to the ethical challenges raised by the use of ESCs and which are considered to be resolved by the use of iPSCs, there is a particular debate on to what extent iPSCs bear moral status. There are three main arguments that have been laid out to address the moral status of iPSC: the potentiality argument; the standard view/relational properties argument; and the genetic basis for moral status argument.[43] Generally, the potentiality argument refers to the capacity of the embryo to develop into a subject. Regarding iPSCs, as was the case for ESCs, the potentiality argument has to do with the capacity of this type of cells to develop into a complete organism.[44] The second argument, the relational properties argument, argues that the criteria for moral status should be based on both relational and intrinsic properties. More specifically, while intrinsic properties of entities are more commonly considered to be morally significant, the relational properties which affect the emergence of those intrinsic properties should also be taken into account during the evaluation of the moral status of something.[45] The genetic basis for moral status argument, finally, begins with the idea that any entity

[39] I. Hyun (2015). From naïve pluripotency to chimeras: A new ethical challenge? Development (Cambridge), 142(1), 6–8. https://doi.org/10.1242/dev.119206.
[40] M. Orzechowski, M. Schochow, M. Kühl, F. Steger (2020). Donor information in research and drug evaluation with induced pluripotent stem cells (iPSCs). *Stem Cell Research and Therapy*, *11*(1). https://doi.org/10.1186/s13287-020-01644-4.
[41] M. Li, M. Chen, W. Han, X. Fu (2010). How far are induced pluripotent stem cells from the clinic? *Ageing Research Reviews*, *9*(3), 257–264. https://doi.org/10.1016/j.arr.2010.03.001.
[42] F. Baylis (2002). Betwixt and between human stem cell guidelines and legislation. Health Law Review, 11(1), 44–50.
[43] A.M. Martinho (2016) Overview of the Moral Status of iPS cells, The New Bioethics, 22:2, pp. 148-154.
[44] K. Devolder (2005). Human embryonic stem cell research: Why the discarded-created-distinction cannot be based on the potentiality argument. Bioethics, 19(2), 167–186. https://doi.org/10.1111/j.1467-8519.2005.00432.x
[45] A.M. Martinho (2016) Overview of the Moral Status of iPS cells, The New Bioethics, 22:2, p.152.

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that has the capacity for moral agency could potentially have moral rights, as moral status derives from the capacity to act with moral reason. Its proponents go on to argue that a single, isolated human cell doesn't have this capacity, and hence they are not rights-holders.[46]

Despite the ethical advantage of iPSCs over ESCs, there are still significant concerns regarding the ability of iPSCs to be used for production of interspecies chimeric animals, human reproductive cloning, or generation of human gametes.[47] Although many of these ethical concerns have already been raised about ESCs, the ease and simplicity of obtaining starting cell sources for iPSC generation together with the fact that these cells might be obtained even without donor consent, highlight the need to develop and apply specific rules and regulations in this regard.

11.2.5 Organoid research

While iPSCs seem to, at least in the current state of research, to overcome some of the ethical problems raised by ESC research, the same does not happen for the new variety of artificial tissue and cell cultures, organoids. Organoids are tiny, self-organized three-dimensional tissue cultures that are derived from pluripotent or somatic stem cells, and which can recapitulate many aspects of structural organization and functionality of their in vivo organ counterparts, thus holding great promise for biomedical research and translational applications.[48] There are potentially as many types of organoids as there are different tissues and organs in the body. To date, researchers have been able to produce organoids that resemble the brain, kidney, lung, intestine, stomach, and liver, and many more are on the way.[49]

In organoid technology, as can be seen from the above definition, two main technologies converge, that of ESCs and iPSCs. However, as will be shown below, organoid research provides opportunities for the development of other technologies and applications such as gene editing,[50] chimeras [51] etc. It is also directly related to the applications of biobanks,[52] requiring a new perspective on biobank governance issues from the perspective of research ethics.

I. Similar to stem cell research, and given that organoids are derived from and have the potential to replicate cells, tissues and organs, they raise a key ethical issue that is found in the range of technologies associated with stem cell research. This question concerns the **status** of the organoid and in particular **its moral value**. The examination of the morality of organoids and their moral value

[46] Ibid, p.152. See also S.M. Liao (2010). The basis of human moral status. Journal of Moral Philosophy, 7(2), pp. 159–179.
[47] Morady *et al*. (2019), pp.84-86.
[48] J.Barbuzano, ''Organoids: A new window into disease, development and discovery'', *Harvard Stem Cell Institute,*November 2017.
[49] I. Cavero, J.M. H. Holzgrefe, H. Henry, Human organotypic bioconstructs from organ-on-chip devices for human-predictive biological insights on drug candidates, *Expert Opinion on Drug Safety*, 2019.
[50] M. Munsie, Ch. Gyngell, Ethical issues in genetic modification and why application matters, Current Opinion in Genetics and Development, 2018. K.. Jongsma, A. Bredenoord, Ethics parallel research: an approach for (early) ethical guidance of biomedical innovation, BMC Medical Ethics, 2020
[51] C. Morata Tarifa, L. Lopez Navas *et al*. Chimeras for the twenty-first century, Critical Reviews in Biotechnology, 2020.
[52] S. Li, M. Wang, J.Zhou, Brain Organoids: A Promising Living Biobank Resource for Neuroscience Research, Biopreservation and Biobanking, 2020.

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adds to the ongoing debate about the moral status of the embryo and raises anew ethical issues related to distinctions between person and thing, or subject and object.[53] Especially in relation to a particular type of organoid, the gastruloid,[54] which shows structural similarities to embryos and their in vitro construction, provides an opportunity to explore complex embryological events in a detailed and highly quantitative manner.[55]However, because of gastruloid's similarity to embryos and their structural resemblance, it is important to revisit the discussion of the moral status of embryos. We therefore suggestthat the examination of ethical issues concerning gastruloids and embryo-like structures should be done in proportion to the ethical debates concerning the embryo.

II. The second ethical issue is **consciousness**, which is inextricably linked to the aforementioned distinctions, and is triggered by the creation of a particular type of organoid: the cerebroid. Cerebroids are organoids derived from brain cells and exhibit some characteristics similar to those of the brain of a 19 to 24-week-old fetus.[56] The idea that cerebroids mimic some of the functions of the brain as an organ, and perhaps experience pain, is central to the debate surrounding whether or not they possess consciousness and is often raised in the literature.

III. The third ethical issue that is raised within organoid research relates to the distinction between **naturalness and artificialness**. This issue, as we have already seen, concerns any intervention in the human genome (gene editing), the creation of living entities in vitro (cloning)[57] and the existence of an organism composed of two genetically distinct types of cells (chimeras).[58] With regard to organoid research, one debate on this issue concerns the fact that organoids can be obtained through 3D printing, a process that seems to artificialize a living entity or parts of it.

IV. The fourth ethical issue relates to **biobanks**. An important advance in organoid research is the understanding of disease development through the use of human tissues, the potential for personalised medicine after research on models similar to the human body, and even the possibility of the transplantation of organs created in vitro from donor cells. However, the various possibilities offered by research on organoids require the provision of biological material to biobanks. Indeed, since organoids are often derived from iPSCs, the question of consent of the donors of these primary cells arises as well. Alongside the issue of consent is the issue of returned results[59]. Also, the

[53] B. Advena-Regnery, H.G. Dederer, F. Enghofer, T. Cantz, T. Heinemann (2018). Framing the ethical and legal issues of human artificial gametes in research, therapy, and assisted reproduction: A German perspective. Bioethics, 32(5), 314–326.
[54] M. Munsie *et al*., ''Ethical issues in human organoid and gastruloid research''. The Company of Biologists Ltd , 2016.
[55] I. Hyun, Engineering Ethics and Self-Organizing Models of Human Development: Opportunities and Challenges, Cell Stem Cell, 2017.
[56] A. Lavazza and Massimini, "Cerebral Organoids", p. 607. See also S. Reardon, "Mini-Brains Show Human-Like Activity", Nature, 2018, vol. 563, p. 453 and A. Olena, "Human Cortical Organoids Model Neuronal Networks", The Scientist, August 28, 2019, https://www.the-scientist.com/news-opinion/human-cortical-organoids-make-brain-waves-66368.
[57] R.P. George (2004). Human cloning and embryo research: The 2003 John J. Conley lecture on medical ethics. Theoretical Medicine and Bioethics, 25(1), 3–20.
[58] A. Nikzad, S.G.A. Jorsaraei (2011). Cloning from the perspective of theology and jurisprudence. Journal of Babol University of Medical Sciences, 13(6), 80–88. See also V.L. Raposo (2019). CRISPR-Cas9 and the Promise of a Better Future. European Journal of Health Law, 26(4), 308–329.
[59] S. Boers *et al*., "Organoids as Hybrids: Ethical Implications for the Exchange of Human Tissues", Journal of Medical Ethics, 2019, vol. 45/2, p. 131-139.

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potential commercialisation of organoids[60] raises the issue of ownership and intellectual property rights. This last issue is more closely related to regulatory requirements. However, these requirements derive directly from an ethical perspective concerning the status of the organoid and the way that donors perceive themselves and their bodies, hence an ethical approach is, also, required.[61]

11.3 Ethical issues: Debates on organoid research

In 10.2.5 we described in short, the ethical issues which are prominent in organoid research and addressed as part of the broader mapping we described following the scoping review we conducted. In this section we aim at presenting more thoroughly the debates that correspond to the aforementioned ethical issues.

The analysis of the various debates on the ethical dimensions of organoid research takes into account comparisons between organoid research and similar technologies. As we have already mentioned, organoid research and organoid clinical applications are complementary to other technologies. The ethical issues raised in debates about organoid research can therefore not be regarded in isolation, but only in relation to the technologies which it uses and develops.[62]

The discussion around a central issue, that of the moral status of the organoid, triggers reflection on other sub-ethical issues that simultaneously concern organoid-like technologies. The answer to the question "*What is the status of the organoid?*" cannot be given directly without examining the ethical implications of the concept of moral status itself. Furthermore, organoid research is not an independent technology, but rather an advance in stem cell technology. Therefore, the analysis of particular ethical issues and the answer to the question about the moral status of organoids will be done through a comparative analysis of the ethical issues raised by similar technologies and extended to the research on organoids.

At this point, it is, also, important to relate this discussion about the status of organoids to our initial identification of three different kinds of uncertainty (ontological, epistemological/methodological, regulatory) that underlies HYBRIDA's approach. The question about the status of organoids permeates all individual applications of organoids, research and clinical, and is only answered by mapping and analysing the ethical issues raised by other technologies. The answer to the fundamental question about the status of the organoid opens up new perspectives in research and enables the creation of a regulatory and ethical framework that will ensure research integrity, protect research participants and formulate appropriate guidelines in order to avoid research misconduct.[63]

[60] D. Choudhury, A. Ashok, M.W. Naing (2020). Commercialization of Organoids. Trends in Molecular Medicine, 26(3), 245–249. https://doi.org/10.1016/j.molmed.2019.12.002
[61] D. Dickenson (2002). Commodification of human tissue: Implications for feminist an development ethics. Developing World Bioethics, 2(1), 55–63. https://doi.org/10.1111/1471-8847.00035
[62] K.R. Jongsma, A.L. Bredenoord (2020). Ethics parallel research: an approach for (early) ethical guidance of biomedical innovation. BMC Medical Ethics, 21(1), 81.
[63] D.B. Waisel (2017). Ethics of research for patients in pain. Current Opinion in Anaesthesiology, 30(2), 205–210.

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11.3.1 Moral status

The examination of the ethical question about the moralstatus[64] takes into account some important distinctions and notions which are related to the moral value of an organoid and afterwards to its treatment during research and clinical activity.These distinctions are between person and thing, and between subject and object.[65] In addition to these distinctions, we will engage with the notion of personhood[66] as it is considered identical with the notion of full moral status. At this point we should note that some ethical consequences in relation to the moral status of human organoidshave also arisen from their ontological and legal status. The question regarding what kind of entity an organoid is and what kind of legal protection it should have (specific or same with other products relating to human biological material)[67] fuels the debate around the ethical question of moral status. But also vice versa; discussions concerning the moral status of organoids may potentially affect the ontological and legal discussion with the need for law adaptation as an ultimate possible consequence.

In the discussion about both organoids and other products which are derived from human material andcontain the ability to simulate in a human organism, there is a special consideration about the kind of these generated entities and therefore about their moral status (person/ thing). From the side of hardcore science, these entities are treated as things. However, the research on these entities as well as their clinical application are subject to specific ethical regulations precisely because they contain the ability to transform into something close to the human organism and possibly to acquire properties that would in part resemble those of the person (consciousness, sentience, etc.)

The distinction between person and thing goes back to Roman Law. According to it, persons and things represent two different ontological entities. Depending on the category to which an entity belongs, it is treated in different ways. This distinction is also central in debates about the moral status of organoids. This distinction, i.e. between person and thing was used by John Locke.[68] Locke separated

[64] R. Hursthouse (2013) Moral status. In: H. LaFollette (ed.) International encyclopaedia of ethics. Wiley-Blackwell, Hoboken, pp 3422–3432. https://doi.org/10.1002/9781444367072.wbiee076. The concept of moral status has many definitions. The most common meaning of the term "moral status" is that it consists a certain characteristic that is possessed or ascribed to certain beings and determines the way in which these beings are treated. The value of the moral status of each entity is ascribedproportionally to the category of Full Moral Status. This category applies to healthy, cognitively – able adults.
[65] R. Streiffel (2005). At the edge of humanity: Human stem cells, chimeras, and moral status. *Kennedy Institute of Ethics Journal*,15(4),347–370.
[66] The concept of personhood is used for the specific category of living beings. As a condition, personhood can be distinguished among different types. Here we are interested in the moral and metaphysical type. The moral type refers to the individual beings who are moral agents. Moral agents engage in behaviour that can be evaluated as moral or immoral, as morally right or wrong, as morally permissible or morally impermissible. Personhood in a metaphysical notion is ascribed to someone or something when we apply some criteria like rationality, moral agency, use of language, ability to initiate action, intelligence, consciousness and self-consciousness. See E.F. Kittay (2005) At the margins of moral personhood,*Ethics* 116 (1): 100–131. See, also, M. Tooley (2009) "Personhood", H. Kuhse, P. Singer (eds.) *A Companion to Bioethics*, Blackwell Publishing, pp. 129-139.
[67] A. Lavazza, F.G. **Pizzetti (2020). Human cerebral organoids as a new legal and ethical challenge†. Journal of Law and the** Biosciences, 7(1), p. 1. https://doi.org/10.1093/jlb/lsaa005.
[68] J. Locke (1948). An essay concerning human understanding, 1690. In W. Dennis (Ed.), Readings in the history of psychology (pp. 55–68). Appleton-Century-Crofts. https://doi.org/10.1037/11304-008.

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biological from the personal substance and highlighted the importance of consciousness and morality in signifying subjectivity. In the field of bioethics this distinction remains. The concept of the person has a normative content because we refer to it as a concept with a moral load and it is linked to the concept of life.[69] Furthermore, in Immanuel Kant's famous 2nd formulation of the categorical imperative,[70] people are persons who ought to be treated as ends and never merely as means. In his work, "*Groundwork of the Metaphysics of Morals*", Kant asserts that "*person and every rational being in general exists as an end in itself, not merely as a means for the arbitrary use of this or that will. Personmust always be regarded as an end in all his actions, whether they are directed towards himself or towards other sentient beings*."[71] Humans, when we refer to the world around us, consider the world of things as a world of means to achieve our ends.

If we follow the above philosophical definitions of the person, then we could easily come to the conclusion that the organoid is a thing, an object. At the current stage of research, according to the literature review, no organoids have been developed that exhibit the complex process of consciousness and, therefore, none are capable of subjective experience,[72] which would give moral status to an entity. In addition, organoid research is governed by purposes related to the well being of people. Organoids are the tools, the means for the achievement of these ends[73] and, therefore, in this sense, they cannot be ascribed the moral status of a person but rather the status of a thing/object. But can we consider an organoid as a "*thing*"? For some types of organoids which resemble the kidney, lung, stomach etc, someone could claim this assumption, but with regard to other types of organoids this kind of considerations are complicated.

The literature review and the various debates emerging in organoid research prove just the opposite, namely that a considerable part of experts and scholars are hesitant in considering organoids merely as things. The literature review indicates that the answer to the question of the moral status of the organoid is only possible through the reduction of this technology to other technologies[74] and, furthermore, through the reduction of the organoid to the "raw material" used for its culture. In this way, the ethical status of organoids is not considered in isolation, Organoids are three-dimensional representations of organs depending on the cells from which they originate. Today, as we have already mentioned, researchers have been able to produce organoids that resemble the brain, kidney, lung,

[69] V. Brower (2003). A live issue and a moving target. EMBO Reports, 4(1), 5–7. https://doi.org/10.1038/sj.embor.embor718.
[70] "So act that you use humanity, whether in your own person or in the person of any other, always at the same time as an end, never merely as a means"[4:429] in Im. Kant (1785/1997) Groundwork of the Metaphysics of Morals", M. Gregor (ed.), Cambridge: Cambridge University Press, p.38.
[71] Ibid, p.38
[72] A. Lavazza, F.G. **Pizzetti (2020). Human cerebral organoids as a new legal and ethical challenge†. Journal of Law and the** Biosciences, 7(1). https://doi.org/10.1093/jlb/lsaa005
[73] C. Palacios-González (2015). Human dignity and the creation of human–nonhuman chimeras. Medicine, Health Care and Philosophy, 18(4), 487–499. https://doi.org/10.1007/s11019-015-9644-7
[74] M. Munsie, C. Gyngell, C. (2018). Ethical issues in genetic modification and why application matters. Current Opinion in Genetics and Development, 52, 7–12. https://doi.org/10.1016/j.gde.2018.05.002.

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intestine, stomach, and liver, and many more are on the way.[75] For the reproduction and representation of the structure and function of cells and organs, the in vitro use and processing of primary tissue or stem cells, embryonic stem cells and iPSCs that are capable of self-renewal, self-organization and exhibit organ functionality for long periods of time is required. Different types of organoids and types of research with them need to be considered differently from an ethical perspective. With regard to the issue of moral status, the most controversial type of organoid is the gastruloid,[76] as it constitutes a three-dimensional construction from embryonic stem cells.

Gastruloids represent some key steps in embryogenesis. Since they are derived from embryonic cells and resemble the early stages of the embryo, the debate on ethical issues and, in particular, on their moral status, concerns in large part the borderline status of embryos.[77] Do embryos belong to the moral category of persons, along with adult human beings? Are they capable of experiencing pain or pleasure, do they have the capacity for self-consciousness?

The debate that develops around ethical issues in ESC technology and the status of the embryo is permeated by a notion of ontological gradualism.[78] According to some researchers/bioethicists, the embryo during the early stages of development does not possess any property which could characterise it as a person. The ascription of moral value to the embryo is constituted on the basis of biological terms, it concerns their maturation[79] and the development of qualities that are appropriate to the status of the person. Its moral value is upgraded according to the natural process of its maturation and development. In this sense, research with embryos before a certain stage of maturity should not be subject to a restriction (the so-called "14-day rule").[80] In this regard, however, there is an ongoing discussion concerning the extension of the 14-day rule to 28 days.[81] Such an extension, insofar as embryonic maturation at this developmental stage does not involve the existence of functional neural

[75] J.Barbuzano, ''Organoids: A new window into disease, development and discovery'', Harvard Stem Cell Institute, November 2017.

[76] I.Hyun, Engineering Ethics and Self Organizing Models of Human Development: Opportunities and Challenges. Cell Stem Cell, 2017.

[77] A.K.M. Andersson (2011). Embryonic stem cells and property rights. Journal of Medicine and Philosophy, 36(3), 221–242. https://doi.org/10.1093/jmp/jhr013. See also G. Bahadur, M. Morrison, L. MacHin (2010). Beyond the "embryo question": Human embryonic stem cell ethics in the context of biomaterial donation in the UK. Reproductive BioMedicine Online, 21(7), 868–874. https://doi.org/10.1016/j.rbmo.2010.10.001 and K. Hug (2008). Derivation of human embryonic stem cell lines. Journal of Stem Cells, 3(1), 43–57.

[78] D.F.C. Tsai (2005). Human embryonic stem cell research debates: A Confucian argument. Journal of Medical Ethics, 31(11), 635–640. https://doi.org/10.1136/jme.2005.011924 , See also J.Koplin (2020), Emerging moral status issues,Monash Bioethics Review, 38:95–104, https://doi.org/10.1007/s40592-020-00124-y.

[79] M. Munsie, I. Hyun, J. Sugarman (2017). Ethical issues in human organoid and gastruloid research. Development (Cambridge), 144(6), 942–945. https://doi.org/10.1242/dev.140111.

[80] D. Zhang, R.K. Lie (2018). Ethical issues in human germline gene editing: a perspective from China. Monash Bioethics Review, 36(1–4), 23–35. https://doi.org/10.1007/s40592-018-0091-0.

[81] See, ISSCR (2021), Guidelines for Stem Cell research and Clinical Translation, May, Available online: file:///C:/Users/user/Downloads/Guidelines%20for%20the%20Field%20of%20Stem%20Cell%20Research%20and%20Regenerative%20Medicine.pdf,https://www.nature.com/articles/d41586-021-01387-z?WT.ec_id=NATURE-20210527&utm_source=nature_etoc&utm_medium=email&utm_campaign=20210527&sap-outbound-id=9330E0F3340C9CA3C35DAB7B27B19DB7CA9C5102https://www.nature.com/articles/d41586-021-01619-2

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connections or a sensory system, would enable scientists to investigate embryonic development between these days and produce important knowledge about human development.

Other perspectives introduce the notion of the future potential of the embryo, particularly its ability to become a person.[82] This view rejects ontological gradualism as applied to embryos, giving them instead a moral status and value from the outset, and hence placing restrictions on research. In any case, all perspectives give the embryo at least some moral status. In some of them the moral status of the embryo is considered as an *a priori* status and in some other perspectives this status is ascribed gradually according to its maturation.

Consequently, as gastruloids mimic embryonic development, they raise ethical concerns about the creation of early human life in vitro,[83] combining the debates on ethical issues in organoid research not only with those of ESCs and Human Embryos but also with those of cloning. If human gastruloids are considered functionally identical to human embryos, then the technology associated with these organoids should follow the same guidelines to decide up to what extent maturation of gastruloids may be allowed.

11.3.2 Consciousness

The ethical dimension of consciousness in organoids is inextricably linked to the question of their moral status and is a constituent element of its conceptualization. The issue of consciousness is fundamental to the ethics of research on organoids, particularly cerebroids, as these organoids are intended to represent and mimic the functions of the brain in order to understand and combat various diseases.[84] Debates about cerebroids are structured around two main views. There is the view which claims that research on cerebroids should be limited as the possibility of acquiring functions consistent with consciousness emerges[85] while the other view focuses on the current stage of cerebroid research and claims that cerebroids are far from acquiring the complexity required to sustain consciousness.[86]

However, both views define consciousness more as a form of sensory perception and has to do with the feeling of pain or pleasure. Other arguments point out that consciousness is something more complex than simple sensation, and presupposes complex neural networks, the ability to interact with and react to the environment, and especially the ability to obtain conscious self-awareness. An organoid

[82] K. Devolder (2005). Human embryonic stem cell research: Why the discarded-created-distinction cannot be based on the potentiality argument. Bioethics, 19(2), 167–186. https://doi.org/10.1111/j.1467-8519.2005.00432.x
[83] R.P. George (2004). Human cloning and embryo research: The 2003 John J. Conley lecture on medical ethics. Theoretical Medicine and Bioethics, 25(1), 3–20. https://doi.org/10.1023/B:META.0000025097.40977.da
[84] A. Lavazza, M. Massimini (2018). Cerebral organoids and consciousness: how far are we willing to go? Journal of Medical Ethics, 44(9), 613–614. https://doi.org/10.1136/medethics-2018-104976
[85] S. Reardon (2018). Lab-grown 'mini brains' produce electrical patterns that resemble those of premature babies. Nature, 563(7732), 453–453. https://doi.org/10.1038/d41586-018-07402-0
[86] I. Hyun, J.C. Scharf-Deering, J.E. Lunshof (2020). Ethical issues related to brain organoid research. Brain Research, 1732. https://doi.org/10.1016/j.brainres.2020.146653 J.J. Koplin, J. Savulescu (2019) Moral Limits of Brain Organoid Research*The Journal of Law, Medicine & Ethics, 47: 760-767*. DOI: 10.1177/1073110519897789.

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could have a minimal or basic degree of consciousness if one believes that consciousness is a property that comes in degrees. Other perspectives call for the development of a theory of consciousness that includes objective, brain-based indicators of consciousness that are independent of sensory processing, executive functions and motor outputs.[87]

Current cerebral organoids[88] lack mature neural networks, have no sensory input and output, and are therefore unable to interact with and react to the environment, making concerns about cognitive function or "thinking" of cerebral organoids unfounded at present. However, if current limitations were overcome through customized bioengineering strategies,[89] research involving human cerebral organoids would begin to raise moral concerns.[90] Such concerns could be further intensified if these structures were to be transferred into chimeric animal models, as discussed below.[91]

One fundamental question that arises here and which may offer us a way of resolving the ethical problem of consciousness is that of the whole and the part. In many respects, it is problematic to attribute properties of the whole to the part. Consideration of this issue is not only relevant to the debate on cerebroids research but runs through all discussions concerning cell and organoid research, as well as discussions about biobanks. According to a strict distinction between part and whole,[92] we cannot claim that the brain can think, because thinking is a function of the organism as such, when it is situated in an environment that provides it with stimuli through receptors. A brain cannot be conscious of anything, nor can it have the slightest sentience that can be translated at the psychic level. The same is especially true of cerebroids, particularly since many of them only replicate a particular region of the brain, and not the brain in its entirety. Further, they have no mature neural networks, and are unable to interact with their environment. They do not, therefore, possess consciousness.[93]

Returning now to the issue of consciousness, we must mention an important distinction which also concerns the question of moral status. The literature review revealed a confusion regarding the use of the term consciousness. Some authors, especially those referring to animal research, tend to equate the term consciousness with term of sentience, in order to set ethical boundaries and strengthen the argument of a moral problem in animal research. On the other hand, some researchers insist that consciousness is a component of a person and refers to its individual awareness of its unique thoughts,

[87] A.Lavazza, M. Massimini. Cerebral organoids and consciousness. how far are we willing to go.
[88] A. Lavazza, F.G. Pizzeti, Human cerebral organoids as a new legal and ethical challenge, *Journal of Law and the Biosciences*, 2020; 1–22.
[89] For example, to refine spatial development and enhance maturation through increased vascularization and/or perfusion, resulting in afferent sensation and complex neural networks
[90] Cheshire, 2014
[91] M. Munsie. Ethical issues in human organoid and gastruloid research.
[92] This is a crucial distinction already addressed in the writings of Plato and Aristotle, regarding the extent to which the properties attributed to the parts constituting a whole are attributed as such to the whole as well, and regarding whether the whole bears other properties and qualities not characterizing the parts. This discussion can be considered relevant to the potentialities deriving from the development of assembloids.
[93] A. Lavazza, F.G. Pizzetti (2020). Human cerebral organoids as a new legal and ethical challenge†. Journal of Law and the Biosciences, 7(1). https://doi.org/10.1093/jlb/lsaa005.

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memories, feelings, sensations, and environments and essentially, its consciousness is the person's awareness of itself and the world around it. This awareness is subjective and unique to the person. By contrast, the notion of sentience refers to the ability to feel pain or pleasure. The combination of consciousness and sentience is characteristic of a person but the existence of sentience without consciousness does not lead to the attribution of moral status of a person to an entity.[94] With regard to organoids the arguments about consciousness are better understood in the context of cerebroids.

Although cerebroids are not capable of developing the complex system of consciousness, their transplantation into brains of animals, such as rats or pigs may differentiate their ability for consciousness.[95] The main argument regarding cerebroids' inability for consciousness development is based on the assumption that consciousness can be developed only in integrated living organism because it is something more than a complex neural network. Through cerebroid transplantation into a brain of an animal, the above argument is overturn. This chimeric brain is then an organ functioning within an organism. It has already been observed that this transplantation normalizes the expression of the genes of neurons, which is altered in vitro cerebral organoids.[96] What will be the moral status of these "humanized" animals, i.e. these chimeras? The same question was also raised in section 11.2.4. in which we discussed the ethical issue of chimeras' nature within the context of iPSC research. Here we revert to this issue with regard to organoid technology. At first glance, there are no direct answers to the question about the moral status of these chimeras but there is an interesting approach, which summarizes the arguments related to this question.

So, the debates about chimeras have focused on four main arguments.[97] The first argument has to do with unnaturalness and the ethics of violating natural species boundaries. The second pertains to the moral status of chimeras.[98] Regarding this argument, the status of these entities cannot be definitively classified as human or non-human. This moral confusion constitutes a main challenge in chimera research. The Borderline-Personhood argument focuses on great apes and concludes that their borderline-personhood confers a high enough degree of moral status to make most, if not all, chimeric research on them impermissible.[99] The Human Dignity Argument[100] claims that it is an affront to human

[94] I. Hyun *et al.* (2020), Ethical issues related to brain organoid research, Brain Research, https://doi.org/10.1016/j.brainres.2020.146653.
[95] N.E. Kopinksi (2004). Human-nonhuman chimeras: a regulatory proposal on the blurring of species lines. Boston College Law Review. Boston College. Law School, 45(3), 619–666.
[96] D. Kwon, "Organoids Don't Accurately Model Human Brain Development", The Scientist, October 23, 2019
[97] K. Kwisda, L. White, D. Hübner (2020). Ethical arguments concerning human-animal chimera research: A systematic review. BMC Medical Ethics, 21(1). https://doi.org/10.1186/s12910-020-00465-7 See also P. Karpowicz, C.B. Cohen, D. Van Der Kooy (2005). Developing human-nonhuman chimeras in human stem cell research: Ethical issues and boundaries. Kennedy Institute of Ethics Journal, 15(2), 107–134. https://doi.org/10.1353/ken.2005.0015.
[98] S.P. Mann, R. Sun, G. Hermerén (2019). Ethical considerations in crossing the xenobarrier. Methods in Molecular Biology, 2005, 175–193. https://doi.org/10.1007/978-1-4939-9524-0_12 See also J.J. Koplin (2019). Human-Animal Chimeras: The Moral Insignificance of Uniquely Human Capacities. Hastings Center Report, 49(5), 23–32. https://doi.org/10.1002/hast.1051.
[99] B. Capps (2017). Do Chimeras Have Minds? Cambridge Quarterly of Healthcare Ethics, 26(4), 577–591. https://doi.org/10.1017/S0963180117000093.

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dignity to give an individual “trapped” in the body of a non-human animal the capacities associated with human dignity. These arguments provide different rationales for evaluating chimeric research and consequently differ in their implications both for the range of chimeric research that is unethical as well as the way chimeric research should be addressed in public policy. The extension of these arguments to organoid research affects directly its own research ethic. In conclusion, we could say that in the application of organoids to the creation of chimeric entities, the ethical issues that arise shift the interest from the ethical dimensions in organoid research to those concerning the creation of chimeras

11.3.3 Naturalness

Another issue that arises from in vitro creation of similar to living beings entities like those that gastruloid research promises or from in vitro creation of similar to human organs entities is ‘’naturalness’’ and its distinction from artificialness.

Life, or more precisely being alive, is a property that characterises certain natural beings manifesting self-organization, autonomy, ability to react, reproduction, evolution, and metabolism, and has long been considered as something given. These characteristics which are ascribed to natural beings are not taken into account in the case of organoid technology. This claim is more associated with gastruloids. The potential of this type of organoid is to create an entity similar to embryos. The natural is perceived as diametrically opposed to the cultural, technical, artificial and human made. In some perspectives, the natural is closely related to the supernatural, the divine, or the spiritual.[101] These perspectives are accompanied by the view that every evaluation of an intervention must be based on the criterion of humanness.[102] The humanness of human beings remains at the core of its natural development.[103] The main issue that rises regarding the above distinction is how these interventions affect humanness.

From the perspective of biology, an intervention like the one made through gene editing does not affect the state of humanness,[104] as long as only such genetic changes are made that lead to genes that are otherwise present in humans. Even if DNA from another organism is introduced in a human genome, this does not necessarily change the humanness of that entity. There is no percentage or sharp

[100] C. Palacios-González (2015). Human dignity and the creation of human–nonhuman chimeras. Medicine, Health Care and Philosophy, 18(4), 487–499. https://doi.org/10.1007/s11019-015-9644-7

[101] European Group on Ethics in Science and New Technologies (2021), Opinion on Ethics of Genome Editing European Group on Ethics in Science and New Technologies, Directorate-General for Research and Innovation. See, also, Habermas, J. (2003) The future of human nature, Cambridge: Polity Press, p.16.

[102] On ‘humanness’ and ‘humanisation’, see ibid pp.16-17

[103] West Germany. Enquete Commission. (1988). A REPORT FROM GERMANY. Bioethics, 2(3), 254–263. https://doi.org/10.1111/j.1467-8519.1988.tb00051.x

[104] X. Kang, W. He, Y. Huang, Q. Yu, Y. Chen, X. Gao, X. Sun, Y. Fan (2016). Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing. Journal of Assisted Reproduction and Genetics, 33(5), 581–588. https://doi.org/10.1007/s10815-016-0710-8.

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threshold beyond which the host is no longer considered to be human.[105] However, the question arises whether a change in the genetic makeup of a human being fundamentally alters the relationship between humans by making them genetically unequal. In this manner, an engineering / design approach in human genomics may undermine the fundamental equality of all human beings, which implies that there are "no discontinuities in the range of humanity that would accord some humans a lower status than others."[106] Such equality implies that all human beings have equal value and are accorded human dignity, without exception. This basic equal regard cannot be earned and is never a matter of merit, desert or design. The question with humanness is how to deal with someone whose genetic starting point was different. How can it be morally classified that man owes his genetic makeup not to fate or nature, but to the deliberate intervention of another human being? One could argue that this intervention is so fundamental that no human being can take responsibility for this intervention, and therefore genome gene editing should be categorically banned. Or does the possibility of intervention make it necessary to take on this responsibility, for example when it allows the prevention of a serious illness?

11.4 Organoids and biobanks

Advances in stem cell research and genomics have made it possible to grow organoids, self-assembling 3-D structures. As already mentioned, organoids closely resemble the architecture and function of real organs. However, since the technology is still so novel, the ethics surrounding them have not yet been fully explored.[107]

As we have mentioned, researchers use several types of stem cells to grow organoids, and can grow organs such as gut, kidney, pancreas, liver, brain and retina. Because organoids are grown from human tissues, they can be used for precision and regenerative medicine, and can be stored in biobanks for future use. However, stem cell research has already sparked fierce ethical debate about consent, ownership, commercialization, intellectual property rights and safety of materials stored in biobanks.[108]

Organoid biobanking is a different type of biobanking[109] because, in many instances, its applications are clinical in the "here and now," with the prospect of making a difference to donor

[105] M.G. Garry, D.J. Garry (2016). Humanized organs in gene-edited animals. Regenerative Medicine, 11(7), 617–619. https://doi.org/10.2217/rme-2016-0096.
[106] M. Baumann (2016). CRISPR/Cas9 genome editing – new and old ethical issues arising from a revolutionary technology. NanoEthics, 10(2), 139–159. https://doi.org/10.1007/s11569-016-0259-0.
[107] S.N. Boers, A.L. Bredenoord (2018). Consent for governance in the ethical use of organoids. Nature Cell Biology, 20(6), 642–645. https://doi.org/10.1038/s41556-018-0112-5.
[108] D. Choudhury, A. Ashok, M.W. Naing (2020). Commercialization of Organoids. *Trends in Molecular Medicine*, *26*(3), 245–249. https://doi.org/10.1016/j.molmed.2019.12.002See, also, J.H. Solbakk, S. Holm, B. Hofmann (eds.) (2009) *The Ethics of research Biobanking*, Springer US
[109] S. Li, M. Wang, J. Zhou (2020). Brain Organoids: A Promising Living Biobank Resource for Neuroscience Research. Biopreservation and Biobanking, 18(2), 136–143. https://doi.org/10.1089/bio.2019.0111.

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treatment outcomes. Consequently, authors highlight a number of areas in which different ethical considerations come into play regarding organoids. First, there is significant commercial interest in organoids because of their applications in precision medicine and pharmaceutical development.[110] Second, they query the type of consent that may be required for their use. In organoid technology, unlike, de-identification is less desirable because it decreases their scientific and clinical value. Furthermore, organoid biobanking lends itself better to consent procedures such as broad consent, tiered consent and dynamic consent.[111] The rapid development of technologies and the need of reusing biological materials for research purposes has exacerbated the need for formation of new types of informed consent. The first type, broad consent is taken at the time of enrollment in the biobanks and then the samples and information can be reused without obtaining a new consent as long as the use appertain to the scope of the original consent.[112] The second type, tiered consent gives research participants the option of giving broad consent only to certain types of research or research uses and only specified institutions and researchers. Also, research participants have the opportunity to choose whether their samples and data are identifiable or anonymized.[113] The last type of consent is dynamic consent. The advantage of this type of consent lies in the fact that the research participant can modify his / her consent at any time with regard to upcoming research projects. Also through this type of consent the research participant is informed about how the sample is used as well as any new risks associated with new studies.[114]

Boers *et al*.[115] suggest that the first step in organoid biobanking is to glean the opinions of all stakeholders, while acknowledging that commercialisation and globalisation are likely to be significant. Rather than seeing these as innately bad, they suggest that sharing results may represent significant benefits to society and the individual. The key is to implement appropriate policies and procedures for organoid biobanking.

The debate on the way organoid biobanks operate gives a further dimension to the evaluation of risks, benefits, and safety.[116] The most frequently mentioned benefits of organoid research are: a better

[110] S. Lu, W. F. J.Y.H. Fuh (2016). 3D bioprinting – An Ethical, Legal and Social Aspects (ELSA) framework. Bioprinting, 1–2, 11–21. https://doi.org/10.1016/j.bprint.2016.08.001.
[111] The issues raised by the different types of consent are explicitly presented in the section on Research Integrity of this report.
[112] R.B. Mikkelsen, M. Gjerris, G. Waldemar, *et al*. Broad consent for biobanks is best – provided it is also deep. BMC Med Ethics 20, 71 (2019). https://doi.org/10.1186/s12910-019-0414-6.
[113] V. Nembaware, K. Johnston, A.A. Diallo, M.J. Kotze, A. Matimba, K. Moodley, G.B. Tangwa, R. Torrorey-Sawe,N. Tiffin (2019). A framework for tiered informed consent for health genomic research in Africa. Nature Genetics, 51(11), 1566–1571. https://doi.org/10.1038/s41588-019-0520-x.
[114] R.B. Mikkelsen, M. Gjerris, G. Waldemar *et al.* Broad consent for biobanks is best – provided it is also deep. BMC Med Ethics 20, 71 (2019). https://doi.org/10.1186/s12910-019-0414-6.
[115] S.N. Boers, J.J.M. van Delden, H. Clevers, A.L. Bredenoord (2016). Organoid biobanking: identifying the ethics: Organoids revive old and raise new ethical challenges for basic research and therapeutic use. EMBO Reports, 17(7), 938–941. https://doi.org/10.15252/embr.201642613.
[116] M. Nakano-Okuno, B.R. Borah, I. Nakano (2014). Ethics of iPSC-Based Clinical Research for Age-Related Macular Degeneration: Patient-Centered Risk-Benefit Analysis. Stem Cell Reviews and Reports, 10(6), 743–752. https://doi.org/10.1007/s12015-014-9536-x.

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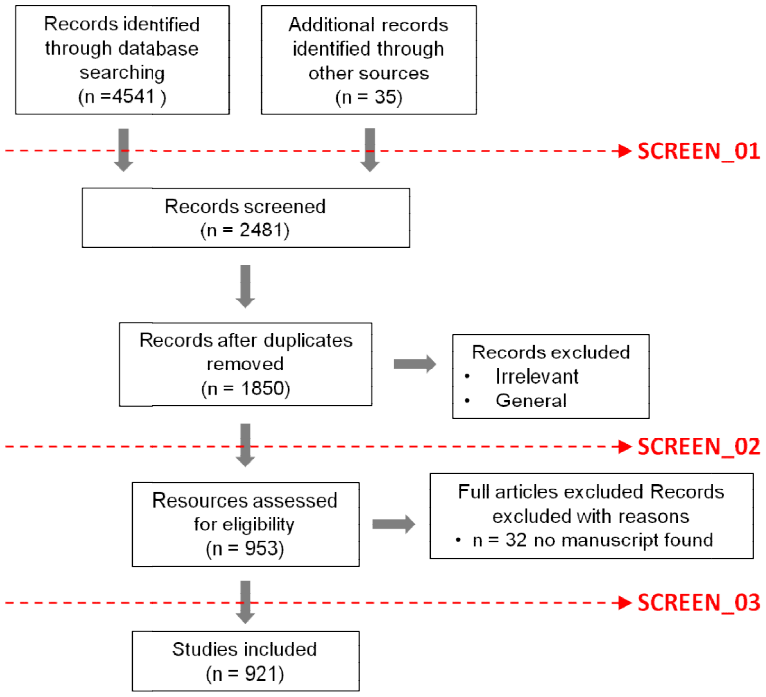
understanding of human diseases thanks to the use of human tissue, the possibility to test drugs on a model close to the human organism in real life and, eventually, the ability to repair defect organs - including the case of brain lesions. Toxicology, pharmacology, and cell therapy are therefore also concerned. Since organoids are often derived from iPS cells, the consent of the donors of the original cells must be obtained - this is also a regulatory requirement. The production of certain organoids (genital tract, brain) could raise some reticence among donors, and raises the question of the degree of consent and information which should be given to them. It also raises the question of the ownership of the resulting organoids, which can be sources of profit, as well as their patentability; in short, the question of who will benefit from the use of organoids must be addressed, as well as the nature of these benefits (financial, therapeutic, etc.). The genetic analysis of organoids also raises a major issue of health data protection, in particular genetic data, which must be taken into account at the consent stage, although it is not easy to say how.

11.5 Scoping review flowchart for research ethics-related resources



11.6 Conclusions

The advancement of technologies like gene editing, cloning, ESC technologies and iPSC technologies, and the emergence of the new technology of organoids promise the further

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understanding of human life and the evolution of diseases from the earliest stages of development, and they further contribute to the development of new clinical applications for therapeutic reasons. However, both organoid research and similar technologies raise ethical issues that have preoccupied researchers in the past and are revert with the emergence of new possibilities. The present work has been based on the hypothesis that the issues addressed individually in these technologies are combined or intertwined in organoid research and might bring the discussions in a new direction. Our work has been carried out on two interrelated levels. One level concerns intervention in human embryos, cells and tissues. At this level we were interested in technologies such as gene editing and cloning. In this way we sought to predict the potential ethical issues that will arise from the combination of organoid technology with the aforementioned technologies in order to contribute to a comprehensive view of not only current but also future ethical concerns. This level was complemented by another level which investigated the ethical issues raised by ESCs and iPSCs research. At this second level, organoid research is considered to be part of the overall research field of Stem Cells, as ESCs and iPSCs. However, the purpose of mapping the ethical issues raised by the research with ESC and iPSCs was not just to show that many of these issues are also transferred to organoid research. The further purpose was to answer an ontological question concerning the status of organoids. Thus, we treated the ESCs and iPSCs as the "raw material" of organoids and investigated their own status in order to specify the status of organoids. By answering this ontological question, the ethical issues raised during the research become more relevant.

Furthermore, it is worth noting that, although organoid research does not raise substantially unique ethical concerns, it is important to continue to monitor its advancement and potential future applications that may require new and more detailed ethical analyses. The ultimate aim of this mapping is to provide a guide to support researchers in integrating ethics into their research protocols in order to ensure the public and other stakeholders' trust and to be able through the continuation of their research to provide benefits for human beings.

12 Legal/Normative frameworks mapping

12.1 Introduction

Organoids have mainly been understood as microcosms of organs able to imitate organ function, which arederived from stem cells. *"Organoids develop upon the culture of pluripotent cells - meaning that organoids may develop into any of a variety of different mature cell types when placed in an amenable environment for growth- hES (human embryonic stem) and hiPS (human induced pluripotent stem) cells"*.[117]

As organoids derive from stem cells, they can be developed into a multitude of different organoid types. The development of biomedical research in vitro and in vivo using organoids, while it has the

[117] M. Myrick, Legal and Ethical Considerations of Brain Organoid Technology; International Webinar on Tissue Engineering and Regenerative Medicine; November 23, 2020; Singapore city, Singapore https://www.imedpub.com/articles/legal-and-ethical-considerations-of-brain-organoid-technology.pdf

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potential to offer insights for diagnostics, precision and personalized medicine, comes with both ethical considerations and debates that demand the interpretation of existing legal frameworks regarding health innovations, especially stem cell-related innovations. As regards the morality of the creation, current and future use of organoids substantial disagreement exist between bioethicists, legal scholars and scientists.

Organoids and relevant technologies raise several legal issues and invite difficult and challenging legal interpretations and applications of existing regulatory frameworks. There are two main points of contestation. One refers to the ontological – and thereby moral - status of organoids and their classification according to existing categories and concepts as these are currently regulated by law (e.g. how the term human embryo is to be understood). The other point of contestation, marked by even more ambivalence is related to their future development and potentials, e.g. the development of some form of consciousness.

The main legal issues for organoids include their current status, the issue (commencement) of personhood, issues pertaining to human dignity human rights and protection of human life, protection of animals, responsible research, regulation for clinical trials, especially in relation to hybrid and chimeric entities, ownership, issues of privacy, donor consent , and data protection. Several other associated legal issues arise while interpreting current legislation with the view to organoids. These are issues shared with bioethicist, something which provide opportunities for a productive and necessary discussion about how to develop synergies and bridges between legal and ethical considerations. In addition, guidelines issued by relevant bodies and scientific associations complement the regulatory framework with scientific advice on relevant issues.

Different legal frameworks may present “sensitive” discrepancies in relation to the aforementioned issues.[118] However the overarching framework and research area that regulates or provides some guidelines regarding organoids and the legal issues these technologies entail is “Bioethics”. Under the umbrella of provisions for bioethics and in line with international legal instruments we are trying to unravel, understand and interpret mainly the limitations and “red lines” that should not be crossed when developing organoid-related health innovations. Dilemmas naturally occur and some of them are critical and remain unresolved or require examination *in concreto*. Any understanding of these new technologies builds on existing regulations and we should acknowledge that there are some rights that are insulated with “absolute” protection by the law (like human dignity or human life). As these technologies continue to develop new challenges might generate new debates something which warrants a careful and well thought study of relevant legal provisions.

Many regulatory issues pertaining to organoids seem already to have been addressed and discussed within the context of genome editing and stem cell research. Thus the legal framework

[118] For a comparative presentation of the Regulatory frameworks for Stem Cells in Europe please see https://www.eurostemcell.org/regulation-stem-cell-research-europe.

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provided below refers to a large extent to these two technologies, but there are some additional issues raised by organoids that need to be considered.

We should emphasize that the short mapping does not relate to national legislations. It tries to provide a structural framework for the understanding of the legal provisions that can be applicable to organoids and relevant technologies as these accrue mainly from International and European legal frameworks. Therefore the mapping that follows does not go in depth into legal analysis but delineates the basic legal provisions that may be used to understand the regulations pertaining to organoids. For this reason and in order to avoid interpretations of legal texts, the exact wording of legal texts is provided in most of the cases (legislation/judicial cases) rather than their analysis.

12.2 General methodological note for the legal framework

We have adopted a top-down approach by first analysing *primary legislation* (Conventions, Treaties, Relevant protocols) and then narrowing down the research *to secondary legislation* at the EU level.

The second step is complementary, analysing some *articles* in major legal journals, short *opinion pieces* published in various formats by well-known experts in the field and presentation of *case studies* (judicial cases) from the European Court of Justice (the exact wording of courts proceedings are provided). Court proceedings are occasionally enriched by opinions from legal scholars which discuss how judicial decisions interpret law and provide critical reflections/opinions on them. The latter might be decisive in elucidating points of ambiguity in legislation where there is either a debate about the interpretation and the meaning of a very abstract provision or abstract ideas that need to be specified more concretely. Wherever there are good points or analyses found in relevant grey literature (but from reliable sources) we also cite them.

As clarified above, in our legal analysis, most of the text constitutes excerpts from legal sources and not analysis. The relevant reference in each footnote indicates the source of the text. Therefore, this is a general mapping of legal issues pertaining to organoids and relevant technologies which neither constitute a legal analysis of relevant legislation nor represent any form of legal advice or opinion.

12.3 Results

12.3.1 International legislative framework

The study of bioethics is characterised by multidisciplinarity, as it concerns ethical issues surrounding health, medicine and associated technologies and involves the examination of social, legal, ethical and other relevant issues. At the International level we identify two major legal instruments: the Universal Declaration on Bioethics and Human Rights (2005) and UNESCO's declarations on human cloning and the human genome (2005, 1997).

In relation to the international framework concerning health innovations and, more specifically, on organoids and stem cells, a basic remark is that relevant studies "*generally, do not expressly*

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reference neural organoids or chimeras. Instead, existing parameters rely on standards from other laws and requirements, largely related to embryonic stem cell (ESC) research. Additional boundaries are found in standards for animal research protections, safety and quality, product approval, and human subjects protection (for donors).”[119]

“The Universal Declaration on Bioethics and Human Rights was adopted by acclamation at the 33rd General Conference of UNESCO on October 19, 2005. It takes note in its preamble not only of a number of major international civil and human rights instruments, but also of a long list of international and regional instruments in the field of bioethics. The latter include the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (the Convention on Human Rights and Biomedicine) and its additional protocols, national legislation and regulations in the field of bioethics, and the international and regional codes of conduct and guidelines and other texts in the field of bioethics. In addition, it recalls the Universal Declaration of Human Rights of December 10, 1948, the Universal Declaration on the Human Genome and Human Rights (adopted by the General Conference of UNESCO on November 11, 1997), and the International Declaration on Human Genetic Data (adopted by the General Conference of UNESCO on October 16, 2003).”[120]

Below we provide some of the basic articles that set the main framework of protection provided by the Universal Declaration on Bioethics.[121]

Article 1 – Scope

1. *This Declaration addresses ethical issues related to medicine, life sciences and associated technologies as applied to human beings, taking into account their social, legal and environmental dimensions.*

2. *This Declaration is addressed to States. As appropriate and relevant, it also provides guidance to decisions or practices of individuals, groups, communities, institutions and corporations, public and private.*

Article 2 – Aims

The aims of this Declaration are: (a) to provide a universal framework of principles and procedures to guide States in the formulation of their legislation, policies or other instruments in the field of bioethics; (b) to guide the actions of individuals, groups, communities, institutions and corporations, public and private; (c) to promote respect for human dignity and protect human rights, by ensuring

[119] Barnes and Bohnman, 2020, International Regulation of Neural Organoids and Chimeras, available at https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiD95OKktHvAhVmx4UKHdDHAtQQFjAHegQIERAD&url=https%3A%2F%2Fwww.nationalacademies.org%2Fevent%2F11-132020%2Fdocs%2FD7833014F7AEF6D2D384AAE33B2816B0339DE57339B1&usg=AOvVaw1bZGX0o4ABPnOPqyrNLm9y (accessed on March 23rd,. 2021)

[120] Law Library Of Congress, U.S. Global Legal Research Directorate. *Bioethics Legislation in Selected Countries*. [Washington, DC: The Law Library of Congress, Global Legal Research Center, 2012] Pdf. https://www.loc.gov/item/2018296058/.(accessed 14/03/2021).

[121] http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html (accessed 27/07/2021)

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respect for the life of human beings, and fundamental freedoms, consistent with international human rights law; (d) to recognize the importance of freedom of scientific research and the benefits derived from scientific and technological developments, while stressing the need for such research and developments to occur within the framework of ethical principles set out in this Declaration and to respect human dignity, human rights and fundamental freedoms; (e) to foster multidisciplinary and pluralistic dialogue about bioethical issues between all stakeholders and within society as a whole; (f) to promote equitable access to medical, scientific and technological developments as well as the greatest possible flow and the rapid sharing of knowledge concerning those developments and the sharing of benefits, with particular attention to the needs of developing countries; (g) to safeguard and promote the interests of the present and future generations; (h) to underline the importance of biodiversity and its conservation as a common concern of humankind. Principles

Within the scope of this Declaration, in decisions or practices taken or carried out by those to whom it is addressed, the following principles are to be respected.

Article 3 – Human dignity and human rights

1. *Human dignity, human rights and fundamental freedoms are to be fully respected.*
2. *The interests and welfare of the individual should have priority over the sole interest of science or society.*

Article 4 Benefit and harm

In applying and advancing scientific knowledge, medical practice and associated technologies, direct and indirect benefits to patients, research participants and other affected individuals should be maximized and any possible harm to such individuals should be minimized.

As it is evident from the first 4 articles the Universal Declaration on Bioethics seeks *"to provide a universal framework of principles and procedures to guide States in the formulation of their legislation, policies or other instruments in the field of bioethics"; "to promote respect for human dignity and protect human rights … consistent with international human rights law"*; and *"to recognize the importance of freedom of scientific research*." In relation to principles the respect for human dignity, human rights and fundamental freedom set the main framework for protection. The primacy and protection of individuals over science and society is also underlined (article 3). With regards to 'Benefit and harm", article 4 stresses the minimization of harm on individuals when applying or advancing scientific knowledge. Furthermore, the Declaration has provisions for individual autonomy, consent, privacy and confidentially and it provides for the establishment of independent ethics committees at the appropriate level for tasks as assessment of *"the relevant ethical, legal, scientific and social issues related to research projects involving human beings,"* provision of advice on ethical problems in the clinical context, contribution to the preparation of guidelines on issues within the scope of the Declaration and fostering of debate and public awareness of bioethics. An important article considering the current state of research, which is transnational to some degree, is article 21, which speaks for the acceptable transnational practices for

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activities undertaken, pursued or funded within the scope of the Declaration and are undertaken in whole or in part in different states.

The Universal Declaration on Human Genome and Human Rights was adopted unanimously and by acclamation in 1997.It was then followed by the Resolution 29 C/I7 entitled 'Implementation of the Universal Declaration on the Human Genome and Human Rights' by which the General Conference set the ground for the implementation of the Declaration.[122]

Below are some important articles of the aforementioned Declaration[123]

A. Human dignity and the human genome

Article 1

The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity.

Article 2

(a) Everyone has a right to respect for their dignity and for their rights regardless of their genetic characteristics.

(b) That dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity.

Article 3

The human genome, which by its nature evolves, is subject to mutations. It contains potentialities that are expressed differently according to each individual's natural and social environment, including the individual's state of health, living conditions, nutrition and education.

Article 4

The human genome in its natural state shall not give rise to financial gains.

Article 6

No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity.

Article 7

Genetic data associated with an identifiable person and stored or processed for the purposes of research

[122] https://en.unesco.org/themes/ethics-science-and-technology/human-genome-and-human-rights
[123] http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html

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or any other purpose must be held confidential in the conditions set by law.

Article 8

Every individual shall have the right, according to international and national law, to just reparation for any damage sustained as a direct and determining result of an intervention affecting his or her genome.

Article 9

In order to protect human rights and fundamental freedoms, limitations to the principles of consent and confidentiality may only be prescribed by law, for compelling reasons within the bounds of public international law and the international law of human rights.

C. Research on the human genome

Article 10

No research or research applications concerning the human genome, in particular in the fields of biology, genetics and medicine, should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or, where applicable, of groups of people.

Article 11

Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organizations are invited to co-operate in identifying such practices and in taking, at national or international level, the measures necessary to ensure that the principles set out in this Declaration are respected.

Article 12

(a) Benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual.

(b) Freedom of research, which is necessary for the progress of knowledge, is part of freedom of thought. The applications of research, including applications in biology, genetics and medicine, concerning the human genome, shall seek to offer relief from suffering and improve the health of individuals and humankind as a whole".

"The UN Declaration on Human Cloning, adopted in 2005, recalls the Universal Declaration on the Human Genome and Human Rights of UNESCO "and in particular article thereof, which states that practices which are contrary to human dignity, such as the reproductive cloning of human beings, shall not be permitted," and also UN Resolution 53/152 of December 9, 1998, endorsing the Universal Declaration on the Human Genome and Human Rights. The General Assembly did not achieve consensus

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in the adoption of the human cloning declaration, however. Several delegations voted against the text because they contended that its reference to "human life" "could be interpreted as a call for a total ban on all forms of human cloning," while the United Kingdom representative saw it as a missed opportunity for adoption of a convention banning reproductive cloning, due to "the intransigence of those who were not prepared to recognize that other sovereign States might decide to permit strictly controlled applications of therapeutic cloning".[124]

12.3.2 Regional legislative framework.

Council of Europe (CoE)

The Oviedo Convention for the Protection of Human Rights and Biomedicine (1997)

The Council of Europe's (CoE) Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, also known as the Oviedo Convention on Human Rights and Biomedicine[125]was signed in 1997 but came into force on December 1, 1999.The Convention is "the first legally binding international text designed to preserve human dignity rights and freedoms through a series of principles and prohibitions against the misuse of biological and medical advances"

The Convention has several chapters on different issues, like consent, providing special protection to persons who are not able to give consent for scientific research or organ removal. The Convention has chapters on the protection of private life and the right to information.*"The Convention, unlike the Declaration, has discrete chapters on bioethical concerns involving the human genome, scientific research, and organ and tissue transplantation; on the prohibition of financial gain in regard to and provision for suitable disposal of the human body and its parts; and on acts constituting infringement of the Convention*".[126]

The summary ofthe Convention states:

"The Convention is the first legally-binding international text designed to preserve human dignity, rights and freedoms, through a series of principles and prohibitions against the misuse of biological and medical advances. The Convention's starting point is that the interests of human beings must come before the interests of science or society. It lays down a series of principles and prohibitions concerning bioethics, medical research, consent, rights to private life and information, organ transplantation, public debate etc.

[124] Law Library Of Congress, U.S.. Global Legal Research Directorate. *Bioethics Legislation in Selected Countries*. [Washington, DC: The Law Library of Congress, Global Legal Research Center, 2012] Pdf. https://www.loc.gov/item/2018296058/.(accessed 14/03/2021).
[125] https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164
[126] Law Library Of Congress, U.S.. Global Legal Research Directorate. *Bioethics Legislation in Selected Countries*. [Washington, DC: The Law Library of Congress, Global Legal Research Center, 2012] Pdf. https://www.loc.gov/item/2018296058/.(accessed 14/03/2021).

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It bans all forms of discrimination based on the grounds of a person's genetic make-up and allows the carrying out of predictive genetic tests only for medical purposes. The treaty allows genetic engineering only for preventive, diagnostic or therapeutic reasons and only where it does not aim to change the genetic make-up of a person's descendants. It prohibits the use of techniques of medically assisted procreation to help choose the sex of a child, except where it would avoid a serious hereditary condition.

The Convention sets out rules related to medical research by including detailed and precise conditions, especially for people who cannot give their consent. It prohibits the creation of human embryos for research purposes and requires an adequate protection of embryos where countries allow in-vitro research.

The Convention states the principle according to which a person has to give the necessary consent for treatment expressly, in advance, except in emergencies, and that such consent may be freely withdrawn at any time. The treatment of persons unable to give their consent, such as children and people with mental illnesses, may be carried out only if it could produce real and direct benefit to his or her health.

The Convention stipulates that all patients have a right to be informed about their health, including the results of predictive genetic tests. The Convention recognises also the patient's right not to know. The Convention prohibits the removal of organs and other tissues which cannot be regenerated from people not able to give consent. The only exception is, under certain conditions, for regenerative tissue (especially bone marrow) between siblings.

The Convention recognises the importance of promoting a public debate and consultation on these questions. The only restrictions are those prescribed by law and which are necessary in a democratic society in the interest of public safety, for the prevention of crime, for the protection of public health or for the protection of the rights and freedoms of others. Additional Protocols are foreseen to clarify, strengthen and supplement the overall Convention.

The Steering Committee on Bioethics (CDBI), or any other committee designated by the Committee of Ministers or the Parties may request the European Court of Human Rights to give advisory opinions on legal questions concerning the interpretation of the Convention."[127]

Below, we present some of the Convention articles that are important and relevant to our study:

"Article 1 – Purpose and object

Parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. Each Party shall take in its internal law the necessary measures to give effect to the provisions of this Convention.

[127] https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164?module=treaty-detail&treatynum=164

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Article 2 – Primacy of the human being

The interests and welfare of the human being shall prevail over the sole interest of society or science.

Article 5 – General rule

An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time.

Article 6 – Protection of persons not able to consent

1. *Subject to Articles 17 and 20 below, an intervention may only be carried out on a person who does not have the capacity to consent, for his or her direct benefit.*
2. *Where, according to law, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law. The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity.*
3. *Where, according to law, an adult does not have the capacity to consent to an intervention because of a mental disability, a disease or for similar reasons, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law. The individual concerned shall as far as possible take part in the authorisation procedure.*
4. *The representative, the authority, the person or the body mentioned in paragraphs 2 and 3 above shall be given, under the same conditions, the information referred to in Article 5.*
5. *The authorisation referred to in paragraphs 2 and 3 above may be withdrawn at any time in the best interests of the person concerned.*

Article 13 - Interventions on the human genome

An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.

Article 28 – Public debate

Parties to this Convention shall see to it that the fundamental questions raised by the developments in biology and medicine are the subject of appropriate public discussion in the light, in particular, of

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relevant medical, social, economic, ethical and legal implications, and that their possible application is made the subject of appropriate consultation.[128]

The Oviedo Convention is accompanied by a number of "additional protocols" that address different aspects and topics of biomedicine. As of today, four additional protocols have been drafted:*"one prohibiting the cloning of human beings (in force since 1March 2001), one on the transplantation of organs and tissues of human origin (in force since 1 May 2006), one on biomedical research (in force since 1 September 2007 and one on genetic testing for health purposes (not yet in force). Another additional protocol on the protection of the human embryo had been planned but was never achieved due to the very divergent positions of the member states of the Council of Europe on the status of the human embryo."*[129]

Protocols[130]

- Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings (ETS No. 168).
- Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin (ETS No. 186).
- Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (CETS No. 195).
- Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes (CETS No. 203).

Note: Not all Countries have ratified the Convention. To date, countries like Germany, Ireland, the Russian Federation, and the UK haven't ratified the Convention. Some countries like France, Denmark. Croatia and others have expressed reservations.[131]

Legal status of the Treaties of the CoE

"The Council of Europe Treaty Series groups together all the conventions concluded within the Organisation since 1949. Whatever they are called ("agreement", "convention", "arrangement", "charter", "code", etc.), all these texts are international treaties in the sense of the Convention of Vienna of 1969 on the law of treaties.

The conventions of the Council of Europe are prepared and negotiated within the institutional framework of the Council of Europe. Negotiations culminate in a decision of the Committee of Ministers to adopt the

[128] https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=090000168007cf98
[129] http://www.comece.eu/dl/KlMkJKJOllkJqx4KJK/20091029PUBIO_EN.pdf
[130] The full text of the protocols can be found at :https://www.coe.int/en/web/bioethics/oviedo-convention
[131] https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164/signatures?module=signatures-by-treaty&treatynum=164

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final text of the proposed treaty. It is then agreed to open the treaty for signature by member States of the Council and, if necessary, by the other States or organisations who have taken part in its elaboration.

The conventions of the Council of Europe are not statutory acts of the Organisation. They owe their legal existence to the consent of those member States that sign and ratify them"[132]

Other relevant legal texts issued by the CoE

- Statement on Genome Editing Technologies by the Committee on Bioethics (2015):[133]

The Committee agrees to investigate innovations on genetic engineering under the principles prescribed by the Oviedo Convention.

- Safety, quality and ethical matters related to the use of organs, tissues and cells of human origin. Council of Europe conventions, recommendations, resolutions and reports. 3rd edition (2017)[134]
- Guide to the quality and safety of tissues and cells for human application. 4th edition, 2019[135]

12.3.3 European legal framework

The following bodies are responsible for various topics related to health issues in the EU in different areas of regulation.

1. European Group on Ethics in Science and New Technologies (EGE): https://ec.europa.eu/info/research-and-innovation/strategy/support-policy-making/scientific-support-eu-policies/ege_en
2. Directorate-General for Research and Innovation: https://ec.europa.eu/info/departments/research-and-innovation_en
3. DG SANTE: Directorate-General for Health and Food Safety: https://ec.europa.eu/info/departments/health-and-food-safety_en
4. European Medicines Agency: http://www.ema.europa.eu/
5. European Data Protection Board (EDPB): https://edpb.europa.eu/

i. Primary Legislation (Treaties)

The overall framework

On the level of the EU there are some limits with regard to its power to regulate health issues On the one hand, *"the EU does not possess the legislative competence to act in areas of policy where*

[132] https://www.coe.int/en/web/conventions/about-treaties
[133] https://rm.coe.int/168049034a
[134] https://freepub.edqm.eu/publications
[135] https://freepub.edqm.eu/publications

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bioethical questions are of central importance".[136]On the other hand, the emergence of new technologies that transcend national boundaries and generate challenges that cannot be addressed at a national level, and *which "are creating a practical necessity for the EU to assume a certain role of responsibility and to take decisions within this domain".* Having said that, we should clarify that *"EU countries hold primary responsibility for organizing and delivering health services and medical care*".[137] To this extent, under the principle of subsidiarity the EU health policy serves as complementary to national policies with the overall objective to ensure health protection in all EU policies. Therefore, the EU exercises subsidiarity monitoring in the area of public health. As the official website of the EU explains:"*Under the Treaty of Lisbon, public health is a policy area where the Union supports, complements or supplements the actions of the Member States (Article 6 TFEU). However, common safety concerns in public health matters are an area where competence is shared between the Union and the Member States (Article 4 TFEU). The dual nature of the competences in the area of public health is reflected in the different types of measures that the EU can take under article 168 TFEU:*

- *On the one hand the EU may adopt harmonisation measures setting high standards of quality and safety for organs, substances of human origins and medicinal products and devices, and also adopt protective measures in the sanitary and phytosanitary fields [art. 168 (4) TFEU];*
- *On the other hand, the EU may also adopt incentive measures in other matters pertaining to the protection and improvement of human health, i.e. for combating major cross-border health scourges, monitoring, early warning of and combating serious threats to health as well as measures which have as their direct objective the protection of public health regarding tobacco and the abuse of alcohol. The harmonisation of national laws and regulations is excluded in these fields. [art. 168 (5) TFEU];*
- *Finally, the EU can encourage and support cooperation between the Member States in the area of public health through the open method of coordination [art. 168 (2) TFEU[138]].*

More specifically,*"EU policies and actions in public health aim to:*

- *Protect and improve the health of EU citizens*
- *Support the modernization of health infrastructure*
- *Improve the efficiency of Europe's health systems.*

Strategic health issues are discussed by representatives of national authorities and the European Commission in a senior-level working group on public health. EU institutions, countries, regional and local authorities, and other interest groups contribute to the implementation of the EU's health strategy".[139]

Health Legislation in the EU

[136] https://ec.europa.eu/health/policies/overview_en
[137] Ibid.
[138] https://portal.cor.europa.eu/subsidiarity/policyareas/Pages/PublicHealth.aspx
[139] https://ec.europa.eu/health/policies/overview_en

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"The EU can adopt health legislation under the Treaty on the Functioning of the European Union: Article 168 (protection of public health), Article 114 (approximation of laws) and Article 153 (social policy). Areas where the EU has adopted legislation include:

- Patients' rights in cross-border healthcare
- Pharmaceuticals *and* medical devices *(*pharmacovigilance, falsified medicines, clinical trials*)*
- Serious cross border health threats
- Tobacco
- Organs, blood, tissues and cells."[140]

Charter of Fundamental Rights (2007)

The main framework and legal text in the EU that protects fundamental rights but also provides answers to the challenges and dilemmas that we encounter in the study of bioethics is the Charter of Fundamental Rights].[141] The Charter establishes a catalogue of fundamental rights (civil, political, social and economic rights). It also establishes a number of principles that aim to address the challenges of modern society (bioethics, data protection, proper administration). The Charter begins with reference to the inviolability of "**human dignity"** in article 1, defining in this way explicitly the importance and primacy of "human dignity" which as a principle and value permeates the whole Charter text.

Below we provide the full text of some of the basic articles that constitute the backbone of legal provisions in relation to bioethics in general and organoids in particular

Article 1: Human dignity

Human dignity is inviolable. It must be respected and protected.

The Charter recognises a "right to life" in its Article 2; however, the Member States do not agree as to whether or not "everyone" includes the human embryo:

Article 2: Right to life

1. Everyone has the right to life.

2. No one shall be condemned to the death penalty, or executed.

Article 3: Right to the integrity of the person

Everyone has the right to respect for his or her physical and mental integrity. In the fields of medicine and biology, the following must be respected in particular:

[140] https://ec.europa.eu/health/policies/overview_en
[141] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2007:303:0001:0016:EN:PDF

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a. *the free and informed consent of the person concerned, according to the procedures laid down by law;*
b. *the prohibition of eugenic practices, in particular those aiming at the selection of persons;*
c. *the prohibition on making the human body and its parts as such a source of financial gain;*
d. *the prohibition of the reproductive cloning of human beings*

Article 8: Protection of personal data

1. *Everyone has the right to the protection of personal data concerning him or her.*
2. *Such data must be processed fairly for specified purposes and on the basis of the consent of the person concerned or some other legitimate basis laid down by law. Everyone has the right of access to data which has been collected concerning him or her, and the right to have it rectified.*
3. *Compliance with these rules shall be subject to control by an independent authority"*[142].

"In the negotiations, not all Member States were able to agree on prohibiting any creation of human embryos for research purposes; on the other hand, several Member States insisted that a lack of a specific provision or prohibition does not imply a justification for the creation of human embryos for research, for example by way of so-called therapeutic cloning. When it comes to the issue of human cloning, it is noteworthy that, unlike the Oviedo Convention of the Council of Europe, the Charter of Fundamental Rights does not prohibit the creation of human embryos for research purposes. It only prohibits reproductive cloning of human embryos. The Explanations on the Charter (prepared by the Bureau of the Convention) explicitly state that whilst Article 3 of the Charter prohibits only reproductive cloning: "It neither authorises nor prohibits other forms of cloning. Thus, it does not in any way prevent the legislature from prohibiting other forms of cloning". This reveals a de facto split among EU Member States when it comes to the interpretation of the fundamental Articles 1 - 3 of the Charter of Fundamental Rights.[143]

<u>*Legal value of the Charter of Fundamental Rights*</u>

"*The Charter became legally binding on the EU with the entry into force of the Treaty of Lisbon, in December 2009 under article 6 (1)and now has the same legal value as the EU treaties. The charter applies to the European institutions, subject to the principle of subsidiarity, and may under no circumstances extend the powers and tasks conferred on them by the treaties. The charter also applies to EU countries when they implement EU law*".[144] Therefore the European Court of Justice (ECJ) has jurisdiction to hear about cases against member state when infringing the Charter and given that they implement EU law.

[142] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2007:303:0001:0016:EN:PDF
[143] AN OVERVIEW REPORT ON BIOETHICS IN THE EUROPEAN UNION, COMECE Secretariat of the Commission of the Bishops' Conferences of the European Community, October 2009, www.comece.euhttp://www.comece.eu/dl/KlMkJKJOllkJqx4KJK/20091029PUBlO_EN.pdf
[144] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=LEGISSUM:l33501&from=EL

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In relation to how it has been addressed by the European Court of Justice before becoming an integral part of the Treaty of Lisbon (2007, came into force in 2009) it is acknowledged that "*the Charter was proclaimed by the European Council at Nice in December 2000. The European Court of Justice in fact did not refer to the Charter of Fundamental Rights until June 2006.Although, before that date, it was often referred to by the Court of First Instance and the Advocates General. In acknowledging the fact that the Charter is not a legally binding instrument, the Court stated clearly that the principal aim of the Charter is not to create any new rights but to reaffirm 'rights as they result, in particular, from the constitutional traditions and international obligations common to the Member States, the Treaty on European Union, the Community Treaties, the [ECHR], the Social Charters adopted by the Community and by the Council of Europe and the case-law of Court and of the European Court of Human Rights. Therefore, even as a "political declaration", the Charter has had a significant impact on EU law.*"[145]

ii. Secondary Legislation

A search performed at Eur-Lex, the official database for European legislation, with the key word "stem cells" has returned 266 results referring both to secondary legislation and judicial decisions (jurisprudence). Not all results are relevant to our study. A selection of the most relevant results is reported below.[146]

Directives and Regulations (selection)

1. Directive 98/44/EC of the European Parliament and the Council of 6 July 1998on the legal protection of biotechnological inventionshttps://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31998L0044&from=EN
2. Clinical Trials Directive2001/20/EC: https://ec.europa.eu/health/human-use/clinical-trials/directive_en. The Clinical Trials Regulation 536/2014 is set to replace the Directive once it comes into application https://ec.europa.eu/health/human-use/clinical-trials/regulation_en
3. Directive 2004/23/EC on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage, and Distribution of Human Tissues and Cells: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32004L0023:EN:HTML
4. Directive 2005/28/EC Laying Down Principles and Detailed Guidelines for Good Clinical Practice as Regards Investigational Medicinal Products for Human Use, as Well as the Requirements for Authorization of the Manufacturing or Importation of Such Products: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF
5. Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation,

[145] AN OVERVIEW REPORT ON BIOETHICS IN THE EUROPEAN UNION, COMECE Secretariat of the Commission of the Bishops' Conferences of the European Community, October 2009, www.comece.euhttp://www.comece.eu/dl/KlMkJKJOllkJqx4KJK/20091029PUBIO_EN.pdf

[146] https://eur-lex.europa.eu/search.html?scope=EURLEX&text=%22stem+cells%22&lang=en&type=quick&qid=1616883545077

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storage and distribution of human tissues and cells (Text with EEA relevance)https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:294:0032:0050:EN:PDF

6. Regulation (EC) No. 1394/2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) No. 726/2004: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF
7. Directive 2009/41 EC Genetically Modified Organism (GMO)aspects for investigational medicinal Products: https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_en
8. Regulation No. 536/2014 of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, Repealing Directive2001/20/EC: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:125:0075:0097:EN:PDF
9. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the Protection of Natural Persons with Regard to the Processing of Personal Data and on the Free Movement of Such Data, and Repealing Directive 95/46/EC (General Data Protection Regulation): http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN
10. Commission Implementing Regulation (EU) 2017/556 of 24March 2017 on the Detailed Arrangements for the Good Clinical Practice Inspection Procedures Pursuant to Regulation (EU) No 536/2014of the European Parliament and Council: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0556&from=EN

iii. Soft law (Recommendations/Statements/Opinions)

1. EGE- Ethics on Genome Editing, Opinion No 32, March 2021 (https://op.europa.eu/en/web/eu-law-and-publications/publication-detail/-/publication/6d9879f7-8c55-11eb-b85c-01aa75ed71a1) - Executive summary of the opinion Ethics of Genome Editing 2021 (https://op.europa.eu/en/publication-detail/-/publication/2060ebc6-a3db-11eb-9585-01aa75ed71a1/language-en/format-PDF/source-search)
2. EGE -Statement on Gene Editing (https://ec.europa.eu/info/sites/default/files/research_and_innovation/ege/gene_editing_ege_statement.pdf) - Statement of the Commission Related to Research Activities Involving Human Embryonic Stem Cells (2013) (https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:373:0012:0015:EN:PDF)
3. Opinion No. 22 - The Ethics Review of hESC FP7 Research Projects (2007) (http://bookshop.europa.eu/ga/recommendations-on-the-ethical-review-of-hesc-fp7-research-projects-pbKAAJ07022/downloads/KA-AJ-07-022-EN-C/KAAJ07022ENC_002.pdf;pgid=y8dIS7GU)
4. Guidelines on consent under Regulation 2016/679, WP259 rev.01 (http://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=623051)
5. Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation(CTR) and the General Data Protection regulation (https://edpb.europa.eu/our-work-tools/our-documents/opinion-art-70/opinion-32019-concerning-questions-and-answers)

iv. Jurisprudence/European Court decisions

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Below we present two cases at the European Court of Justice (ECJ) that are important for the definition of a human embryo and hence for deciding the critical point regarding the protection of a human life and being and all relevant rights that stem from that.

(I)

Judgment of the Court (Grand Chamber) of 18 October 2011.
Oliver Brüstle v Greenpeace eV.
Reference for a preliminary ruling: Bundesgerichtshof - Germany.
Directive 98/44/EC - Article 6(2)(c) - Legal protection of biotechnological inventions - Extraction of precursor cells from human embryonic stem cells - Patentability - Exclusion of 'uses of human embryos for industrial or commercial purposes' - Concepts of 'human embryo' and 'use for industrial or commercial purposes'.
Case C-34/10

The Court states that:

"*26. Although the text of the Directive does not define human embryo, nor does it contain any reference to national laws as regards the meaning to be applied to those terms. It therefore follows that it must be regarded, for the purposes of application of the Directive, as designating an autonomous concept of European Union law which must be interpreted in a uniform manner throughout the territory of the Union.*

35. Accordingly, any human ovum must, as soon as fertilised, be regarded as a 'human embryo' within the meaning and for the purposes of the application of Article 6(2)(c) of the Directive, since that fertilisation is such as to commence the process of development of a human being.

36. That classification must also apply to a non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted and a non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis. Although those organisms have not, strictly speaking, been the object of fertilisation, due to the effect of the technique used to obtain them they are, as is apparent from the written observations presented to the Court, capable of commencing the process of development of a human being just as an embryo created by fertilisation of an ovum can do so.

[…]

48. It is raised in a case concerning the patentability of an invention involving the production of neural precursor cells, which presupposes the use of stem cells obtained from a human embryo at the blastocyst stage. It is apparent from the observations presented to the Court that the removal of a stem cell from a human embryo at the blastocyst stage entails the destruction of that embryo.

49. Accordingly, on the same grounds as those set out in paragraphs 32 to 35 above, an invention must be regarded as unpatentable, even if the claims of the patent do not concern the use of human embryos,

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where the implementation of the invention requires the destruction of human embryos. In that case too, the view must be taken that there is use of human embryos within the meaning of Article 6(2)(c) of the Directive. The fact that destruction may occur at a stage long before the implementation of the invention, as in the case of the production of embryonic stem cells from a lineage of stem cells the mere production of which implied the destruction of human embryos is, in that regard, irrelevant".[147]

From the shot text provided above from the court proceedings on the specific case, we understands that the Court provides an interpretation of important legal terms which is not the usual case. As Heger and Spranger explain"… the ***ECJ defined a uniform and very broad concept of the term "embryo"*** *for the field of patent law. An embryo is, subsequently, each human egg cell from the stage of its fertilization onward. Even unfertilized egg cells, which gain the potential to develop into complete organisms through artificial means (cell nuclear transfer constructs, parthenogenesis, etc.), were included in this definition. Regarding cell types that are extracted from embryos in the blastocyte phase, the ECJ found that it is the business of the national courts to decide, in light of the technical development, whether the cells have the ability to develop to complete organisms and thereby fall within purview of this definition.*

Regarding the term "use," the ECJ decided that every invention regarding a process that includes the prior destruction of embryos, or their use as source material, represented an industrial or commercial use of embryos. According to the court, it is immaterial whether the process—such as in the current case—did not refer to the use of human embryos. Finally, the court did also find that using embryos for research purposes is an industrial or commercial use in terms of the biopatent directive and thus leads to the exclusion of patentability."[148]

(II)

Case C-364/13: Judgment of the Court (Grand Chamber) of 18 December 2014 (request for a preliminary ruling from the High Court of Justice (Chancery Division) — United Kingdom) — International Stem Cell Corporation v Comptroller General of Patents, Designs and Trade Marks (Reference for a preliminary ruling — Directive 98/44/EC — Article 6(2)(c) — Legal protection of biotechnological inventions — Parthenogenetic activation of oocytes — Production of human embryonic stem cells — Patentability — Exclusion of 'uses of human embryos for industrial or commercial purposes' — Concepts of 'human embryo' and 'organism capable of commencing the process of development of a human being')

According to the proceedings of the Court:

13. *By its question, the national court asks, in essence, whether Article 6(2)(c) of Directive 98/44 must be interpreted as meaning that an unfertilised human ovum whose division and development to a*

[147] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:62010CJ0034&qid=1616883545077&from=EN
[148] M. Heyer, T.M. Spranger (2013) The European Court of Justice's Decision Regarding the Brüstle Patent and Its Implications for the Legality of Stem Cell Research Within the European Union**,** *Stem Cells and Development,* Dec 2013.50-53http://doi.org/10.1089/scd.2013.0357.

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certain stage have been stimulated by parthenogenesis constitutes a 'human embryo' within the meaning of that provision.

22. *The Court notes as a preliminary point that the purpose of Directive 98/44 is not to regulate the use of human embryos in the context of scientific research and that it is limited to the patentability of biotechnological inventions (see judgment in Brüstle, EU:C:2011:669, paragraph 40).*
23. *Moreover, 'human embryo', within the meaning of Article 6(2)(c) of that directive, must be regarded as designating an autonomous concept of EU law which must be interpreted in a uniform manner throughout the territory of the Union (see judgment in Brüstle, EU:C:2011:669, paragraph 26).*
24. *As regards that interpretation, the Court held, in paragraph 34 of the judgment in Brüstle(EU:C:2011:669), that, as follows from the context and aim of Directive 98/44, the EU legislature intended to exclude any possibility of patentability where respect for human dignity could thereby be affected and that it follows that the concept of 'human embryo' within the meaning of Article 6(2)(c) of that directive must be understood in a wide sense.*
25. *In paragraph 35 of that judgment, the Court stated that, accordingly, any human ovum must, as soon as fertilised, be regarded as a 'human embryo' within the meaning and for the purposes of the application of Article 6(2)(c) of that directive, since that fertilisation is such as to commence the process of development of a human being.*
26. *The Court specified, in paragraph 36 of that judgment, that that classification must also apply to a non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted and a non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis. The Court added that, although those organisms have not, strictly speaking, been the object of fertilisation, due to the effect of the technique used to obtain them they are, as is apparent from the written observations presented to the Court in the judgment in Brüstle(EU:C:2011:669), capable of commencing the process of development of a human being just as an embryo created by fertilisation of an ovum can do so.*
27. *It thus follows from the judgment inBrüstle (EU:C:2011:669) that* a non-fertilised human ovum must be classified as a 'human embryo', within the meaning of Article 6(2)(c) of Directive 98/44, in so far as that organism is 'capable of commencing the process of development of a human being'.
28. *As the Advocate General observed, in essence, in point 73 of his Opinion in the present case, that term must be understood as meaning that, in order to be classified as a 'human embryo', a non-fertilised human ovum must necessarily have the inherent capacity of developing into a human being.*
29. *Consequently, where a non-fertilised human ovum does not fulfil that condition, the mere fact that that organism commences a process of development is not sufficient for it to be regarded as a 'human embryo', within the meaning and for the purposes of the application of Directive 98/44.*
30. *By contrast, where such an ovum does have the inherent capacity of developing into a human being, it should, in the light of Article 6(2)(c) of that directive, be treated in the same way as a fertilised human ovum, at all stages of its development.*

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31. *In the judgment in Brüstle (EU:C:2011:669), it was apparent from the written observations presented to the Court that an unfertilised human ovum whose division and further development have been stimulated by parthenogenesis did have the capacity to develop into a human being.*
32. *This is precisely why, on the basis of those observations, the Court held, in that judgment, that, in order to define the term 'human embryo', within the meaning of Article 6(2)(c) of Directive 98/44, a non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis should be treated in the same way as a fertilised ovum and, therefore, be classified as an 'embryo'.*
33. *However, in the present case, the referring court, as is apparent from paragraph 17 of this judgment, stated in essence that, according to current scientific knowledge, a human parthenote, due to the effect of the technique used to obtain it, is not as such capable of commencing the process of development which leads to a human being. That assessment is shared by all of the interested parties who submitted written observations to the Court.*
34. *Moreover, as was observed in paragraph 18 of this judgment, in the case in the main proceedings, ISCO amended its applications for registration to exclude the prospect of the use of additional genetic manipulation.*
35. *In those circumstances, the case in the main proceedings relates solely to the classification, in the light of Article 6(2)(c) of Directive 98/44, of a human parthenote in itself, and not of a parthenote which is the subject of additional manipulation falling within the scope of genetic engineering.*
36. *It is for the referring court to determine whether or not, in the light of knowledge which is sufficiently tried and tested by international medical science (see, by analogy, judgment in Smits and Peerbooms, C-157/99, EU:C:2001:404, paragraph 94), human parthenotes, such as those which are the subject of the applications for registration in the case in the main proceedings, have the inherent capacity of developing into a human being.*
37. *If the referring court were to find that those parthenotes do not have such a capacity, it should infer from this that they do not constitute 'human embryos', within the meaning of Article 6(2)(c) of Directive 98/44.*
38. *In view of the foregoing considerations, the answer to the question referred is that Article 6(2)(c) of Directive 98/44 must be interpreted as meaning that an unfertilised human ovum whose division and further development have been stimulated by parthenogenesis does not constitute a 'human embryo', within the meaning of that provision, if, in the light of current scientific knowledge, that ovum does not, in itself, have the inherent capacity of developing into a human being, this being a matter for the national court to determine"*[149]

At this case again emphasis is placed on what constitutes a 'human embryo". The Court does not provide a clear answer but brings new perspectives regarding "parthenotes" that should be taken into consideration by the referring court. Thus while "*within the meaning of Article 6(2)(c) of Directive 98/44, a non-fertilised human ovum whose division and further development have been stimulated by*

[149] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:62013CJ0364&from=EN

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parthenogenesis should be treated in the same way as a fertilised ovum and, therefore, be classified as an 'embryo'(paragraph 32) at the current case examined by the Court "*according to current scientific knowledge, a human parthenote, due to the effect of the technique used to obtain it, is not as such capable of commencing the process of development which leads to a human being.(paragraph33).* In the end the Court allows the national court to determine the definition of "human embryo" and "*if, in the light of current scientific knowledge, that ovum does not, in itself, have the inherent capacity of developing into a human being" (paragraph 38).*

12.4 Insights/debates

The literature presents some interesting points regarding the challenges that organoid research have generated. Many of these challenges relates research on and with brain organoids. Some of these challenges are discussed below.

Regarding the development of consciousness Hyun et al. (2020) explain the ambiguity of the term "consciousness" and the several possible meanings it may conceive.[150] Consciousness may mean a "*basic neuronal activity in a cortical region upon stimulation (what one might call pre-conscious sensory stimulation without subsequent subjective awareness of the sensory input)*",[151] and in this sense, according to the authors these organoids are "ethically innocuous." On the other hand, if an interpretation of "consciousness directs to something much more complex –"*in ascending order: conscious access to sensory stimulation; wakefulness; vigilance; focal attention; sentience; and lastly, subjective self-awareness – then the ethical stakes might indeed be raised, although, in our opinion, in inverse proportion to the scientific likelihood that these other forms of consciousness could emerge in brain organoids and assembloids.*"[152] The authors believe though that "*each of these more complex conscious states requires, at minimum, the global integration and activation of cortical neurons across long distances and involving multiple brain regions simultaneously.*[153]*Brain organoids and assembloids lack this complex network structure, the full complement of cell types, and the sensory inputs necessary to give rise to any discernable subjective experiences.*"[154]

In relation to what constitutes a human subject, and at which point we identify a subject and its legal protections Lavazza and Pizzetti provide a concrete analysis. By referring to Italian and Europeancase-law they state that an embryo should be considered *a "human subject", and not merely a "possess", if (and only if) it contains the "origin of human life", which means that it must have the "intrinsic" ability to self-develop into a human being*"[155]. The way Lavazza and Pizzetti approach the

[150] S. Dehaene (2014). *Consciousness and the Brain*. Penguin Books, New York, as cited in Hyun et al, p.146653 and alsoN. Block (2002), "Some Concepts of Consciousness", in D. Chalmers (ed.), *Philosophy of Mind: Classical and Contemporary Readings*, 2002, Oxford, OUP (revised version, available online: epa.psy.ntu.edu.tw).
[151] I. Hyun, J.C. Scharf-Deering, J. Lunshof (2020) Ethical issues related to brain organoid research, *Brain Research,* Volume 1732, 2020.
[152] I. Hyun et al, p.146653.
[153] I. Hyun et al, p.146653.
[154] I. Hyun et al, p.146653.
[155] A. Lavazza, F.G. Pizzetti (2020) Human cerebral organoids as a new legal and ethical challenge, *Journal of Law and the Biosciences*, Volume 7, Issue 1, January-June 2020, lsaa005, https://doi.org/10.1093/jlb/lsaa005.

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issues of human cerebral organoid is interesting. They claim that *"a human cerebral organoid (HCO) is a never-born entity: an HCO, in fact, was not born from a womb, and is also profoundly different from a human embryo. The cerebral organoid, in fact, is the product of sophisticated genetic techniques on adult (and not embryonal) stem cells, which does not show any aptitude to self-develop into a complete human being. As a conclusion, cerebral organoids cannot be considered, under any legal circumstances, as "subjects" or, a fortiori, as "persons."*

The authors acknowledge, on the other hand, that if human cerebral organoids develop conscious capabilities and become more sophisticated sentient entities the law should deal with this potential differently but by also keeping in mind that many countries like Italy *"currently protects animals—which are living but not human entities, and which do not have legal personhood—against torture, cruelty, severe suffering both in clinical and cosmetic trials*".[156] To this extent it seems reasonable and essential from a legal standpoint for the law *"to promulgate new rules for clinical trials to prevent "suffering" in human cerebral organoids, even if they are neither human legal subjects nor human legal person".*[157]

Therefore according to the analysis provided by Lavazza and Pizzetti according to the rulings of current legislation it can *"be concluded that HCOs have no right to any special legal protection, as they do not fall into any category other than that of biological material, which is subject to its own specific rules*".[158] Certainly any future developments and evidence but also the case of unexpected development of capabilities especially in relation to the "consciousness' of HCOs would require further ethical and legislative scrutiny.

Although the moral status of organoids[159] is mainly an ethical issue, it is a topic that is considered important from a legal perspective as well. The maturation and increasing complexity of organoids and the extent to which they resemble human embryos creates questions about the creation of human life in vitro.

Literature also stresses the importance for the definition of the "human embryo" due to the variety that the definition of human embryo presents across jurisdictions. While there are countries that do not provide a definition in their respective legislation some others *"define an embryo as the product of the union of sperm and egg but leave open the possibility of reconsidering the definition, which many jurisdictions have done in light of advances in human somatic cell nuclear transfer. In a number of countries, including Germany, the regulations consider developmental potential in the definition of an embryo, which could capture a broad range of experimentally derived entities. The Dutch and Belgian Embryo Acts define the embryo as a cell or a collection of cells "with the capacity to develop into a human being." The Australian legislation defines the embryo as including "any other process that initiates organised development of a biological entity with a human nuclear genome or altered human*

[156] Lavazza and Pizzetti, ibid.
[157] Lavazza and Pizzetti, ibid.
[158] Lavazza and Pizzetti, ibid.
[159] M. Munsie *et al*. (2017) "Ethical Issues in Human Organoids and Gastruloid Research", *The Company of Biologists*, vol. 144, p. 942.

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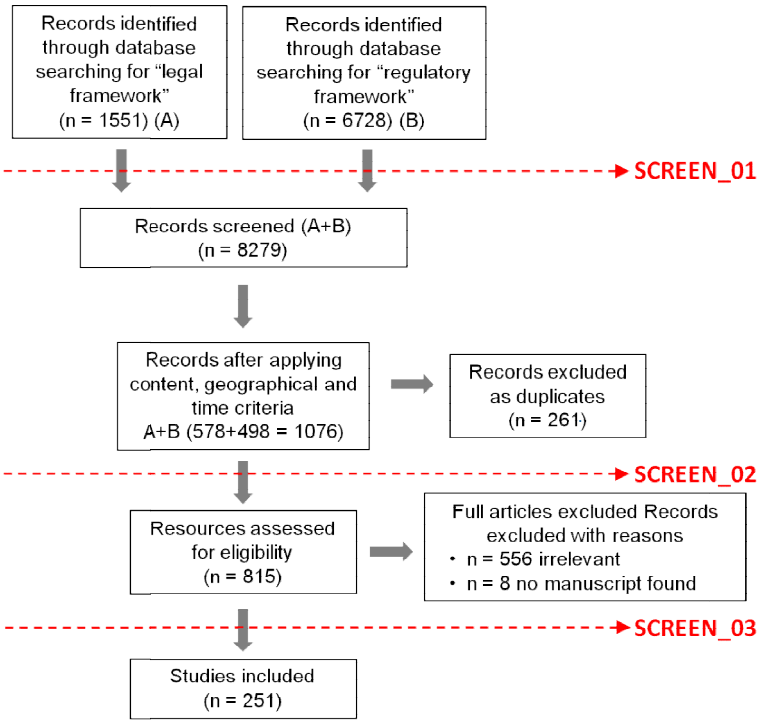
nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears.[160]

In this section only a few insights were presented as they accrue from literature. As the scoping review of articles has shown there are many more studies and papers that address these sensitive issues, However, a detailed literature review that could have revealed additional points of contestation and debates puzzling legal scholars in relation to organoids and relevant technologies, is not part of this mapping report.

12.5 Scoping review flowchart for legal/normative-related resources



12.6 Conclusions

The current legislative framework provides several safeguards and rights that demand "absolute protection" when applying health innovations. Despite the international legal framework provided by The Oviedo Convention and European legislation there are still several discrepancies in national legislations that allow for different approaches as health issues remain to be regulated mainly by Member States with the EU holding a subsidiarity oversightin the area of public health and bioethics-

[160] M.F. Pera, G. de Wert, W. Dondorp, R. Lovell-Badge, C.L. Mummery, M. Munsie, P.P. Tam (2015). What if stem cells turn into embryos in a dish? *Nature Methods*, *12*(10), 917-919 https://doi.org/10.1038/nmeth.3586.

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related issues. However, in spite of this duality in legislative powers,[161] fundamental rights and liberties are not under contestation. Core values and rights like the protection of human life from very early stages, and human dignity, are sufficiently protected and set the limits and provide acceptable boundaries in human activity and research regarding health innovations and biomedical interventions.

The dilemmas and ambiguities, in relation to organoid research, are due to their nature and due to the uncertainty about the potential clinical applications and not to legal provisions related to organoid research. The main problem is that there is still uncertainty and doubt about what to anticipate with regard to the development of such health innovations. Legislation is expected to provide protection and set the rules for scientific research. Legal provisions are general and abstract but at the same time very specific on the level of protection they provide. New advancements in health research should be examined under the prism of existing legislation by taking into consideration the rapid growth of scientific research while ensuring the protection of human life and human dignity as their main priority. Finally, as the study of Bioethics in which organoids and relevant technologies are included, constitutes a broad area of research with interdisciplinary character, the development of synergies between scholars and scientists from different disciplines is essential in order to provide answers the debates raised by organoid research.

13 Research Integrity framework mapping

13.1 Systematic scoping review results

The Scoping Review study resulted in 92 peer reviewed articles about research integrity-related guidelines, frameworks or debates. Among this limited number of peer reviewed articles (by comparison with the number of retrieved articles related to the research ethics and legal/normative parts of the study) the majority deal with data management. Of the 92 articles retrieved, most of them are relevant to data management practices targeting mainly biobanks and collaboration between different biobanks (as seen in Figure 6). Such articles study ICT technologies utilized by biobanks to safeguard anonymity of donors, like Blockchain, and discuss how to strike the right balance between the privacy of donors and requirements for Open Data.

A second, but significantly smaller, portion of articles explores strategies for Quality Assurance and Risk Management applied by biobanks or research consortia. Another portion of articles delves into the necessary requirements that render collaboration among biobanks effective. Specifically, these articles present recommendations for harmonization of data and metadata structures and development of standard operating procedures to render data from different biobanks equally FAIR (although this is not the term used). Finally, a batch of articles addresses the challenges of communicating with the

[161] For the differences among member states in relation to stem cell legislation a good overview is provided at: G. Charalambous, Genakritis (2013) Bioethics and European Union Legal Records Regarding Stem Cells, Health Science Journal, 7(2), 155-166.

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public and public engagement. The "Other" category includes a spectrum of different topics, like parliamentary debates, collaboration between private and public research performing organizations, conflicts of interest and challenges for translating findings from the lab to the clinic.

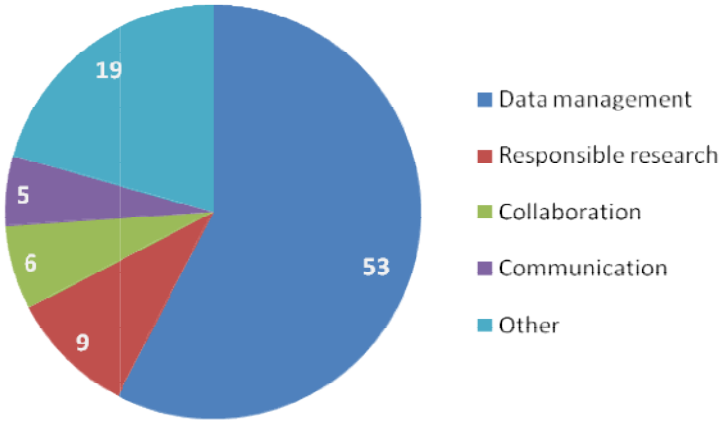

Figure 6: Diagram that depicts the research integrity-related categories which appeared in the 92 peer reviewed articles retrieved from the scoping review relevant to research integrity frameworks and debates. The numerals correspond to the number of articles in each category. The research integrity-related categories were named following the taxonomy developed by the SOPs4RI project.

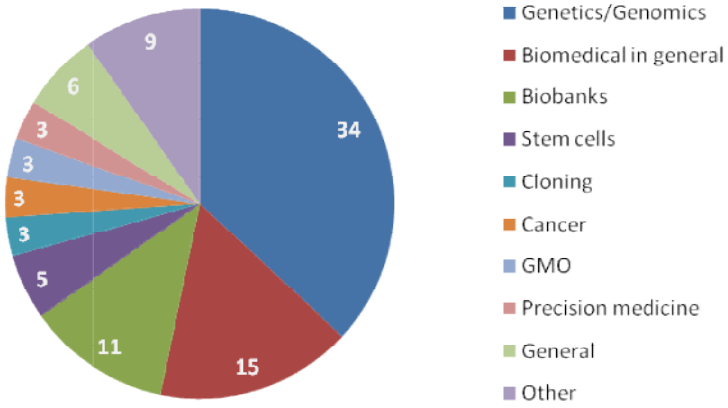

Figure 7: Diagram that depicts the fields of research related to the 92 peer reviewed articles retrieved from the scoping review relevant to research integrity frameworks and debates. The numerals correspond to the number of articles in each field of research.

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As seen in Figure 7, 34 articles were relevant to Genetics/Genomics research, including also discussions of biobanks in the context of these specific fields of research. Two smaller groups of articles were relevant to biomedical research and biobanks in general, without any reference to a specific technology. A few articles were relevant to Stem Cells, Cloning, Cancer, Genetically Modified Organisms and precision medicine. Finally, 6 articles discussed overarching issues, like health care organization, while the "Other" category includes other fields of research that appeared only in one article.

As a result, there was no article retrieved from the scoping review to be directly related to organoid research. They only provide "umbrella" recommendations, equally or more relevant to other types of research fields that have the common characteristic of using material derived from humans.

13.2 Grey literature

The bulk of information on research integrity-related guidelines were drawn from the search in grey literature that was conducted via Google search, as presented in Section 7.3. The most comprehensive collection of guidelines have been published by the American Society for Cell Biology (ASCB),[162] which formed a task force with Society members (including researchers, several of whom play critical roles in developing organoid systems; ethicists; and patient advocates) to generate recommendations and best practices to increase the impact of the field of organoid research. A set of recommendations have been drafted and an outline of research integrity-relatedpoints is presented below, as contained in the above mentioned guidelines[162] (with blue, italic letters):

" • The results from organoids have to be complemented by whole-organism studies in model systems and compared with actual human development, tissue organization, and physiology.

- *"Gold standards" and best practices must be defined for the study of organoids.*
- *The protocols for the derivation and culture conditions of organoids have to provide sufficient details to enable reproducibility.*
- *Criteria need to be developed that allow investigators to compare cell types and structures in an organoid to the composition and organization of the respective organ.*
- *The long-term advancement of organoid research relies on the distribution of tissue sources that are renewable and readily comparable between laboratories.*
- *The entry of new researchers at different career stages into this field should be encouraged and facilitated by establishing training sites where investigators can acquire and adapt organoid technology.*
- *Because of the rapid advancement in tissue culture techniques and the intricacy of materials and time frame needed to generate an organoid from a renewable tissue source, either existing facilities or practicing laboratories may offer better opportunities for training than more traditional training courses.*

[162] R. Lehman, C.M. Lee, E.C. Shugart, M. Benedetti, R.A. Charo, Z. Gartner, B. Hogan, J. Knoblich, C.M. Nelson, K.M. Wilson "Human organoids: a new dimension in cell biology" The American Society for Cell Biology (2019) DOI:10.1091/mbc.E19-03-0135.

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• *The potential of organoids for research and medicine brings with it ethical uncertainty and public concern. A clear definition of what organoids are and what they are not, as well as a realistic description of the opportunities they offer, should be articulated by scientists and scientific organizations in their communications.*"

To safeguard the reproducibility of organoid research results, after taking into account the potential sources of variability, the above-mentioned guidelines list a number of precautionary measures, a brief exposition of which is presented below, as contained in the above mentioned guidelines[162] (with blue, italic letters):

"• *Organoid protocols must be described in great detail in initial publications and all relevant data for the reagents used at every stage (cell isolation; organoid culture conditions; differentiation induction methods; isolation of differentiated cell types) must be provided*

• *Knowledge transfer should be made by by means of lab visits, facilities, and repositories that routinely culture and grow organoids; such practices are considered as more effective*

• *Criteria (transcriptomic profiles, surface antibody arrays, 3D reconstruction, single-cell analysis, and behavior after transplantation) need to be established for comparing the differentiated cell types and structures obtained in organoids with cell types and tissue organization present in normal tissues.*

• *It is likely that genetic background can affect the behavior of iPSCs carrying disease-associated mutations. It is therefore recommended that lines are derived and banked from multiple patients.*"

With regard to the sharing of materials and results, the following recommendations are relevant,as contained in the above mentioned guidelines[162] (with blue, italic letters):

"• *Set standards for quality of material preservation*

• *Develop standard procedures for organoid culture*

• *Engage in training*

• *Respect and enforce restrictions made by the donor through data depositories*

• *Facilitate communications with the donor for special consent (i.e., transplantation, embryoid generation, or germ cells/gamete manipulations)*

• *Distribute materials with accurate information, detailing quality-control protocols used for cell, tissue, organoid generation, and maintenance*

• *Collect and distribute biospecimens for broad distribution that were modified by individual labs, for example, to correct a specific genetic defect.*"

In addition, there are specific guidelines for sharing the outcomes of organoid research, as contained in the above mentioned guidelines[162] (with blue, italic letters):

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“ • Data and samples for research should be available for use by approved investigators without geographical restrictions

• Data and biospecimens should be distributed after the requesting approved researcher and their institution have agreed to and signed an appropriate Material Transfer Agreement (MTA) and, if needed, submitted an Institutional Research Board approval/exemption from their institution

• In the interest of rapid dissemination of data and findings, advancement of knowledge, and replicability of data, the MTA should include language in support of data sharing

• Investigators should agree to return generated data and modified biospecimens to a biobank or make materials available within an agreed-upon time or by the time of publication, whichever comes first.

• The sharing language could encourage or require the deposition of results in www.bioRxiv.org or a similar preprint server to facilitate free access.”

In communicating with the public the following recommendations have been produced, as contained in the above mentioned guidelines[162] (with blue, italic letters):

“ • Describe what organoids are and what they are not

• Clearly describe the potential opportunities of organoids to your research

• Articulate key discoveries that have resulted from organoids that would not have been possible using other approaches

• Acknowledge the unknowns and challenges

• Avoid talking about unpublished, non–peer-reviewed results

• Consult with researchers in other cutting-edge fields about their experiences working with the press and other audiences.”

In general, codes of conduct, guidelines, recommendations or best practices relevant to research integrity with a focus on organoid research are rather rare and difficult to find. It is characteristic that at the International Compilation of Human Research Standards (2020 Edition),[163] which compiles thousands of guidelines from all over the world, there is not a single document with reference in its title to organoids, while there are 117 documents for Cloning, 144 for Genetics and 180 for Stem Cells (i.e. the technologies that have been recognized as having relevance to organoid research at the GA document of HYBRIDA).

[163] International Compilation of Human Research Standards, Office for Human Research Protections, U.S. Department of Health and Human Services (2020).

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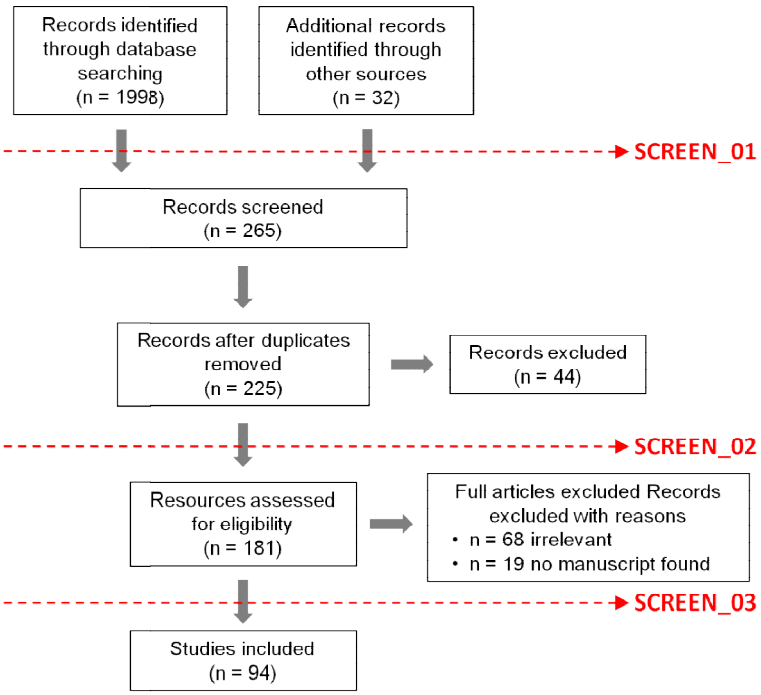
13.3 Scoping review flowchart for research integrity-related resources



13.4 Conclusions

Research integrity issues or debates directly related to organoids are less abundant in the literature than research ethics or legal/normative issues or debates related to organoids. This is probably related to the fact that research integrity-related issues are of a more cross-disciplinary character. As mentioned in section 12.1 the authors of this report have used the taxonomy of research integrity-related issues of the SOPs4RI project; this selection was made, based on the fact that the specific taxonomy has been created through an extensive empirical study, while the SOPs4RI guidelines that have been structured in line with this taxonomy have been adopted by the European Commission as a reference document in the new Horizon Europe framework programme. Here there is a link to the Horizon Europe standard application form – Version 3.0 (26 May 2021); the link to the SOPs4RI guidelines for research performing organizations is at page 5, Declaration point 6, "Appropriate procedures, policies and structures".

In the table below the nine SOPs4RI broad topics of research integrity relevant to research performing organizations are listed. The authors of this report have categorized them as "cross-disciplinary", when they do not have any kind of disciplinary focus. When an indirect connection to organoid or relevant technologies can be drawn, it is specifically described.

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Table 13.1: The disciplinary specificity of research integrity-related areas, according to the taxonomy of the SOPs4RI project.

No.	Research Integrity topic	Breadth of application
1	Research environment	Equally relevant to all disciplines
2	Supervision and mentoring	Equally relevant to all disciplines
3	Research integrity training	Equally relevant to all disciplines
4	Research ethics structures	Relevant to stem cell research in general [*e.g. informed consent, return of results/incidental findings*]
5	Data practices and management	Relevant to biobank procedures in general [*open data, FAIR data, (pseudo)anonymisation procedures, quality standards, data/metadata structures*]
6	Research collaboration	Relevant to biomedical research in general [*e.g. collaboration between public research performing organizations and industry*]
7	Publication and communication	Equally relevant to all disciplines
8	Declaration of interests	Equally relevant to all disciplines
9	Dealing with breaches of research integrity	Equally relevant to all disciplines

14 Expert interviews

14.1 Disclaimer

At the time of the drafting of the pre-final version of this deliverable, in July 2021, only 6 out of 18 interviews had been transcribed and securely sent to the NTUA team. As a result, the version that was submitted on time, i.e. at the end of July presented a limited part of the expert-interview study. For this reason NTUA with this new version of D3.1 that was submitted in August 2022 presents the comprehensive summary of all 18 interviews that were securely retrieved by NTUA on the 1st of October 2021

14.2 Results from the interviews

In the following sections we present the most important issues discussed during the interviews as conducted based on the three different questionnaires prepared for the three different types of interviewees.

14.2.1 Position of organoid research

There are two broad ethical and oversight issues for organoid research which stem from different spheres of research ethics. The first reflects the consensus that research ethics has to be scientifically justified, and the second reflects the opinion that organoid research has to be conducted with oversight

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over any material originating from human beings. These two broad issues provide the primary connections between organoid research and the fields of research ethics and research integrity.

Organoid research is a subcategory of the overarching domain of scientific research that uses human biomaterial. More particularly, it relates to the further subcategory of scientific research with human biomaterial, which either would be maintained in culture or transferred to an animal model (Figure 8). By way of comparison, when someone refers to cloning, several different meanings may be given to this specific research field. In the case of reproductive cloning, such research is prohibited. If we refer to research cloning, to obtain specific embryo types for basic research, then that falls under the area of biomedical research with human material in vitro, so there is some overlap in this case with organoid research (Figure 9).

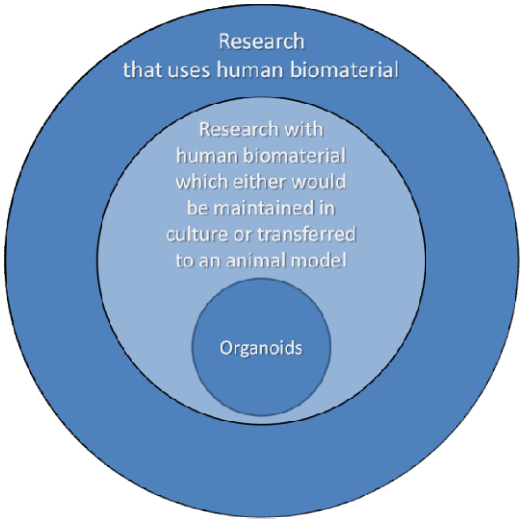

Figure 8: The position of organoid research within wider research fields.

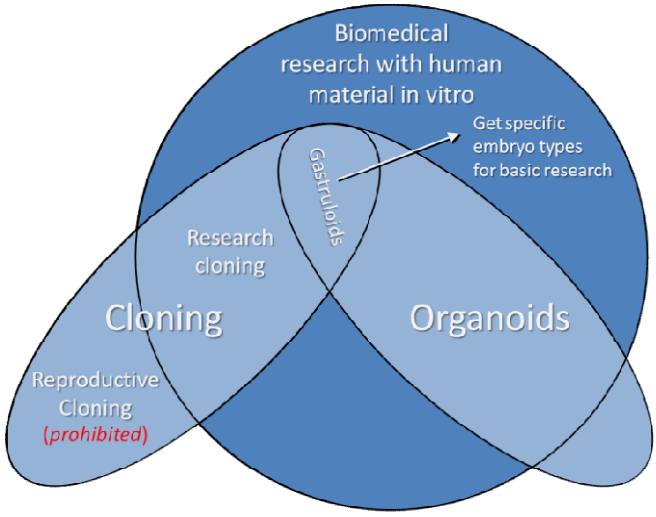

Figure 9: Relation of organoid and cloning research fields, in the context of biomedical research with human material in vitro.

Similarly, in gene editing, the relevant context depends on how this technology is used. Is it somatic cell gene editing? If it is gene editing of embryos or gametes, then we are closer to research with biomaterials, and we are not talking about transfer toward either use or reproduction, which is along the same line as reproductive cloning, meaning that no one is applying this type of research right now. In organoid research, what is important is that human biomaterials are utilized and there is further manipulation of these cells, to form organoids, cells being induced to make these small, three-dimensional models. At present such research is mostly confined to a dish. This is the closest relation of organoid research with Stem Cell research. As a bioethicist mentioned:

"That's the place where I would put the closest association with organoid research, it would be in vitro SC research."

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In the case of international guidelines for human Stem Cell research, there are typically three categories of concern which are utilized:

- **Category 1**, which is the least problematic, does not need full ethical review. The researcher needs to inform the administrator roughly about the content of the research. Traditionally this has been defined as use of an established SC line for in vitro study of cell differentiation. That was thought to be the least controversial, not in need of any kind of review or special oversight.
- **Category 2**, which is closer to more controversial work. Typically, this might involve experimentation on moving the cells into an animal model or proposing moving them into a human patient.
- **Category 3**, which is prohibited research; you are not supposed to do this work, which includes the breeding of chimeras, the transfer into the uterus of a modified human embryo, etc.

Organoid research traditionally would have been in category 1, and now it is being questioned whether or not we need to move it to category 2:

> *"It is no longer true that you can say with much confidence that we don't need to worry about simply in vitro work with established cell lines"*

The issues are becoming much more complex. In the past it was thought:

> *"What can be controversial about this work if you have proper informed consent, proper procurement of the cell line or the original starting materials, and you are not going to put it into a human or an animal? It is just going to be cells in a dish—we think that it is unproblematic to let SC develop into cardiac cells or nerve cells in a dish, and just end it there."*

The problem pointed out by our interviewees is that organoids are three-dimensional, self-organizing, and more complex than just driving a stem cell culture into a particular kind of cell type. The questions that arise are: When would you ever move this research to another category? Is there a particular type of organoid research that you would move out of category 1? What would be the reason? What would be actually reviewed? What questions would be asked during the review of an organoid protocol?

At present the connections of organoid research to other fields mostly fall within the continuum of the use of human cells for in vitro research. Viewing ethical issues in organoid research in terms of those raised for other fields fail to take into account the novelty of organoid research. The questions that were brought to the discussions by the interviewees were:

- Even if there are connections to other areas of research, what concerns did you not see clearly in the other areas?
- What would you be reviewing for in vitro research?
- Why should anybody be worried about what is happening in a culture dish, if it is not going into an animal or a human?

There is a need to explore further what kind of ethical issues warrant special review and oversight, and what the focus of that review should be.

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14.2.2 Ethical dimensions of organoid research

According to most interviewees, in order to respond to questions concerning ethical issues, one should first take into account the type of organoid. Specifically, if it involves organoid models of "less controversial human organs" like gut or liver organoid research, then, as one interviewee put it:

"It would be a good question to ask to researchers, but in my sense, researchers that do work on organoids other than brain organoids just don't really think that there is an ethical issue there, except maybe questions around informed consent of the original cell line donor."

It was also pointed out that a researcher could start to see what might be considered developmental incidental findings while working with an organoid model. For a control group of healthy volunteers, this is different from genetic incidental findings, since someone cannot detect problems until the organoid has been developed. Only then could research reveal some interesting, clinically relevant factors or properties of the original donor that wouldn't have been discovered through a genetic screening. The question then arises about the responsibilities of the researcher to get this information back to the original cell line donor. The key issue here is that the suspicion of a developmental incidental finding has to be validated.

The interviewee, whose quote is mentioned at the beginning of this section, emphasized that in the case of brain scan research or genetic research, there are ways to validate an initial suspicion with clinical tests, but there is nothing like that for organoids, since researchers are still validating organoid models themselves, i.e. their accuracy for recapitulating human development. Researchers are very excited about organoids, because this could be one particular way to personalized medicine, by taking a sample from a patient to create an organoid model and test it for various drug interactions. As a bioethicist put it:

"That's almost like a little mini-patient customized to the regular cell donor."

Coming to the ethical issues organoid researchers are already aware of, according to the interviews analysed at the time this deliverable was finalized, all interviewees supported the opinion that researchers are aware of how much informed consent has to be specific to any kind of organoid research. This knowledge goes hand in hand with questions like: Can you just use a commercial cell line? Can you just assume broad consent for this type of work? The opinion of one of the interviewees is that researchers do not worry too much about not having specific consent for, e.g., kidney organoid research. However, brain cells to grow cerebroids are something that people might care about. In addition, there could be research groups that are starting to worry about what to do with developmental incidental findings. As one bioethicist pointed out:

"That's the only other thing I can think of as generic across all organoid research: informed consent and incidental findings."

For brain organoid research, people will have a lot more to say. In this case, researchers and bioethicists are more concerned about questions around consciousness. So, it depends on what type of

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organoid research is at issue. For example, researchers question themselves whether a cerebroid is conscious or if it can develop consciousness (see also section 10.3.2), a question which would not come up for other organoid research groups. In the case of brain organoid research, one might argue for requiring the explicit consent of the original donors, because there is something special about brain organoid models when compared with other organoids.

14.2.3 The kind of help a REC member needs when assessing projects related to organoid research

According to most of the interviewees, it will be extremely helpful if a research ethics committee has members, or at least, be able to consult with experts in various fields of research, if not directly related to organoid research. For example, in the case of research on cerebroids the research ethics committee should be facilitated to consult with a neuroscientist. As a bioethicist pointed out, this could prove helpful:

> *"Because there are too many assumptions, and, I think, uneducated assumptions, about what brain organoids can possibly do in terms of supporting consciousness or mental states."*

Another bioethicist stressed that the composition of a REC should be based on how a project is going to be expanded, i.e. if it is going to involve surgery. In such cases, a really multidisciplinary composition is needed, where its members must have expertise in neurology, neurosciences, and neurosurgery, if necessary. However, RECs should involve ethicists in their composition. There were specific comments, from another bioethicist with additional expertise in Research Integrity:

> *"Eight times out of ten, there is no ethicist. You may need to have like a baseline foundational set of values and principles. And then as you branch off to different types of organoids, where there are specific concerns, based upon the potential function, and outputs of those organoids, then you would need to have additional principles and values."*

Some organoid researchers, even some members of research ethics committees, do not have the necessary overarching knowledge. When a neuroscientist responds to the query whether she thinks that a cerebroid has developed consciousness, then the response would likely be that it just does not have the organization needed; it does not have the number of cells and all the necessary cell types. As a result, a conscious cerebroid is out of the question right now. It would be helpful if a committee member or a bioethicist understood what is thought to be minimally necessary for minimal consciousness, not just for human brains but also for mouse brains, i.e. for any mammalian brain. Without that kind of knowledge of what is required for this kind of experience, the bioethicist mentioned that:

> *"People on these committees, bioethicists, they can kind of let their imagination go a little bit too wild. Key to brain organoid research is to have a qualified consultant, who is an expert in brain development and an expert in what is necessary for architecture*

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and cell types and regional communication to support what we understand so far of our consciousness, and in animals."

For research on other types of organoids some basic knowledge of the current guidelines for Stem Cell research in vitro will be helpful and support research ethics committees' work, in order to be aware of the current framework and what is recommended by societies such as the ISSCR.

This kind of worry might be even more relevant for research on "linked organoids" or organoid systems; there are researchers who will be more interested in such guidelines, especially if the organoids system includes a cerebroid. For example, a research group connected a brain organoid with a spinal cord organoid and a muscle organoid. Their aim was to study how the electric signals transmit from brain organoid to muscle and back; they successfully established a very basic model. For "linked organoids" it might be useful to have advice from experts who understand more of these kinds of human systems during the research ethics committee review.

Another example, brought about from one interviewee was related to the transfer of human brain organoids to rodents. Specifically, a studywas mentioned where the researchers aimed to study if human brain organoids form connections and survive when transferred into a mouse brain, and the answer obtained was affirmative. The interviewee explained that there are practical realities that should pose limits to how radical the transfer of human organoids in rodents can get. However, one cannot decide to give permission or ban such research without going into the details.

In order to transfer a brain organoid, parts of the animal's brain have to be removed, so as the organoid to be accommodated. Therefore, there are limits to the size and the number of the organoids you can put in. The ethical questions, in this instance, are whether such transfer would affect the animal's behavior, mental properties or experience. There are limits on how many and where brain organoids can be put in a mouse: only at the surface of the skull - not deep in the middle of the brain. So, it would be interesting to ask: What if you used a larger animal model, with a larger skull, that would allow you to put more organoids or bigger ones? This would have to be scientifically justified: why are you doing that, can't you just use a mouse?

If it could be proved that the human brain organoid transplant has an effect on cognition or it is a source of novel behaviors, then we could envision the transfer of brain organoids to recover functions in patients with brain damage. That clinical implication would be so enormous that researchers, bioethicists and society at large could overlook whatever ethical failures might have happened in the animal model. An interviewee added this part of the conversation by stating:

"That is where I would like to focus my energy as a bioethicist, not so much on the mouse experience. So, this organoid research using animal models, either it is too small to do anything, organoids aren't changing behavior, or if it did, then there will be this new issue to worry about."

In general, there are a lot of guidelines about other things like procuring cells, informed consent, and cell lines, and also about research sharing. In terms of actual guidelines for organoid research itself,

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there is little guidance, except for the related issues around it as mentioned previously. As a bioethicist mentioned:

> *"I don't think it's going to give you [meaning the current set of guidelines for organoid research] a lot of guidance for organoids but it gives you everything else you need to know about biomedical research with stem cells. There is no specific guidance for organoids. […] the field is still so young that there is not much even to know what to review, because this is not complex enough."*

Communities, like the International Society for Stem Cell Research (ISSCR), does state that there is a need to keep an eye on protocols that combine multiple organoids, or create assembloids of the brain, but these are both fields of research in their infancy. Right now, there are not relevant guidelines, since researchers do not know exactly what the technology is capable of doing. There is thus a tendency to give researchers space to further develop the field.

A Sociologist of Science and Technology raised the issue that RECs, as they function during the time of prevailing liberal bioethics, are not sufficient to ponder on ethical issues produced by highly innovative biomedical research. According to this person's opinion the environmental issue should be at the heart of bioethical reflections, i.e. how life is related to technologies like organoids, as well as issues of resources and production. Bioethics should be at least aware of the link between the two.

A biomedical researcher explained that if the technology would arrive to a point where organoid-derived organs could be transplanted into a patient, then we would have to consider ethical issues more seriously. For example, in the case of the liver, it would be the same as for liver transplantations, i.e. there should be the same ethical constraints in place. However, transplanting brain organoids is exceptional. Currently, there is a gap of understanding and strong regulations will be required. The researcher put autologous transplantation as a different issue, but it would still require a huge debate but the scientific community should consider it as something that can be applied. The same researcher would not consider non-autologous transplantation of brain organoids, based on the fact that since it is not done with the organ it should not be allowed to happen with cells. The same should also happen with embryo-derived structures, like blastoids or gastruloids, i.e. it should not be forbidden, as with structures that have capacity to reproduce by themselves. For the case of chimeras, the researcher mentioned:

> *"I think this should be strongly regulated and absolutely forbidden. That's my personal opinion. I think anything that could have the potential to give rise to a new species should be absolutely forbidden. Anything that could have even minimal risk of giving rise to an entity that is alive and can reproduce; I think should be absolutely forbidden."*

A way that the organoid field could look for existing guidelines is to define whether they can be used for human enhancement.

14.2.4 The terminology for communicating organoid research

Brain organoids too often are being called "mini-brains". The ISSCR has been discussing what terminology scientists should use when they talk to the media about their work. Similarly, there is much

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discussion on whether animal models with human cells should be called "chimeras." This term is problematic because, while it could be misunderstood by the public, it is already widely used in the published scientific literature. Researchers have thus resisted dropping that term, because scientific literature studies reveal that this term goes back to the seventies, i.e. to the history of developmental biology. Consequently, they are reluctant to turn their back on their history.

Currently, the term "chimera" is still in use in the guidelines, but as little as possible. There is an effort to use instead "a model of human disease" and to specify what kind of animal model this is, what researchers have done to create the animal model. The ISSCR actually uses the term "chimera," but only on rare occasions; the community is fully aware that it needs to be very cautious with the use of terms in official documents since there are multicultural studies showing that people interpret these words in very different ways.

For the use of the term "organoid," finding an alternative is much more challenging, since it is used much more broadly in the scientific literature. But, at least, it is less misleading than using terms as "mini-organs." Another term that raises some controversy is the one that should be used to refer to embryo models. A far-fetched term would be "synthetic embryo"; the ISSCR decided to use the term "stem cell-based embryo models", because that describes more precisely what they are. Some researchers call them gastruloids, because they present a model of gastrulation. This is an ongoing debate concerning how to be more careful about the terms used in science. An interviewee from the USA described the debate as follows:

> *"If people want to read up on new developments in kidney organoid research, they will use the key terms "kidney organoids" for a scientific literature search. I don't know what alternatives there are, especially for the work on organoids that would be truthful for a multicultural discussion, not US-centric discussion. It is like having a name for a person, that makes the initial impression. Naming things is very important socially."*

A researcher explained that there are difficulties to pass the ethics-related message to the press and to the public. This interviewee actually put it in the following way:

> *"And this is where we are failing now. Well failing…This is where we have to become better because, unfortunately, the message does not come across so well […] So there's a tendency to some journalists' interpretation of what we are doing, which is extremely different from the goals."*

According to an expert in Clinical Ethics, a public discussion about ethical implications of organoid research should involve European values around justice and social solidarity. According to this opinion:

> *"Americans' unfortunate tendency to veer towards personal liberty and autonomy skews many discussions in bioethics as you know, you do clinical ethics. It's very important to have something of this magnitude discussed with full attention to solidarity, balancing the strong voice for autonomous decision-making principles. I think we have to come together to think about are there any cultural narrative that we need to think about as people proceed."*

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The same expert describes that they always look backwards first and that this is "a habit" of people trained in scholarly attention to philosophical and religious texts. For communicating research, people have to have acquired some science literacy. For this to be achieved there has to be early work in trade unions, in parent teacher associations, and in religious organisations. However, also scientists have to gain a level of understanding of philosophy and religion. For this, a robust training in philosophy that will allow scientists to understand that the discipline of ethics is just as important and just as intricate and just as intellectually challenging as that of science, is really important.

For a bioethicist that was interviewed, the optimal way of communicating is to take into account the cultural specificities of the audience. Specifically, the language codes that a science communicator or a researcher will have to make use of depends on the audience, i.e. whether it is primarily secular or primarily religious. The same bioethicist stressed that a communication platform has to address a breadth of cultural and philosophical meanings if it is to be used all around the world. The message to be conveyed has to be tailored to the particular jurisdiction and the particular communities. This means to take into account the way(s) one culture perceives scientific advancement. The example of Africa was put forward, where there are cultural aspects with magical, religious beliefs.

For another, European, bioethicist the main point is to be honest about what (brain) organoids are. The public is sometimes "trapped" between the language of the scientists and the language of ethicists. As put in the interviewee's words:

"Scientists sometimes tend to minimize the potential risks on the ethical level, and on the other side, ethicists and people against this kind of experiments tend to exaggerate the dimensions of organoids and tend to call them mini-brains, instilling the idea that there are real brains growing in a dish, something like the thought experiment of Hilary Putnam, the brain in a vat."

The same bioethicist explained that making people consider rationally and dispassionately some scientific topics may be not possible. Again, the correct approach is to be completely honest and clear on what scientists do not know. Both scientists and bioethicists have to be less assertive than they usually are in public communication, so as to describe the omnipresent margin of uncertainty.

For another bioethicist, the **first step** is to create a glossary for lay people of terms that are associated with organoids and organoid research. This is similar to what a Sociologist of Science and Technology described: *"Credibility is an important matter. I have to be extremely rigorous. Rigor is what allows you to go from one world to another."* In a similar tone, a biomedical researcher mentioned the difficulties produced from the fact that there is no definition of tissue in the European directives or guidelines. The researcher mentioned that sometimes researchers define a tissue as something that is not an organ, i.e. it is not autonomous, but as it mentioned "*it is true that it is not very clear in terms of definition.*"A **second step** would be to produce animations, like create "*a little cartoon type thing*", since people nowadays like that kind of communication. A **third step** would be a great launch something like a town hall meeting, in order to formally engage with the community.

For a bioethicist from North America, a best practice for communicating with the public is not to use philosophical jargon or technical terminology but to use metaphors. As he/she puts it:

"The best way to communicate with people is to understand what is familiar to them and then make a connection to that."

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Another point is that researchers or science communicators must not only consider things that have moral status and therefore moral considerability as "sensitive" when explaining them to lay people. According to its opinion, there are other things without moral status but they should be taken seriously morally. An example was human embryonic stem cell lines. As the bioethicist stated:

> *"Nobody thinks you can violate the right of a human embryonic SC, but because of where they came from and what you can do with them, and the place they might have in the lab or translational research, we have to treat them with a lot of care. For instance, a heart for transplantation, nobody says you can wrong the rights of a heart, but you had better not destroy it because it is morally very important. So, how do I make this distinction between moral status and moral considerability? Using metaphors, like the metaphor of the heart, an actual heart for transplant. It is better than an organoid, it is an actual heart. Nobody says there is nothing to worry about, there is a lot to worry about a heart for transplantation."*

A biomedical researcher advocated the use of very simple language, because, as he/she said:

> *"we should be worried in the words. Because it can jeopardise totally the [organoid] field. [...] But the hope can be destroyed by too much hype, and not being balanced or accurate. There are some researchers that are not fully accurate, I would say. They are because everybody has their own way of doing things of course. And journalists also read things in their way that they can be misinterpreting things."*

The same researcher explained that brain organoids is an exceptionally sensitive example, since it has huge implications as almost all people have a relative that suffers from a neuro-degenerative disease. But they pointed out that that does not leave all other types of organoids aside, since cancer organoids are equally "sensitive" in nature: "*So yeah brain organoids, but also say I would say cancer organoids [are overhyped].*"

An expert in Ethics of Technology described that in science communication to lay audience, in addition to presenting some hard facts, there must be ways to talk about ethical issues without necessarily framing them in terms of moral principles or values or norms, which has to be looked at on a a case-by-case basis. A sub-optimal practice would be to focus on extreme cases or things that will not be possible for the next 20 years.

An expert in bioethics of emerging technologies added that a good practice is to use scenarios that can make the audience more distant from their personal lives and make them produce a recommendation on the issue discussed. As he/she clearly described it:

> *"The more personal it gets the more you are going to hear about stories of themselves, health problems, whatever, and it does not go into this underline set of values. We should talk at the level of policy decisions – looking at the greater good. So it should not be about their opinion but about the good of society. Not about what they would do, but about what the policy should be and the regulatory oversight on ethics. Also you can try to make them take a decision as a group. So, it is not about talking, but about making a recommendation."*

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14.2.5 On the novelty and exceptionalism of organoids as a field of research

There is no novelty in growing in a culture dish some sort of self-organized entity that is recapitulating basic functions. However, what is novel with organoid research is its enormous broad spectrum of possibilities. There is, for instance, a possible or anticipated breakthrough in the research on development. An expert in brain organoid research mentioned:

> *"Right now, researchers study how the brain develops and they are willing to wait over a year to culture their brain organoids, to get all the different cell types that they can possibly get from their organoid models. I know a team that have studied organoids for over twelve months, up to two years."*

Another approach of organoid research is to perceive and use organoids as "tools" to do other kinds of research. Specifically, this realm of organoid research strives to manipulate organoids. In this instance, there is a substantial connection with bioengineering. The researchers that fall into this realm of organoid research want the organoid to develop very fast, in order to have them at their disposal as instruments of achieving other goals. There is a continuum, and it is this latter part of the continuum that is novel: the one that treats the organoid as a tool. A bioethicist put it in the following words:

> *"It is not the organoid work and the stem cell work itself that is novel; it is the partnering with the bioengineers that makes it novel, that is new about the current state of organoid research as opposed to a decade ago. We have a lot more bioengineering now. And in the top of that we have the possibility of doing genetic engineering. Like unnatural organoid research, engineered, built for purpose organoid research; that's novel."*

Here there is a more novel organoid-related area of research that is occupied with more "unnatural" entities and the possibility of combining developmental biology with bioengineering. In this instance, the studies focus not only on the creation of unnatural aggregates of cells, but on the "mixing" of living and non-living components. So, it is crucial for a bioethicist to be able to understand what is the exact focus of research in each case. For instance, in embryo modeling (gastruloid) work, there are researchers who want to compare embryo models with natural embryos, in order to study whether the gastruloids that they have developed recapitulate the natural embryo. Other researchers strive to use a gastruloid as a model to test a drug. A bioethicist described it as follows:

> *"It is like building things; they have to make it fast and make a lot of them, and scalable. That is not what developmental biology is about. You can imagine, for other organoids, that you don't want to model every part of the organ, you just want to model one part because you want to use it for something, as a tool."*

Another example from the organoid/bioengineering realm can be found in the case of brain organoids; the bioengineer might perceive a brain organoid as a quick way to build neural networks. This

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does not necessarily have to be a complete brain model, but just a "human" neural network to pair to something else. As a brain organoid expert mentioned:

"It is like emergent biology. You don't understand exactly how the cells do, but they self-organize and there is this merging behavior, especially if you are talking about emergent neural network behavior, then you are talking less about "mini-brains" and more about using cell-based computing, which is very odd."

An analogous case can be that of the research of using DNA as a storage tool for data. As a result this kind of research, which is not confined only to the organoid field, is about utilizing natural components for engineering purposes. It was stressed in some interviews that there are no committees or guidelines for that kind of combinatorial work. For example, there is no bioengineering ethics committee, despite the fact that there are actually research ethics committees for stem cell research. A bioethicist put it quite bluntly:

"I think that is where all the controversy is going to come from."

Finally, one interviewee articulated that a specific field of research thatcould aid the organoid field to progress further is that of vascularization. Vascularized organoids are expected to grow larger, to be maintained for longer periods of time, and to be linkable to one another. This is a point where bioengineers come in: artificial vasculature can be achieved by linking an organoid with an organ-on-a-chip. In addition, if vascularization of an organoid can be achieved, it can be connected to another organoid, yielding the organoid version of an organ-on-a-chip system. A researcher described the repercussions of such research in the following words:

"It can look disturbing to some people. It does not look like any kind of biology at all, these red and blue color channels; nobody would think that this is a biological system at all. I think how things look also matters for people, and this is related to the terminology issue, also how something looks matters."

An expert in Sociology of Science and Technology mentioned that the novelty in organoids is in the potential of numerous different applications. However, the variations in the application are not significant if the general pattern is taken as a benchmark. Specifically, there are new applications on an almost daily basis, rendering breakthrough as the norm. Nowadays, the logic behind the biomedical progress is to go faster, to bypass the process of clinical research by doing translational research. According to this expert, organoids are on the same line as bio-printed tissues, in the sense that it is research that strives to accelerate clinical applications. In addition, if organoids are conceived as entities used to grow a type of a self-organized aggregate of cells that is recapitulating basic functions, it is not novel in the sense of having a new field with no prior history. The exceptional about organoids, as described from the interviewee is the following:

"That is what is novel about organoid research, the possibility of bringing together developmental biology with engineering, and you make these weird things that don't

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exist in nature, weird mix of living and non-living components, and you are answering an engineering question, you are not trying to answer a developmental biology question."

A biomedical researcher described the exceptional character of organoid research, as being at the boundary of studying biology and applying bioengineering:

"*So, we are helping the cells, the stem cells to do what they know how to do. And we are just like finding the boundary conditions that allow them to like to do what they normally do during embryological. So this is very different from doing engineering, but, at the same time, it still requires to have like an engineering state of mind, in many aspects to the tuning, the environment in which the stem cells grow is very, very important.*"

14.2.6Cultural differences

All experts that were interviewed were asked to share their uptake of cultural differences in different parts of the world, not necessarily focusing on organoid technologies. Their experience from different places in the world came either from their working in these places or by cooperating with researchers or bioethicists in these places.

In Europe, experts agree that there is more of a communitarian spirit. European research is armed with so called European values, as they are found in the European Charter of Fundamental Rights. While USA and Europe are similar in basic liberal democratic values, there are differences in accents in the USA, where there is less of an emphasis on issues of social equality and solidarity and community and more of an emphasis on individual rights and the individual person.

Similarly with Europe, in Australia there is emphasis on research to help people. However, it does come down to the individual researcher because even in Australia and in the EU, there are researchers from all over the world, and this produces a complex environment of merging values. As one bioethicist described it:

"*so, you may have a research team with ten people on it from five or six different places of the world, which can also make research a little hard to do because those people will all have different values that some experiences and drives and reasons why they' re doing research and some may go back to their home country. They may only be in the EU for a period of time. But they're going to go back to their other place. So, they may not change their values that you know, same it's really complex really complex.*"

In the USA the working ethos revolves around being very innovative and always aiming at commercialism and developing technologies that can be patented. In the USA the discussions always keep in the forefront intellectual property, there are spin-off companies for commercial purposes. This was explicitly described in the following way:

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"They don't really care about helping people. It's not in their value set. They care about making money. It's unfortunate. It's one of the reasons why I left America because I just didn't agree with the values."

With regard to organoids, an expert in Law described that the use of organoids for therapeutic reasons is absolutely required. The expert based this response on the Jewish and Anglo-Saxon tradition where the preservation of life is of fundamental importance. This was presented to be in difference with the values at the European Continent, where the "one drinks the other dies" tradition is not so straightforward, since the value of life of an individual is applied indifferent ways. Another interesting reference to the Jewish tradition, made by an expert in Clinical Ethics, is that according Jewish law the moral status is fully achievable only at birth of the embryo, while in the Catholic Christian tradition an embryo should be regarded as having the same moral status as a person.

These differences in scientific cultures and religious traditions play an important role and should be taken into account when international scientific societies draft ethics guidelines that should be accepted by the majority of scientists all over the world. These scientific societies must reflect the views of the diversities of views worldwide. According to an expert in Clinical Ethics:

"As far as I know, we can always agree on some basal levels of things that are acceptable to everyone. And as far as I know, for example, the transfer of human blastoids into a uterus is unacceptable to everyone."

14.2.7 Knowledge gaps

Renowned organoid researchers were asked to pinpoint knowledge gaps. This section is an exposition of their responses.

Long-term behavior of organoids: Currently, there is a lack of the *in vivo* proof of concept to show their functionality over time. With organoids, there is a whole spectrum of risks to be managed that do not apply to organs. Some questions are: Are organoids going to proliferate too much or not enough? Will one part of the cells take precedence over the other aspects of the functions? Will the cells maintain themselves harmoniously?

How to "nudge" the cells: Currently, there is a gap of knowledge on how we get cells to behave and become more like an adult cell, even in the cases for organoids that have been grown from adult tissues.

"Cells seem to revert back to an either regenerative state that maybe resembles a more earlier a state of the embryo where they basically lose certain aspects of the adult tissue. People are now making more complex multicellular organoids, but that is still really in its infancy. So, there's a lot of stuff missing and that also the needs of any of those interactions and functional implications are simply not there in the system yet."

Lack of stroma: Currently, only the epithelial part of the tissue can be expanded. The researchers still miss all the supporting cells, basically the stroma, i.e. endothelial cells, mesenchymal cells, fibroblasts, and immune cells that are present in the tissue.

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"So, going from what I would call organoids 1.0 to more multicellular complex structures, where we now incorporate cells of the different germ layer origins. Basically, for the adult-derived organoids we've always been working on the epithelia cell type of the tissue, but we're missing the other cell types. And I think this is one of the main gaps. So, incorporating endothelial cells, mesenchymal cells, stroma cells, immune cells."

Structure of organoids: Currently, there is difficulty in recapitulating the tissue architecture for the adult tissue-derived organoids. Intestinal or stomach organoids recapitulate very well the epithelium, but they still lack the stroma. Liver or pancreas organoids recapitulate very well the epithelia but they lack the stroma, i.e. they lack the architecture of the tissue. For instance, intestine or stomach organoids are very simple, but the liver and pancreas are much more complex organs with some division of labour between the different parts of the tissue that organoids cannot recapitulate. As a result, there is still lack of maturity for all the cells in the epithelial state.

Types of cells to begin with: There is a need to capture the SCs in a dish in a much better stage, in a stage that much better represents the embryo. Currently, the stages used as starting points are not good enough.

Lack of comprehensive knowledge of human embryo: In order to improve blastoids there must be a more comprehensive understanding of human embryos, especially after implantation. Such a knowledge gap prevents researchers from understanding whether blastoids are actually good models of embryos. As one researcher puts it:

"All models are wrong, but some are useful and you have to know what your model is good at. And by benchmarking it very closely to the real thing, we can know what it is good at modeling and what it's not good at modeling. For example, it is very good at modeling signaling pathway interactions between the cells, it is very good at modeling more for genetic processes. On the other hand, we know that it is very bad at modeling the metabolism because, you know, we are growing those structures inside an incubator which is very different from the human body. So we have to know what it's good at in order to tackle the right questions."

14.2.8 Legislative challenges for organoid research

The legal experts conveyed their opinion on which existing legal framework(s) are currently the most relevant for organoid research. According to one legal expert there are two primary directives that apply, from a legal point of view, in the EU, if someone perceives/defines organoids as tissue cultures. Since there is no concern of organoids escaping the laboratory, the only thing that needs to be taken into account is the protection of workers against any risk that might be attributed. At the time being, it is certain that organoids cannot infect anyone. A second concern would be relevant to the directive for the contained use of genetically modified material, which would include gene edited microorganisms. A microorganism is defined very broadly, i.e. it is not just a prokaryote.

Organoids can be derived from SCs, in which case there might be no regulation so than the two above mentioned which apply. However, if the organoids are derived from ESCs there are several issues, which would have to be taken into account. According to one of the legal experts:

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"There is a political compromise agreed within the EU that says that the production of embryonic stem cells cannot be funded through EU funding. It is only the production of stem cells that cannot be funded through EU funding, but their use can be."

Based on the above argument the point of derivation from which organoids grow is important, in legal terms. This creates situations that could have analogies with ethics dumping within Europe. For example, a researcher could get British funding to make the SCs and then use them using European funding, while in Germany you're only allowed to use certain defined ESCs, which were identified at a particular point in time, and no new ones. Such examples were put forward to describe the complexity of the European landscape in legal terms, with regard to the "raw material" of organoids.

Another legal expert stressed that legal frameworks do not expressly reference organoids, while there are parameters that rely on standards from other laws and requirements, widely related to ESCs research. Moreover, there are additional boundaries in standards for animal research protections, safety and quality, product approval, and human subjects protection (for human donors). Further considerations for a regulatory framework relate to: embryos (specific informed consent for donated embryos; exclusion of embryos created specifically for research; period when an embryo may be used for research purposes); permitted/prohibited research uses of biological material; human cloning and import or export of cloned materials; animal welfare (including limits on sources, use, and transfer to animals); good manufacturing practice (GMP) for the use of stem cells; donor informed consent, and Institutional Review Board (IRB)review for human subjects donors of stem cells for research protocols.

As already mentioned, despite the fact that specific regulations for organoids are not available, there are international and national legislations with relevance to organoids, like the use of human embryos (HEs) and human embryonic stem cells (hESCs) or the banning of human cloning. Some countries favor the use of embryos from discarded in-vitro fertilization (IVF) rather than *de novo* creation.

For what concerns Good Manufacturing Practice (GMP) for safe and appropriate SC utilization, European Medicines Agency (EMA) set up specific guidelines. GMP is a quality assurance tool, which is used across a range of industries, including medical and food manufacturing. In general, legal instruments lay down the principles and guideline of GMP in the EU: Regulation No. 1252/2014 and Directive 2003/94/EC, applying to active substances and medicines for human use; Directive 91/412/EEC applying to medicines for veterinary use, Directive 2001/83/EC and Directive 2001/82/EC lay down related provisions.

The ATMP Regulation also classifies tissue-engineered products including SC-based products. Such regulations are not quite specific for organoids. Regarding IRB review of research protocols, in general, they are not specifically related to organoids or SC protocols. About animal welfare for research, the situation is heterogeneous as well. In some countries, there is no single law addressing animal protection (e.g., China), while in other ones we have (e.g., UK, Japan, and EU). Moreover, we have to assess organoids from a multidisciplinary point of view, in order to support healthcare decision makers. One tool is represented by the well known methodology of health technology assessment (HTA), also

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including a legal domain that is the evaluation of the impact of the technology considered on current/future regulation/law level.

14.2.9 Researchers' awareness of the ethical challenges raised by organoids

Bioethicists that were asked to comment on the researchers' awareness of ethical challenges raised by organoids responded in various ways. Some of them commented that most researchers come from a simple biological imperative to discover new knowledge in a scientific area and this fact make them not so receptive to thinking about philosophical, ethical, and moral issues, relevant to the consequences of their research. They find some difficulty to interact with scientists when it comes to ethical issues, but they recognize that there are researchers who are available for conversation. In an effort to interpret this non-optimal interaction between bioethicists and researchers, one bioethicist mentioned that:

> *"We raised mixed feelings, so to speak. But I believe that ethicists have the role to foresee potential developments. In this sense, we are doing different work, and it is a good thing."*

Another bioethicist explained that awareness and reflectivity are two different things, so a researcher may be aware of ethical challenges but disregard them for the sake of discovering new knowledge. According to the same bioethicist a significant portion of researchers "*are very scientific [...] and they don't often think about what we call the softer things, the more humanistic things. Which is unfortunate because those people sometimes can get into trouble too because they're so tunnel-visioned*."

For an expert in the Sociology of Science and Technology researchers lack the curiosity to provide answers for simple questions, such as: what is the status of the bio-objects they are working on, whether these bio-objects are natural or artificial, what are the boundaries of life? The interpretation given by the interviewee was that biomedical researchers follow a techno-scientific logic that does not leave space for such endeavors, since they cannot provide technical answers and there is no room for these questions in their education and professional practice.

An interesting point raised by a legal expert was that a human cell line, according to the law, is a microorganism; that is something that baffles scientists. Researchers who are not aware of that, they don't realize that that applies.

Biomedical researchers who were interviewed provided a somehow different picture, since they were perfectly aware of ethical challenges and described that in their research groups there can be significant debates on ethical issues not only in their field of research but with regard to the work of other research groups. Two researchers shared the following, which are characteristic of their interest on ethical issues:

> *"Around the time when these CRISPR babies were reported, that led to massive discussions in my lab. So, it shows basically that researchers are aware and actively thinking about ethics and moral implications of what they do. Thinking about it, the discussion of the CRISPR babies … that really stirred something in my team at the time. […] And so that the problem lies much deeper than just sort of being bullied into signing*

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an approval form. It's actually sort of at the educational level where things already go wrong. So there I think that it may be helpful is sort of making sure that people have access to the right information and the different viewpoints."

"The other concern would be genetics. If we start sequencing people and then being able to identify these people, for instance. I think it's very dependent on the country you work in. [..] There are countries that have much less rules than other countries. The EU, I think this is very clear. I don't think anybody would dare to take a sample without having obtained the ethical consent from the patient. I think the EU in that sense is quite ahead of probably the US as well, despite I've not worked in the US. I definitely believe if that was not the case, nobody would have done CRISPR into people like it happened in China. So that is strong evidence that the rules are not followed or not written equally everywhere. But I think worldwide standards should be applied on that, otherwise we can always enter into that problem that happened with CRISPR in China."

An expert in Ethics of Technology explained that researchers would be aware of the typical ethical issues that apply to biomedicine and not more specific ones that pertain to organoid research. The more overarching ethical concerns would be relevant to research on stem cells, embryos and foetuses, use of human cells and tissues, and with genetic modification. The same researcher also mentioned that in the biomedical fields, there is a greater awareness of ethical issues than in other engineering fields. So that could be a limitation that some people never had proper training in that domain.

"They think that to follow ethics is to follow ethics guidelines. By discussing ethical dimensions in brain organoid and embryo models research they take into account ethical issues. But how much they think of ethical issues depends on how much they are exposed to ethical issues in their everyday work."

14.2.10 Vulnerable populations

Experts defined vulnerable populations as populations who are vulnerable due to (a) social or (b) medical reasons. It should be mentioned that experts did not recognize a new type of vulnerable population that has been brought forward by organoid research. The list of the vulnerable populations following the above mentioned categories is:

(a) <u>Vulnerable populations due to social reasons</u> include:

- People who are discriminated, marginalized, disenfranchised due to their particular culture
- People in prison, incarcerated people.
- People that lack language skills, less literate. As it was stated: *"Lack of knowledge is probably the highest vulnerability."*
- People who are in a politically oppressed situation.
- Women.
- Poor people.
- People in nursing homes.
- Homeless people.

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- First-generation immigrants.
- People that belong to ethnic minorities.
- Children.

(b) Vulnerable populations due to medical reasons include:

- Donors with health problems who accept to give some tissue or other biological materials for research aims.
- People in extreme ages, namely very old and very young people.
- Populations with particularly severe pathologies orwith mental or physical disabilities or chronic health issues, or genetic defects.

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15 Concluding remarks

At the time the systematic scoping review had been finalized and the expert interviews were being conducted by all WP3 partners, the ISSCR Guidelines for Stem Cell Research and Clinical Translation[164] (henceforth referred to as "Guidelines") were published, in late May 2021. The Guidelines did not contain any specific set of guidelines, instructions or best practices directly related to organoid research. The only parts directly related to organoids were the following:

- The decision that the research review category that organoid research falls into is the "Category 1"; that means that organoid research is "exempt from review by a specialized process".
- A provision: "*At this time, there is no biological evidence to suggest any issues of concern, such as consciousness or pain perception with organoids corresponding to CNS* [Central Nervous system] *tissues, that would warrant review through the specialized oversight process. However, researchers should be aware of any ethical issues that may arise in the future as organoid models become more complex through long-term maturation or through the assembly of multiple organoids*."

Simultaneously, a paper authored by Robin Lovell-Badge, head of the taskforce that updated the ISSCR guidelines, was published in Nature.[165] Lovell-Badge did not specifically mention organoid research; the closest he got to organoid research was a generic statement about animal-human chimeras, as an example of "*scientific advances* [that are] *scary and uncomfortable.*"This paper was articulating the decision of the ISSCR to relax the so called "14-day-rule", i.e. the rule that ISSCR (and several countries) abided to until recently that human blastocysts/embryos that were grown in the laboratory should be destroyed before they reach 14 days.

These two recent publications, which appeared two months before this report was finalized for submission, reflect the findings of the Systematic Scoping Review : that organoid research "*is still so young that there is not much even to know what to review, because this is not complex enough*" as one bioethicist described during one of the interviews. There is still no evidence that organoid research will raise any new ethical, legal or research integrity-related issues. However, exactly because it is a field of research that provides a substantial breadth of potential applications the recognition of organoids' non-exceptionalism might not hold in ten or even in five years from now.

Organoids may be exceptional due to the fact that they may provide answers to various questions, related to drug discovery, developmental biology, organogenesis, cognitive research, synthetic biology, bioengineering, and research on chimeras. They may be exceptional due to the fact that this breadth of potential applications renders organoid research a focal point, where virtually all ethical, legal and research integrity-related issues converge. Even if organoid research will prove to be non-exceptional, in

[164] Guidelines for Stem Cell Research and Clinical Translation, International Society for Stem Cell Research, Version 1.0, May 2021.
[165] R. Lovell-Badge. "Why stem-cell guidelines needed an update" *Nature*593 (2021) 479.

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the sense described above, it will be challenging to follow the transformations of old ethical and legal issues under a new perspective, as in the case of cloning.[166]

The results and conclusions of this systematic scoping review will inform the ethical, legal and research integrity-related frameworks and guidelines to be developed by WPs 5 and 6, with the aim to regulate organoid research and anticipate future challenges that might emerge as this field of research will progress.

[166] F. Neresini. "And man descended from the sheep: The public debate on cloning in the Italian press" *Public Understanding of Science*9 (2000) 359-382.

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Part 4: ANNEXES

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16 Annex 1: Initial contact with potential interviewees

This is the initial invitation letter sent to all potential interviewees. The e-mails of all potential interviewees were either retrieved from the internet, i.e. they were freely available, or provided by HYBRIDA consortium partners or Advisory Board members that have established cooperation and acted as liaison. In the latter case an e-mail was sent from the liaison to the potential interviewee in order for the liaison to ask permission to send partners her/his e-mail to WP3 partners so that the initial invitation letter could be sent.

Invitation to participate in an interview organized by the HYBRIDA project

Dear Sir/Madam *[replace by name of WP3 partner]*,

We invite you to take part in an interview organized by the European project HYBRIDA (Embedding a comprehensive ethical dimension to organoïd-based research and resulting technologies)in the context of Work Package 3: Mapping and comparison of normative, RE and RI frameworks.
HYBRIDA is funded by the European Commission as part of the SwafS (Science with and for Society) program within Horizon 2020. HYBRIDA aims to develop a comprehensive regulatory framework for organoid research and organoid-related technologies.

As part of the project, we plan to conduct 20 interviews (10 across Europe and 10 in non-European countries) with expert researchers in organoid and organoid-related technologies (i.e. gene-editing, cloning technologies and IPS technologies, and embryonic stem cell technologies), bioethicists, experts in research integrity and biobanks, and policy makers.

In your capacity as an experienced*[type of stakeholder]*, we would like to invite you to participate in one of these interviews.

We are interested to collect and elaborate on the debates that have occurred in the past, and are still ongoing, regarding the regulatory, ethical and integrity-related dimensions of organoid and/or some of the organoid-related technologies (i.e. cloning and iPS, organ-on-a-chip and embryonic stem cell technologies). In addition, we are interested to identify relevant regulatory environments and cultures that deal with the abovementioned technologies and gather existing knowledge on codes of conduct, SOPs and guidelines regulating organoid research and the selected technologies/families of technologies.

The interview will take place at a date/time convenient to you; so we would be very grateful if you could indicate your availability.

If you have any questions concerning the project and/or the details of the interview, please contact Prof. Costas A. Charitidis (charitidis@chemeng.ntua.gr) or Dr. Panagiotis Kavouras (kavouras@chemeng.ntua.gr).

Kind regards,

[replace by name of WP3 partner]

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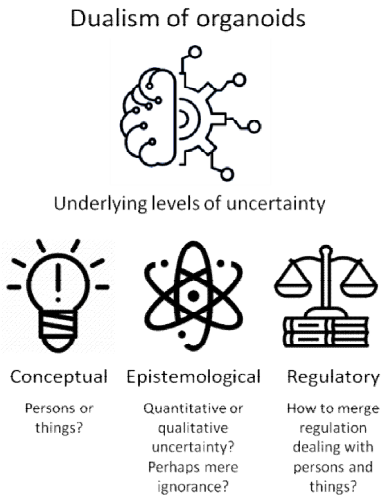
Together with the invitation, a one-page letter of information was also sent to the potential interviewee as an attachment.

Background for the interview study

HYBRIDA (*Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies*) is a three-year (February 2021 – January 2024), multi-partner project funded by the European Commission. HYBRIDA aims to develop a comprehensive regulatory framework for organoid research and organoid-related technologies.

HYBRIDA departs from the fact that 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 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. i.e. the conceptual/ontological, epistemological & methodological, and regulatory uncertainties (see figure). HYBRIDA is bound to address how these three kinds of uncertainties arise in organoid research and to develop a conceptual and regulatory framework able to overcome this dualism between persons and things.



The interview study has the objective to address the third type of uncertainty, i.e. the regulatory uncertainty and is being conducted in the context of WP3: Mapping and comparison of normative, RE and RI frameworks.

The focus of the interviews

The focus of the interviews will be to collect and elaborate on the debates that have occurred in the past, and are still ongoing, regarding the regulatory, ethical and integrity-related dimensions of organoid and /or some of the organoid-related technologies (i.e. cloning and iPS, organ-on-a-chip and embryonic stem cell technologies).

All issues discussed in the interview are confidential. The interview will be audio recorded and the subsequent interview transcriptions will be anonymized and handled in alignment with the European Union's General Data Protection Regulation as outlined in the project's **privacy policy document**and in the **consent form** that participants will receive prior to the interviews.

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17 Annex 2: Preparing for the interview

As soon as the potential interviewee accepted to participate in the interview, the interviewer sent, as attached files, the Privacy Policy document that describes the safeguards put in place by WP3 leaders to preserve the anonymity of the interviewee and her/his right to step out of the interview at any time without providing justification, and the Informed Consent form. The informed consent form was already signed by the interviewer and also contained the date of the interview. Both documents are provided below.

Privacy Policy

This document describes the privacy policy that all research activities conducted in work package 3 are committed to follow.

Data collection, processing, storage and usage

Collection, storage and use of the data collected during the interviews will be in alignment with the European Union's General Data Protection Regulation The ethical approval of the interview study in work package 3has been obtained from the Research Ethics and Deontology Committee of the National Technical University of Athens, which is the leading entity of work package 3.

Before the interview, all interviewees will be provided with an information letter and an informed consent form, which includes information on the project's purpose, funding, recruiting processes, methodologies, expected risks/adverse effects, beneficiaries of research results, communication of research results and all matters concerning collected data as described in this document.

In order to be able to transcribe and analyse the input of the interviewees, the interviews will be audio recorded. The subsequent interview transcriptions will be anonymised. Informed consent forms will be stored separately from the audio files and transcripts. All data material will be stored safely at NTUA's secure server. All data will be stored encrypted for 5 years after the last publication from the study. The findings from the interviews will be analysed, published and made publicly available. No personal identifiable information will be mentioned or disclosed at any point. Data preservation will comply with GDPR regulations, and it is the responsibility of the WP3leader, Prof. Costas A. Charitidis (charitidis@chemeng.ntua.gr) to ensure that sensitive data is secured and deleted in accordance with the GDPR regulations.

Each participant in the interviews may at any time demand removal of his/her interview data by a simple request to Prof. Costas A. Charitidis(charitidis@chemeng.ntua.gr). However, anonymised data, which have already been published, as part of deliverables or scientific publications, cannot be removed.

To promote open science and avoid research waste, anonymised data from the interviews will also be made available on the project's website: *[to be added when launched]*. Here, all names and other identifiers (information on country, university etc.) will be removed to ensure full anonymity.

In case of a data breach, affected participants will be contacted and data will be temporarily removed from the compromised storage. All internal transfer of sensitive data will be done through secure pathways.

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Informed Consent for participation in HYBRIDA interview study

Description of the Project

HYBRIDA aims to develop a comprehensive regulatory framework for organoid research and organoid-related technologies. HYBRIDA is funded by the European Commission as part of the SwafS (Science with and for Society) program within Horizon 2020. Its overall concept is that the ethical and regulatory challenges raised by organoid research cannot be dealt within a socially robust way without addressing three different kinds of uncertainty: conceptual uncertainty, epistemological uncertainty and regulatory uncertainty.

Aim of the interviews

In the interviews, we wish to learn from the participants' expertise and experience. We are interested to collect and elaborate on the debates that have occurred in the past, and are still ongoing, regarding the regulatory, ethical and integrity-related dimensions of organoid and/or some of the organoid-related technologies (i.e. cloning and iPS, organ-on-a-chip and embryonic stem cell technologies). In addition, we are interested to identify relevant regulatory environments and cultures that deal with the abovementioned technologies and gather existing knowledge on codes of conduct, SOPs and guidelines regulating organoid research and the selected technologies/families of technologies.

The study poses a small risk of discovering sensitive information, for instance concerning issues related to how specific institutions deal with ethical issues on organoid research. By signing this informed consent form, interviewers agree to maintain the confidentiality of the information discussed during the interview. Interviewees will have the opportunity to view, and if relevant, comment on their interview's transcription.

Use of data and dissemination of research findings to participants

The interviews will be audio recorded and the subsequent interview transcripts will be made fully anonymous, meaning that all names and other identifiers (information on country, university etc.) will be removed to ensure full anonymity. Informed consent forms will be stored separately from the audio files and interview transcripts. All data material will be stored encrypted and safely at a secure server in NTUA's facilities, for 5 years after the last publication from the study.

Each participant in the interviews may at any time demand removal of his/her interview data by a simple request to the coordinator of the study, Prof. Costas A. Charitidis (charitidis@chemeng.ntua.gr). Anonymised data, which have already been published, as part of deliverables or scientific publications, cannot be removed.

The findings from the interviews will be analysed, published and made publically available. The project report (i.e. related deliverable) detailing the findings of the study will be sent to all participants when the report has been finally approved by the European Commission. No personal identifiable information will be mentioned or disclosed at any point.

Data breach

In case of a data breach, affected participants will be contacted and data will be temporarily removed from the compromised storage. All internal transfer of sensitive data will be kept to a minimum. This means that as soon as the interview has finished the audio recordings will be saved at

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NTUA's secure server and immediately deleted from the interviewer's personal computer or any other type of device used for recording the interview. In addition, the transcripts will be also kept at the same secure server, until they have been fully anonymized and double-checked for the assessment of the anonimization procedure applied.

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 Prof. Costas A. Charitidis (charitidis@chemeng.ntua.gr).

By signing the consent form, you indicate that you are in agreement with all of the statements below:

1. 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.
2. 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.
3. I give consent to the audio recordings of the interview.
4. I give consent to the collection and use of my interview data in line with established data protection guidelines and regulations (GDPR).
5. I give consent to having my interview data safely stored for five years on NTUA's secure server after the last publication from the study.
6. I give consent to having my anonymised transcribed interview data made publicly available. I understand that this means that the anonymised data can be used for research purposes other than the ones described above. I am also aware that this means that my anonymised information may be used in countries outside of Europe and that the regulations for data processing and storage in those countries may not comply with those of the European Union.
7. I want to participate in this study.

Participant's signature: Contact's signature:

[Interviewee name] *[Interviewer name]*

Day/month/year

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18 Annex 3: Questionnaires

Three different questionnaires were prepared for the expert interviews, reflecting the three different broad categories of stakeholders targeted by the interview survey: Researchers in the biomedical field (Organoid and related technologies, as described at Section 7), Research Ethics/Integrity experts, Experts in Law. For more details, please refer to Section 7. The questionnaires were sent together with HYBRIDA's privacy policy and Informed Consent form (see Annex 2).

Questions for the interviewee (Biomedical researcher)

1. What is an organoid for you? How would you describe it in a few words?

2. What types of organoids and what kind of organoid applications are you working on?

3. When considering the creation and use of organoids, what would you indicate as the most important knowledge gaps?

4. What is your uptake of the current ethical debates on (Blastoids, Gastruloids, Placenta, "Brain" organoids) technology?

5. What ethical dimensions of organoid research do you think researchers are aware of?

6. What kind of support do you think a researcher on organoids needs when conducting experiments?

7. How would you define vulnerable population? Is it possible to have a new type of vulnerable population in organoid research?

8. How do you usually translate technical terminology on organoids into "everyday language" supposedly to be understandable by non-experts?

Questions for the interviewee (Research Ethics/Integrity expert)

1. What is your domain of expertise?

2. How did you get involved in research ethics and, specifically, regarding their relation to organoid research?

3. How relevant to organoid research do you find the ethical framework for technologies like cloning, gene editing, iPSC, embryonic stem cells, organ-on-a-chip research?

4. What ethical dimensions of organoid research do you think researchers are aware of?

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5. What kind of help/advice/knowledge sources do you think a Bioethicist/Research Ethics Committee member needs when assessing projects related to organoid research?

6. How would you define vulnerable population?

7. How do you usually translate philosophical terminology or the core of ethical debates related to organoids or similar technologies into "everyday language"?

Questions for the interviewee (Expert in Law)

1. What is your domain of expertise?

2. How did you get involved in studying issues related to organoid research?

3. What are the major challenges that legislation needs to address in relation to organoid research?

4. Have you experienced uncertainty in interpreting regulations on organoids?

5. What are the specific challenges that cerebral organoids, including their potential resemblance to human brain activity, raise to legislation?

6. How adequate is the information to patients/donors of tissue in current consent procedures? How could it eventually be improved?

7. When debating about production and use of organoids, what do you indicate as the most important gaps in the existing legal framework?

8. In discussions with researchers/scientists or lay people, have they expressed concerns, considerations, fears, and expectations to you?

The questionnaire for the interviewer contained probes and tips in order for her/him to be able to obtain a more nuanced response from the interviewee. The table below is a combined matrix of the questions for all three types of questionnaires that was sent by WP3 leaders to all WP3 partners that conducted the interviews:

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Biomedicine	Research Ethics/Bioethics	Legal experts
Context and general considerations		
1. What is an organoid for you? How would you describe it in a few words? Comments: To help us capture something of the "uptake" on organoids and non-formal definitions of an organoid.) Tip: we should avoid long answers in this question.	**1. What is your domain of expertise?** Comments: E.g. clinical ethics, research ethics. Tip: we should avoid long answers in this question.	**1. What is your domain of expertise?** Comments: E.g. national law, international law. Tip: we should avoid long answers in this question.
2. What types of organoids and what kind of organoid applications are you working on? Comments: E.g. Blastoids, Gastruloids, Placenta, "Brain" organoids, etc.	**2. How did you get involved in research ethics and, specifically, regarding their relation to organoid research?** Comments: Here we have to leave room for the relevant technologies (cloning, gene editing, iPSC, embryonic stem cells, organ-on-a-chip), if we know beforehand that the interviewee has not experience in organoid-related ethical issues.	**2. How did you get involved in studying issues related to organoid research?** Comments: Here we have to leave room for the relevant technologies (cloning, gene editing, iPSC, embryonic stem cells, organ-on-a-chip), if we know beforehand that the interviewee has no experience in organoid-related legal issues.
In depth questions		
3. When considering the creation and use of organoids, what would you indicate as the most important knowledge gaps? Comments: Without reference to ethical, legal	**3. How relevant to organoid research do you find the ethical framework for technologies like cloning, gene editing, iPSC, embryonic stem cells, organ-on-a-chip research?**	**3. What are the major challenges that legislation needs to address in relation to organoid research?** Comments: We have to leave room for the

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or research integrity issues. We need input on the way(s) the interviewee develops the organoids she/he studies, e.g. through embryonic stem cells, induced pluripotent stem cells, etc. We are also interested in the researcher's sources, e.g. biobanks, commercial cell lines, donors, etc.	Comments: If 'not' why? If 'yes' why?Thesewill vary per country: you might want to be more specific on the other technologies.We need input on lessons to be learned from other technologies andif there points of convergence or specific points we can draw from the ethical framework that governs relevant technologies.We also need to realise whether perceptions of exceptionalism are prevalent among the interviewees.	relevant technologies, if we know beforehand that the interviewee does not have expertise in organoid-related legal issues.
4. What is your uptake of the current ethical debates on (Blastoids, Gastruloids, Placenta, "Brain" organoids) technology? Comments: We could try and draw a line with the previous question, since the purely scientific gaps of knowledge will be reflected on the current ethical debates.		**4. Have you experienced uncertainty in interpreting regulations on organoids?** Comments: We have to leave room for the relevant technologies, if we know beforehand that the interviewee does not have expertise in organoid-related legal issues.
5. What ethical dimensions of organoid research do you think researchers are aware of? Comments: For the researcher and for her/his colleagues. Do they actually take them into consideration when designing their research? If no, can you explain why?	**4. What ethical dimensions of organoid research do you think researchers are aware of?** Comments: Do they actually take them into consideration when designing their research? If no, can you explain why?	**5. What are the specific challenges that cerebral organoids, including their potential resemblance to human brain activity, raise to legislation?** Comments: You can use the following follow up questions: • What are the boundaries that should be anticipated by law in the development of organoid research? • Brain is the most complex organ, but we have already legislations on stem cells research and commodification of organs. Does that give an open frame that should be adopted to organoids or act as an exemplar case?
6. What kind of support do you think a researcher on organoids needs when conducting experiments?	**5. What kind of help/advice/knowledge sources do you think a Bioethicist/Research Ethics Committee member needs when**	**6. How adequate is the information to patients/donors of tissue in current consent procedures? How could it eventually be**

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Comments: Input on current, upcoming or needed Codes of conduct, SOPs, guidelines, advisory bodies, RECs. What is already there and what is missing?	**assessing projects related to organoid research?** Comments: Input on current, upcoming or needed Codes of conduct, SOPs, guidelines.	**improved?** Comments: A connection to the existing legal framework of biobanks can be made here.
This cell was left intentionally blank	*This cell was left intentionally blank*	**7. When debating about production and use of organoids, what do you indicate as the most important gaps in the existing legal framework?** Comments: What are the lessons learned from the debates in the context of similar technologies? A connection to the existing legal framework of biobanks to be made here too. We are not starting from nothing; we should underline the eventual new legal questions raised by oganoids research, in terms of hybridation and definitions of chimeras.
Communication/Interaction with the public		
7. How would you define vulnerable population? Is it possible to have a new type of vulnerable population in organoid research? Comments: Leave this question generic at the beginning. If the interviewee asks for clarification you can rephrase: Can you identify among donors or patients a population that would be particularly threatened by organoid research and that we should consider as vulnerable?	**6. How would you define vulnerable population?** Comments: Leave this question generic at the beginning. If the interviewee asks for clarification you can rephrase: Can you identify among donors or patients a population that would be particularly threatened by organoid research and that we should consider as vulnerable?	**8. In discussions with researchers/scientists or lay people, have they expressed concerns, considerations, fears, and expectations to you?** Comments: To inform WP4 but also to have a first glimpse on the debates from another perspective.
8. How do you usually translate technical terminology on organoids into	**7. How do you usually translate philosophical terminology or the core of ethical debates**	*This cell was left intentionally blank*

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"everydaylanguage" supposedly to be understandable by non-experts? Comments: Input on how to avoid unfounded hyped or doomsday scenarios (e.g. “mini brains”), when communicating with policy makers or with lay people. Clarify what are the concerns, considerations, fears, and expectations expressed to the interviewee by her/his peers, policy makers or lay people. To gain knowledge on first-hand experiences on the debates.	**related to organoids or similar technologies into "everyday language"?** Comments: If the question is not clear to the interviewee, we are going to use some examples of philosophical terminology, e.g. epistemology, personal identity, mind-body distinction, consciousness, free will, autonomy, and how the interviewee translates them into “everyday language”.	

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19 Annex 4: Ethics approval

NTUA, as leader of WP3, obtained ethics approval for the conduct of the expert interview study. After informing NTUA's Data Protection Officer, the NTUA team sent an official request to the Research Ethics and Deontology Committee of NTUA. The ethical approval was granted on the 9th of December 2020. The official certification, issued by the Research Ethics and Deontology Committee of NTUA, was issued in the Greek language. The original document is kept in NTUA's premises and can be sent to the Project Officer or to the external evaluator upon demand.

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20 Annex 5: Resources from SwafS projects relevant to HYBRIDA's WP3

This annex lists all SwafS projects that provided elements to the knowledge base of WP3 of HYBRIDA. For reasons of completeness the table below lists the specific deliverables that informed for both D3.1 and D3.2.

No.	Type of resource	Title of resource	Project	WP3 deliverable
1	Deliverable	D2.2 Analysis of the legal and human rights requirements for genomics in and outside the EU	SIENNA	D3.1 and D3.2
2	Deliverable	D3.2: Analysis of the legal and human rights requirements for Human Enhancement Technologies in and outside the EU	SIENNA	D3.1 and D3.2
3	Deliverable	SIENNA D2.3: Survey of REC approaches and codes for genomics	SIENNA	D3.1
4	Deliverable	SIENNA D3.3: Survey of REC approaches and codes for human enhancement	SIENNA	D3.1
5	Deliverable	D3.4: Ethical Analysis of Human Enhancement Technologies	SIENNA	D3.1
6	Deliverable	D2.5: Public views on genetics, genomics and gene editing in 11 EU and non-EU countries	SIENNA	D3.1 and D3.2
7	Deliverable	D3.5: Public views of human enhancement technologies in 11 EU and non-EU countries	SIENNA	D3.1 and D3.2
8	Deliverable	D2.6: Qualitative research exploring public attitudes to human genomics	SIENNA	D3.1 and D3.2
9	Deliverable	D3.6: Qualitative research exploring public attitudes to human enhancement technologies	SIENNA	D3.1 and D3.2
10	Deliverable	D5.6: Recommendations for the enhancement of the existing legal frameworks for genomics, human enhancement, and AI and robotics	SIENNA	D3.1
11	Deliverable	D2.3 Normative analysis of research integrity and misconduct	PRINTEGER	D3.1
12	Deliverable	D2.4: Legal analysis	PRINTEGER	D3.1
13	Deliverable	D3.4: Codes and legislation	PRINTEGER	D3.1

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14	Deliverable	D5.1: Policy brief for science policy makers and research managers	PRINTEGER	D3.1
15	Final report	Guidelines for tailoring the informed consent process in clinical studies	PRINTEGER	D3.1
16	Deliverable	D1.1: Report on guidelines, standards and initiatives for improving informed consent in the healthcare context.	i-CONSENT	D3.1
17	Deliverable	D1.2: Report on gender and age-related issues associated with the acquisition of informed consent.	i-CONSENT	D3.1
18	Deliverable	D1.3: Ethical and legal review of gender and age-related issues associated with the acquisition of informed consent	i-CONSENT	D3.1
19	Deliverable	D1.4: Ethical issues concerning informed consent in translational / clinical research and vaccination	i-CONSENT	D3.1
20	Deliverable	D1.5: Legal issues concerning informed consent in translational/clinical research and vaccination	i-CONSENT	D3.1
21	Deliverable	D1.6: Patient group insights on improving guidelines for informed consent, including vulnerable populations, under a gender perspective	i-CONSENT	D3.1
22	Deliverable	D1.7: Socio-cultural, psychological and behavioural perspectives toward informed consent process	i-CONSENT	D3.1
23	Report	Final Global Code of Conduct	TRUST	D3.2
24	Report	National and International Compliance Tools	TRUST	D3.2
25	Report	Document 4 – Collection of experiences on research ethics and integrity	GRACE	D3.1
26	Report	GRACE Flyer – Reflection Tool	GRACE	D3.1
27	Report	Reflection Tool for RRI Initiatives	GRACE	D3.1

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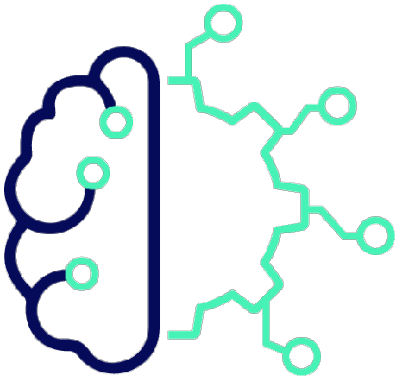

HYBRIDA

CONSORTIUM MEMBERS

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