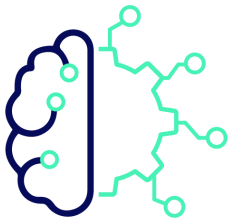
HYBRIDA



HYBRIDA

D3.2: Comparative analysis

Authors: Vana Stavridi, Eleni Spyrakou, Panagiotis Kavouras, Anastasia Deligiaouri
Reviewer: Maxence Gaillard
Editors: Costas A. Charitidis, Jan Helge Solbakk

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

Project acronym: HYBRIDA

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HYBRIDA

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Project full title

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

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D3.2: Comparative analysis

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Authors:	Eleni Spyrakou, Vana Stavridi, Panagiotis Kavouras, Anastasia Deligiaouri
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ABSTRACT:	This report presents the results of the survey conducted within Task 3.3 of WP3 of the HYBRIDA project, focusing on the comparison of relevant regulatory frameworks in Europe and beyond. The aim of this report is to identify relevant regulatory environments and cultures that deal with the selected technologies (gene editing, cloning technologies and IPS technologies, and embryonic stem cell technologies) and gather existing knowledge on codes of conduct, SOPs and guidelines regulating organoid research and the selected technologies/ families of technologies. Following the thorough mapping of the existing regulatory, Research Ethics and Research Integrity frameworks regarding organoid research and similar technologies presented in D3.1, the results reported hereto depict the way and the extent to which the technologies of gene editing, cloning, and IPS and ESC technologies are being regulated in the following countries and respective research environments: the European Union, the United Kingdom, Russia, Israel, the USA, China, Japan, Australia. Furthermore, it is attempted to present a comparative analysis among the abovementioned cases with the aim of placing emphasis on the criteria that will enable the HYBRIDA project, at its next phases of development, to suggest appropriate guidelines and Codes of Conduct for organoid research which, hopefully, will be endorsed at the international level.
Keyword List:	Organoid, Gene-editing, Cloning, induced Pluriponent Stem Cells(iPCS), embryonic Pluripotent Stem Cells (PSC), Chimera,Precision medicine, Personalised medicine, Drug development, Ethics, Bioethics, Moral status, Regulatory,Biobank, Operational guidelines, Legal framework, Regulatory framework, Regulation, Code of conduct, Ethical framework, 14-day rule, Embryo status, Culture, Cultural diversity, Cultural differences.

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Part 1: INTRODUCTION

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1 The HYBRIDA project

An organoid is aself-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 – thatchallenge 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).

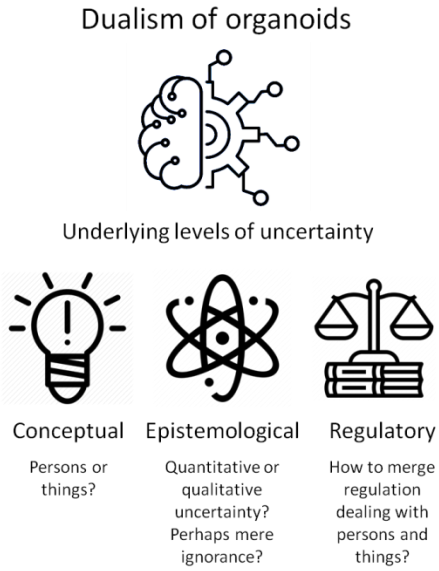

Figure 1: Levels of uncertainty stemming from the dual nature of organoids.

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

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

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

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

2 Executive summary

The aim of this report is to identify relevant regulatory environments and cultures that deal with the selected technologies (gene editing, cloning technologies and IPS technologies, and embryonic stem cell technologies) and gather existing knowledge on codes of conduct, SOPs and guidelines regulating organoid research and the selected technologies/ families of technologies. The results presented here derive from the survey conducted within Task 3.3 of WP3 of the HYBRIDA project, focusing on the comparison of relevant regulatory frameworks in Europe and beyond, as well as from inputs received from the interviews conducted with experts. Following the thorough mapping of existing regulatory, Research Ethics and Research Integrity frameworks regarding organoid research and similar technologies presented in D3.1, the results reported depict the way and the extent to which the technologies of gene editing, cloning, and IPS and ESC technologies are being regulated in the following countries and respective research environments: the European Union, the United Kingdom, Russia, Israel, the USA, China, Japan, Australia. Furthermore, it is attempted to present a comparative analysis among the abovementioned cases with the aim of placing emphasis on the criteria that will enable the HYBRIDA project, at its next phases of development, to suggest the appropriate guidelines and Codes of Conduct for organoid research which, hopefully, will be endorsed at the international level. The comparative analysis attempted reveals the particularities pertaining to national or regional research environments as well as to the selected technologies of interest. Moreover, it highlights points of similarity and common approach among these environments that could enablethe formulation of regulationsaimed at international cooperation and overarching regulation of organoid research with mutually respected standards thus transcending local particularities while at the same time respecting local and cultural differences.

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3 How to read this report

D3.2 presents the results of the survey conducted within Task 3.3 (of WP3) which focuses on the comparison of relevant regulatory frameworks in Europe and beyond. The aim of D3.2 is to identify relevant regulatory environments and cultures that deal with the selected technologies (gene editing, cloning technologies and IPS technologies, and embryonic stem cell technologies) and gather existing knowledge on codes of conduct, SOPs and guidelines regulating organoid research and the selected technologies/ families of technologies. We have proceeded with a mixed methods approach similar to the one applied in Task 3.2 and described in D3.1, i.e. a combination of literature review and expert consultations, resulting in the compilation and classification of the findings in order to suggest appropriate operational guidelines, draft a Code of responsible conduct for researchers, as well as contribute to the existing ethics and normative frameworks (WP5 and WP6, respectively).

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 done in a modular fashion, according to the interests of the reader. As Task 3.3 and, consequently, D3.2 build upon knowledge obtained within Tasks 3.1 and 3.2 and D3.1, it is expected that, to a great extent, they share the same methodology and sources of information, both already explicitly described in D3.1. However, for the purpose of completeness and capability of autonomous reading of this report, some elements regarding the background of the survey and its methodology, are repeated and included in this report as well.

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 earlyin 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 inputs 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
- **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

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technologies, and embryonic stem cell technologies) – i.e. elements from the WP3 repository

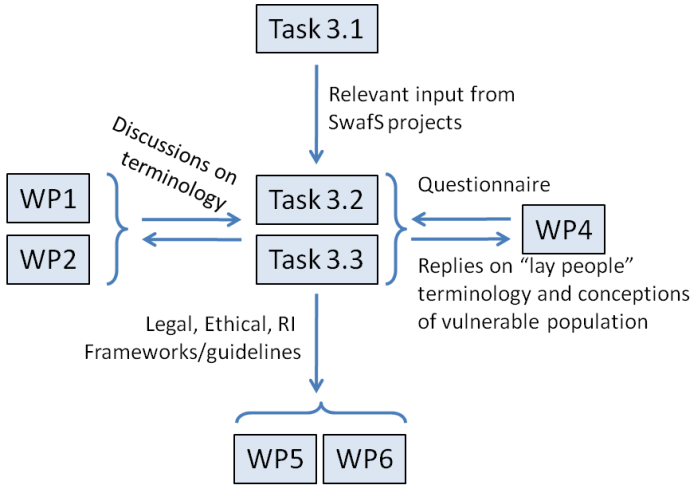

Figure 2: A flowchart depicting the flow of information from and to WP3.

5 Timeline of work package 3 activities

WP3 had to streamline a significant number of different tasks in a relatively short time (6 months) from the start of HYBRIDA. This is the reason why WP3 leaders began to plan all activities foreseen by the DoA before the official start 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 forTasks 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).

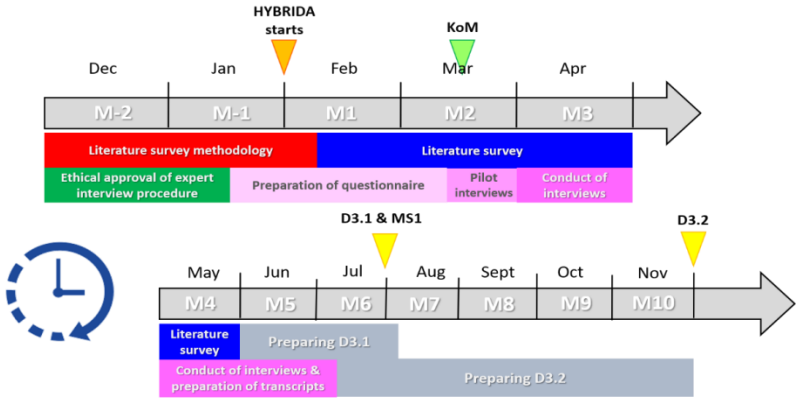

Figure 3: Timeline of WP3 activities.Orange arrow indicates the official starting date of HYBRIDA, the green arrow indicates the date of the kick off meeting and yellow arrows indicate the delivery dates of D3.1 and D3.2, as well as the only WP3 milestone.

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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 interviewswith two members of the HYBRIDA Advisory Board were conducted. 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 lasted until the end of August 2021. The preparation of D3.1 was mainly done in June and July 2021 (grey bar at Figure 3). The preparation of D3.2 was mainly done during September, October and November 2021.

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Part 2: METHODOLOGY

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6 Underlying methodology

Deliverable 3.2 has been drafted to present the outcomes of a wide survey of the legislation and other means of regulations (guidelines, SOPs, Codes of Conduct) regarding the selected families of technologies (gene editing, cloning, iPS and ESC technologies) and selected countries/research environments.The type of survey used for D3.2 was a **Systematic Scoping Review**, in the sense that part of the information used for D3.2 was the result of the systematic scoping review already conducted for D3.1. More particularly:

- A mixed-methods approach 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]
- The resources planned to be reviewed were of a complex and heterogeneous nature:
    - National legislation and regulation of the selected countries, relevant to the selected families of technologies
    - 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

7 Systematic scoping review protocol

7.1 Set the objective of Task 3.3

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.

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.
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.

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7.2 Context (geographical, cultural, disciplinary factors)

Task 3.3had 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.

7.3 Interaction with other SwafS projects

As already described in D3.1., there has been a study of related SwafS projects with publicly available outputs (i.e., deliverables, policy briefs, brochures). Theones that had publicly available outputs with a meaningful relevance were i-CONSENT, PRINTEGER, GRACE and TRUST. The only project that contributed,in a substantive manner, to 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 and 3.3 conducted 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 focus on the European Research Area. This focus was selected due to 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 memberswho 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 researchboth inside and outside Europe.

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This led to the conclusion that the division of the interviewees workingin European and non-Europeansettings did not serve the initial purpose. As a result, the authors decided that the outcomes of all eighteen interviews were going to feed both D3.1 and D3.2. To achieve this, the questionnaire for all expert interviews was the same. However, 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 works in Europe and the other half works in the rest of the world. All 20 interviews were going to be analysed in the context of Tasks 3.2 and 3.3. For the context of Task 3.2 the interviews werebound to provide input that will mostly targetthe 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). Therefore, 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 had to 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 with regard to 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 at Karlsruhe Institute of Technology (expert in Technology assessment) and Professor Megan Munsie at 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).

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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 responsible to conduct each interview.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**
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	

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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 whohave 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 couldbe 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 3.3 required the gathering and analysis of a large amount of bibliographic and empirical evidence. The work within Task 3.3, followed the methodology applied, also, for Tasks 3.1 and 3.2, and was divided into four subtasks (see Figure 4), three of which had to be applied simultaneously:

- **Preparation:**Setting of the objectives and research questions for the Task 3.3 study, deciding the methodological framework and applying the initial methodological steps.
- **Search and retrieve:** Gathering of the resources (legislation, guidelines, peer reviewed articles and grey literature)
- **Extracting and charting:** Study of the gathered resources and initiation of D3.2 drafting
- **Interviews:** Conduct of interviews with the experts who work in Europe

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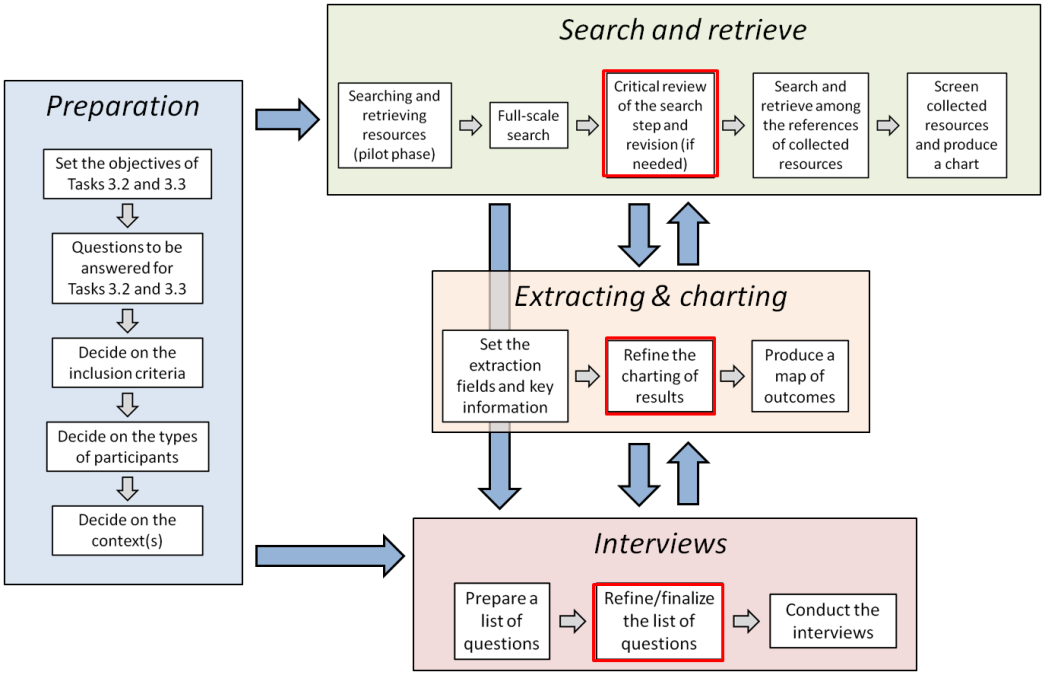

Figure 4: Schematic diagram of the four subtasks and their mutual interaction (blue arrows) within the context of Task 3.2.

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.

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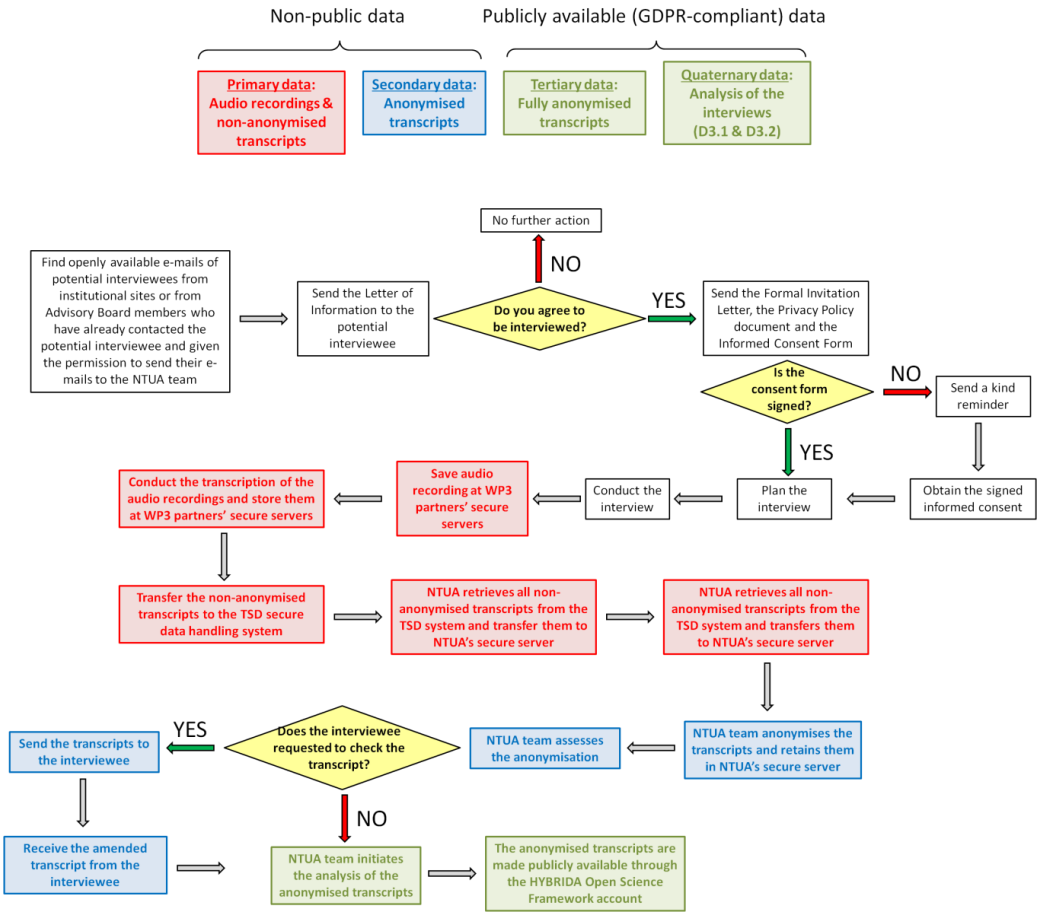

Figure 5: The procedure of data handling, starting from the initial contact with the potential interviewee until the storage of the anonymised transcripts in the Open Science Framework platform.

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Part 3: RESULTS

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11 Comparative analysis of relevant regulatory environments and cultures

11.1 Introduction

Organoids have imposed great challenges to legal and ethical research. The main challenge stems from their disputed nature, the complexity they entail as entities and the uncertainly – accompanied with reservations- regarding their future development and what this development will bring in relation to their characteristics and their abilities.

The ambiguity governing the future development of organoids and relevant technologies has also given rise to the "precautionary principle"[2]. According to the main rationale of this principle, as we can't rule out the possibility that e.g., some brain organoidscan evolve into sentient entities, there is the need for urgent regulationensure that research won't overstep some limits, even at a stage when their evolvement is not clear or predictable[3]. This anticipatory trend is shared by other scholars as well who perceive the need for urgent regulation in the area consistent with ethical principles and by taking into consideration challenges that may arise in the future[4].

To date, there are no specific regulations or guidelines for the use of organoids in research. Inorder toproduce appropriate guidelines for achieving the ethical use of organoid technology, an approach that is capable of outlining the ethical and legal dimensions applicable to research and technology that are similar to organoid research should be followed. Therefore, our main interest in this report is to highlight these dimensions through a comparative analysis of the current legal and regulatory frameworks of research and technologies which raise similar ethical and legal challenges, as e.g.,ESC research, cloning and gene editing. However, we should underline that apart from the similarities in ethical and legal dimensions, organoids are related in other ways toESC, cloning and gene editing.

ESCs is considered the raw material for the creation of organoids. Therefore, issues concerning the permissibility of the use of ESC for research or clinical purposes greatly influence the debate on the ethical conduct of research on organoids. In the context of our analysis for ESC research, we also examine the legal definition of the status of the embryo. The way each

[2] Birch, J & Browning (2021) Neural Organoids and the Precautionary Principle, *The American Journal of Bioethics,* 21:1, 56-58, DOI: 10.1080/15265161.2020.1845858

[3]Ibid., p.56.

[4]Sawai, T., Hayashi, Y., Niikawa, T., Shepherd, J., Thomas, E., Lee, T. L., ... &Sakaguchi, H. (2021). Mapping the Ethical Issues of Brain Organoid Research and Application. *AJOB neuroscience*, 1-14.

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country defines legally the status of the embryo determines whether and to what extent the use and derivation of stem cells is allowed. Regarding the analysis of the regulatory framework for ESC research, we make a specific reference to the 14-day rule.[5] The adoption of this rule is directly related to the permissibility of ESC research and the degree of this permissibility. Some countries seem to weigh the risks of stem cell research againstthe potential benefit of this researchand set specific grounds on when such research is allowed. Some countries adopt a very restrictiveline prohibiting any kind of stem cell research or research on embryos, while some countries provide specific preconditions for this type of research.

In the same context we examine the regulatory framework for cloning. Human cloning is a replication technique related to stem cell research insofar as it represents a possibility to produce embryos from which ESC can later be obtained. Depending on the goals of the cloners, the technology one can distinguishbetween 'therapeutic cloning' and 'reproductive cloning'.[6] If one of the future developments in organoid research is the creation of models that mimic the functions of the (human) embryo, the ethical and legal challenges associated with cloning will significantly influence the creation of a regulatory framework for organoid research.

Subsequently, we proceed with the presentation of the regulatory framework for gene editing. Gene editingtechniques can be applied to edit genes in ESCs, iPSCs, germ cells, somatic cells or even human embryos and hold great therapeutic potential. Also, they are considered as the main tool for future development of organoid research. Organoids can be modified with different genetic engineering methods such as CRISPR/Cas. The genetically edited organoids can be further utilized for various applications/fields of study including biological developmental models and translational/precision medicine.[7]

The content of regulations and the means by which each country regulates this type of research and technologies are different. This difference relates to the countries' specific cultural, religious and economic characteristics.On an international or supranational level many attempts have been made in the direction ofharmonizing the regulations for hESC research, cloning and gene editing. However, despite these attempts, no consensusabout regulations with a binding character has been achieved within the global community.[8]

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[5] The 14-day rule is more often associated with the 1984 U.K. report authored by the Committee of Inquiry into Human Fertilisation and Embryology (Warnock 1984). Referred to as the Warnock report after the committee's chair Dame Mary Warnock, the report recommended restricting human embryo research to the 14th day post fertilization.
Warnock, Mary (1984). *Report of the Committee of Inquiry into Human Fertilisation and Embryology*. London: Her Majesty's Stationery Office. See also Warnock, Mary (2017)."Should the 14-Day Limit on Human Embryo Research Be Extended?" BioNews. January 9, 2017. http://www.bionews.org.uk/page_755759

[6]Prainsack, B. (2006). *"Negotiating Life." Social Studies of Science, 36(2), 173–205.* doi:10.1177/0306312706053348, p. 178.

[7]Mollaki, Vasiliki. (2021). "Ethical Challenges in Organoid Use" *BioTech* 10, no. 3:12.https://doi.org/10.3390/biotech10030012.

[8] Campbell A, Nycum G. (2005) Harmonizing the International Regulation of Embryonic Stem Cell Research: Possibilities, Promises and Potential Pitfalls. Medical Law International. 2005;7(2), p. 114. doi:10.1177/096853320500700202.

Roman Wagner. (2020). Research with Human Embryonic Stem Cells, drze,https://www.drze.de/in-focus/stem-cell-research.

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Nevertheless,it is important to underline that international conventions, recommendations and international instruments that are ratified by countries play an important role in the way nations regulate health innovations and sensitive legal issues related to them. Developing regulations at an international level is very important as it would provide a safe and commonly agreed ground for ethical research. As sensitive legal issues arise due to recent developments in the life sciences some scholars argue in favor ofmore nuanced legal interpretations of basic notions such as for example the notion of "legal personhood". There is much debate surrounding these developments with opposing views that challenge legal thought and established categories and these debates are likely to continue and puzzle scholars struggling to provide answers to demanding questions.

Current international regulatory frameworks, as e.g. the Oviedo Convention, the Universal Declaration on Bioethics and Human Rights and European legislation, emphasize several safeguards and rights that demand "absoluteprotection" when applying health innovations.[9]But in spite of this,[10]there are still several discrepancies innational legislations that allow for different approaches sincehealth issues, as well as public health and bioethicsrelated issues,remain to be regulated by countries. Despite this duality in legislative powers,[11] it is certain that fundamental rights andliberties are not under contestation. Core values and rights like the protection of human life from veryearly stages and human dignity are sufficiently protected and set the limits inhuman activity and research regarding health innovations and biomedical interventions.

Of particular importance in the context of the discussion about the limits and acceptable boundaries in research is the 14- day rule. This rule is found in several international scientific and medical societies' guidelines. The most comprehensivereference to thisis found in the Guidelines from the International Society for Stem Cell Research (ISSCR).In 2016 stem cell research guidelines from (ISSCR), which represents more than 4000 scientists worldwide,[12] included a 14-days limit on human embryo research.[13] However, the 2021 updated report of

[9] For more information about the International regulatory framework see at D3.1, section ''Legal/Normative framework mapping''. See also https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf

[11]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.

[12]https://www.isscr.org/news-publicationsss/isscr-news-articles/article-listing/2021/05/26/the-isscr-releases-updated-guidelines-for-stem-cell-research-and-clinical-translation

[13]ISSCR (International Society for Stem Cell Research). Guidelines for Stem Cell Research and Clinical Translation (2016). www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical translationd67119731dff6ddbb37cff0000940c19.pdf?sfvrsn=4Google Scholar. See also,Kimmelman J, Hyun I, Benvenisty N et al. (2016). Policy: global standards for stem-cell research. *Nature* 533(7603), 311–313 (2016).Crossref, Medline, CAS and Daley G, Hyun I, Apperley JF et al.(2016). Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines. *Stem Cell Reports* 6(6), 787–797.Crossref, Medline.

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ISSCR suggests the expansion of the 14-day limit and indicates that ''balancing the potential value of this researchwith the ethical and societal concerns raised by it and taking into account the social responsibility to be transparentthroughout the process, the guidelines recommend that,before a committee responsible for the specialized scientificand ethics review process may even consider applicationsfor human embryo research beyond formation of the primitive streak or 14 days, national academies of science, academic societies, funders, and regulators should lead publicconversations on the scientific significance as well as thesocietal, moral, ethical, and policy issues raised by allowingsuch research''.[14]

In our analysis we will try to show how these values are issued in national regulatory frameworks. The history, the particularities related to religions and the economy play a crucial rule on how a nation perceives these values. In addition, the perception of the values and rights affect the legal and regulatory framework. Our review starts with the analysis of the legal and regulatory frameworks of European Union Member States. As we will see in this part, the cultural heterogeneity of the European Union is captured also in Members States' laws and guidelines for ESC research, cloning and gene editing. The selected countries in the European Unionare Germany, Austria and Italy with very restrictive legislations and France, Spain, Sweden, the Netherlands and Belgium with more liberal legislations and different approaches according to criteria of research.

Following the selected EU countries, we proceed with the presentation of the rest of the countries we have examined. The very order of appearance of the examined countries in this report has been a matter of decision for the authors, as there are different ways of appropriate ordering, based on various criteria. One way would be to classify the countries based on the regulatory authorities specific to each country. For example, we could first present countries which do not regulate ESC research, cloning and gene editing by law but through guidelines, and, then, we could gradually move to countries where there is a mixed regulatory situation and conclude with countries that have regulated the abovementioned type of research and technologies by law. However, we have decided to present the countries following the geographical proximity to the European Union, by putting EU in the imaginary centre of our mapping followed by theUK, Russia, Israel, USA, China, Japan, and Australia. For each country we present the laws or/ and guidelines related to hESC research, cloning and gene editing.

After the presentation of the abovementioned regulatory frameworks of each country, we proceed with the provision of a table where we summarize the differences or similarities in the way that the national regulations, laws or/and guidelines define the status of embryo and regulate ESC research, cloning and gene editing. This will be a step before the comparative

[14]Lovell-Badge, L., Anthony, E., Barker, R., Bubela, T., Brivanlou, A., Carpenter, M., Charo, R.A., Clark, A., Clayton, E., Cong, Y., et al. (2021). ISSCR Guidelines for Stem Cell Research and Clinical Translation: The 2021 Update. Stem Cell Reports 16, in press. Published online May 27, 2021. https://doi.org/10.1016/j.stemcr.2021. 05.012.

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analysis. As we will see in the last section, there are a number of differences in national legislationswith regard to stem cell research and relevant technologies. Differences are due to various traditions, history and policies of each country but, also, because of the different cultures that accept or not a specific level of health innovation and its related technologies.

11.2 National legal and regulatory frameworks on hESC research, cloning, gene editing

11.2.1 The European Union

In spite of the heterogeneity in legislation of the Member States the European Union seems to play an important role in the rule of law at an international level, and also with regard to raising ethical concerns.[15]Withinthe context of the European Union, we will analyze the regulatory framework of some selected countries and we will highlight their differences.

We should underline that the legal architecture and the legal tradition in each country/state provides for different regulatory layers. The membership of a state in a supranational organization like the EU has also implications on the applied regulations sinceEU legislation supersedes national legislation. However, specific competencies that the EU holds and the principles of subsidiarity and proportionality affect the legal framework and the hierarchy between national and European legislation.[16] The European legal landscape exemplifies different regulatory and cultural norms as these are evident from the comparison of the legislation in Member States. There are several discrepancies noted in national legislations and oversight bodies. Recognizing heterogeneity and pluralism, the institutions of the European Union formulate opinions and recommendations in order to emphasize the importance of safeguarding human dignity, without, however, regulating how and to what extent research should be conducted. This decision concerns the Member States.Here we provide some highlights on different countries, which have dominated the results of our survey, that show the discrepancies in national legislations in relation to hESC research, cloning, gene editing and definition of embryo.

[15] A. Elstner, A. Damaschun, A. Kurtz, G. Stacey, B. Arán, A. Veiga, J. Borstlap. (2009). The changing landscape of European and international regulation on embryonic stem cell research, *Stem Cell Research*, Volume 2, Issue 2,p.102.
[16]https://ec.europa.eu/health/policies/overview_en

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Austria: The ESC research in Austria is regulated bythe *Reproductive Medicine Act 2004*.[17] The Austrian law does not contain a precise definition of an embryo but states that ''Fertilized oocytes and cells derived from them shall be considered viable cells.''[18]Austriaprohibits ESC research and cloning. Under the *Reproductive Medicine Act 2004*, the procurement of cells from a human embryo for research purposes is prohibited. And also "embryos cannot be used for any purpose other than for assisted reproduction".[19]

In Austria, gene editing is governed by the *Gene Technology Act* of 1995. The *Act* stipulates that an intervention on the human germline is strictly prohibited. Gene analysis, as it is defined in this *Act,* comprises molecular biological investigations of human chromosomes, genes or DNA segments for the identification of disease-causing mutations. Such examinations are allowed only for research or medical purposes. In paragraph 67, the *Act* states that it is prohibited for employers and insurance companies to collect, demand, or use data derived from genetic tests (paragraph 67).[20]

Germany: The use of embryos is heavily restricted under the relevant *Embryo Protection Act*[21] and the German Constitution that provides for the protection of embryos and human dignity as an inviolable right.[22]On the other hand, "Germany permits embryonic stem cell research only if carried out on imported stem cell lines derived from embryos that were created before May 1, 2007, for reproductive purposes".[23] Several Constitutional tendencies are acknowledged to this extent as human life and human dignity are protected but also the right to scientific research.

The *Act* bansall forms of human cloning. And article 5 of the *Act*, states that the intentional alteration of germline cells and embryos is prohibited by criminal law.[24] The legal definition of embryo reflects the restrictive policy on ESC research, cloning and gene editing. According to this definition an ''Embryo is any totipotent cell which, if the necessary conditions are met, is able to divide and develop into an individual. For the purpose of this act, the embryo is the fertilized, developable human oocyte from the time of nuclear fusion, and any totipotent cell taken from an embryo, which, if the necessary conditions are met, can be divided and

[17] https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf
[18] https://www.eurostemcell.org/regulation-stem-cell-research-austria. See also*Reproductive Medicine Act (1992, amended 2001, 2004, 2008, 2009, 2010, 2014, 2015, 2018) 275 (1992).* www.ris.bka.gv.at/defaultEn.aspx
[19] https://www.eurostemcell.org/regulation-stem-cell-research-austria
[20] *Austrian Gene Technology Act (in English) (1995). https://www.eshg.org/fileadmin/www.eshg.org/documents/Europe/LegalWS/AustrianGeneTechnologyAct_English.pdf*
[21] https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf
[22] https://www.eurostemcell.org/regulation-stem-cell-research-germany
[23] Law Library of Congress (2012 Global Legal Research Center LL File No. 2012-008118), p.17-19
[24] Carsten Hjort, Jeff Cole, Ivo Frébort, European genome editing regulations: threats to the European bioeconomy and unfit for purpose, EFB Bioeconomy Journal, Volume 1, 2021

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become an individual (1990 Act)''.[25]

France: French legislation on ESC research dates back to a 1994 bioethics law that prohibited the creation of embryos for research as well as experimentation on embryos.[26] That law was changed in 2004, with the passage of a law on *Research on the Embryo and Embryonic Cells*.[27]The new law permits research on human embryos and embryonic stem cells provided it meets all of four criteria: that it has "scientific relevance"; it is performed toward "a medical end"; it "cannot be done without resorting to these embryos or the embryonic stem cells"; and it respects ethical principles.[28]French legislation allows the use of surplus IVF embryos but prohibits the creation of human embryos for research and more specifically the creation of transgenic human embryos.[29]The French law doesnot define precisely the embryo status and although French legislation permits hESC research doesnot specify any developmental limit. Related to gene editing, France ratified the Oviedo Convention[30]in 2011 and thus formally accepted the principles of Article 13 of the Convention, regarding the prevention of the introduction of any modification of the human genome into the genome of descendants.[31]

Italy: The ESC research, cloning and gene editing in Italy is regulated by *Law 40* which came into effect on March 10, 2004.[32] Under this law, the embryo is recognized as a subject of rights from the moment of fertilization. The law prohibits the use of embryos for any research unless it is specifically aimed towards improving the therapeutic and medical condition of the embryo concerned.[33]

[25]Kirstin RW Mathews& Daniel Morali (2020), National Human embryo and embryoid research policies: a survey of 22 topresearch – intensive countries. Regenerative Medicine, pp.1905-1917. See also S. Chaturvedi & al., *Science and Technology Governance and Ethics A Global Perspective from Europe, India and China.*

[26]https://www.thenewatlantis.com/publications/appendix-e-overview-of-international-human-embryonic-stem-cell-laws#_ftn39

[27]Ibid.

[28]https://www.eurostemcell.org/regulation-stem-cell-research-france

[29]Academy of Medical Sciences. (2016). The European Landscape for human genome editing. A review of the current state of the regulations and ongoing debates in the EU. p.23. https://acmedsci.ac.uk/file-download/41517-573f212e2b52a.pdf

[30] Council of Europe. (1997). *Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine,* Article 13. The Council of Europe throughthe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, provided an international instrument aiming to prohibit the misuse of innovations in biomedicine and to protect human dignity. The Oviedo Convention incorporates provisions to address concerns relating to research into the human genome. Under the Article 13, the modification of the human genome, for reasons other than health-related is generally prohibited.

[31] Academy of Medical Sciences. Ibid., p.29.

[32]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf

[33]https://www.eurostemcell.org/regulation-stem-cell-research-italy

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Italian law is very restrictive for all three types of research and technology. Its restrictions are summarized in the following statementswhich forbid:

- a procedure aimed to obtain a human being from one cell, possibly identical, in terms of genetic patrimony, to a different human being whether dead or alivecreating human embryos for the purpose of doing research or experimenting on them;
- all forms of eugenic selection, including procedures that would manipulate or somehow artificially alter the genetic patrimony or predetermine genetic traits of the embryo or gamete;
- cloning by transferring the nucleus, by early scission of the embryo or by ectogenesis; and,
- fertilizing a human embryo with the gamete of a living entity of a different species.[34]

Spain: The ESC research in Spain is regulated by *Biomedical Research Law (2007, amended 2014).* [35] The law permits the research on ESC on therapeutic and research purposes but it doesnot permit the creation of embryos exclusively for research purposes[36]. Spanish legislation on ESC research sets a limit of 14 days. The establishment of this limit is in line with the legal definition of the embryo. Regarding this definition, the law states that ''embryo is the stage of embryonic development from the moment the fertilized oocyte is implanted in the uterus until the onset of organogenesis, which ends at 56 days post fertilization. Pre-embryo is an in vitro embryo from the fertilization of the oocyte through 14 days post fertilization.''[37]Spain belongs to the countries that have passed legislation banning human reproductive cloning but allow therapeutic cloning.[38]Germline gene editing, is illegal provided that it affects someone's descendants. The legal stature of basic science involving germline gene editing remains unclear. The final decision should be adopted in a case-by-case analysis by corresponding ethics committees. [39]

[34] Andrea Boggio. (2005), Italy enacts new law on medically assisted reproduction, Human Reproduction, Volume 20, Issue 5, May 2005, p.1154. https://doi.org/10.1093/humrep/deh871

[35]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf. See also the Law: Biomedical Research Law (2007, amended 2011) 14 (in English) (2017). https://www.isciii.es/QueHacemos/Financiacion/solicitudes/Documents/SpanishLawonBiomedicalResearchEnglish.pdf

[36]https://www.eurostemcell.org/regulation-stem-cell-research-spain

[37]Kirstin RW Mathews& Daniel Morali (2020), National Human embryo and embryoid research policies: a survey of 22 top research – intensive countries. Regenerative Medicine, pp.1905-1917. See also S. Chaturvedi & al., *Science and Technology Governance and Ethics A Global Perspective from Europe, India and China.*

[38] Kathryn Wheat and Kirstin Matthews. World Human Cloning Policies, *Stem Cells: Saving Lives or Crossing Lines,* p.6.https://www.ruf.rice.edu/~neal/stemcell/World.pdf

[39]Poli, L. (2020). *The Regulation of Human Germline Genome Modification in Italy. Human Germline Genome Modification and the Right to Science, 335–357.*

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Sweden:The Swedish law provides a comprehensive regulatory framework for stem cell research.ESC and embryo research is allowed in Sweden for both therapeutic and research purposesfor up to 14 days after fertilization and their destruction afterwards.[40] However, it doesnot allow the creation of embryos exclusively for research purposes.[41]Nowhere in the law is there a definition of embryo;instead the term fertilized eggis used .[42] The creation of human embryos using SCNT (somatic cell nuclear transfer) - 'cloning technology' - is legal in Sweden, and it is governed by legislation.[43] Regarding gene editing, the legislation forbids scientists from carrying out germline gene therapy research, stating that 'the purpose of experiments must not be to achieve hereditary genetic effects or to develop methods for that purpose'.[44]

The Netherlands: The Netherlands's key laws on hESC research, cloning and gene editing are the *Act Containing Rules Relating to the Use of Gamete and Embryos (Embryos Act)* (July 1, 2002) and the *Commercial Surrogacy Act* (November 1, 1993). [45]Thelawspermit and regulate ESC research adopting the 14-day rule and ban human reproductive cloning, gene editing and the creation of hybrids and chimeras. The law makes a distinction between cloning for reproductive purposes and research-oriented SCNT. The creation of human embryos for research purposes is illegal under the law.[46] In Netherland the embryo is defined as a "cell or a set of cells with the capacity to grow into a human."[47]

Belgium: Belgium belongs to the countries that allow the creation of embryos for research purposes under certain conditions.ESC, embryo research and gene editingare regulated by the Law on *Research on Embryos In Vitro.*[48] Research on embryos is allowed for up to 14 days.The law prohibits reproductive cloning, the creation of embryos for research purposes, non-medical sex selection or treatment for eugenic purposes, and the creation of chimeras or hybrid embryos.

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[40]https://www.eurostemcell.org/regulation-stem-cell-research-sweden
[41]https://www.eurostemcell.org/regulation-stem-cell-research-spain
[42]Kirstin RW Mathews& Daniel Morali (2020),ibid.
[43]Richard Gardner and Tim Watson. (2005) A Patchwork of Laws. Scientific American, https://www.scientificamerican.com/article/a-patchwork-of-laws/
[44]Law on Genetic Integrity (2006, amended 2009, 2010, 2013, 2014, 2016, 2017, 2018, 2019) 351 (in English). https://www.icj.org/wp-content/uploads/2013/05/Sweden-Genetic-Integrity-Act-2006-eng.pdf
[45] https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf
[46]https://www.thenewatlantis.com/publications/appendix-e-overview-of-international-human-embryonic-stem-cell-laws#_ftn48. See also, van Beers, B. C., de Kluiver, C., & Maas, R. (2020). The Regulation of Human Germline Genome Modification in the Netherlands. In A. Boggio, C. Romano, & J. Almqvist (Eds.), *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies* (pp. 309-334). Cambridge University Press. https://doi.org/10.1017/9781108759083.012
[47] Ibid.
[48]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf

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11.2.2 The United Kingdom

In the UK, the law states that the use of embryos in stem cell research can only be carried out with authority from the Human Fertilisation and Embryo Authority (HFEA). As the *Human Fertilisation and Embryology Act (1990)* and in the subsequent *Human Fertilisation and Embryology (Research Purposes) Regulations 2001*[49]outline, licenses are only granted if the HFEA is satisfied that any proposed use of embryos is absolutely necessary for the purposes of the research.[50]

Two legal advisory committees have been most directly involved with this change: the Chief Medical Officer's Expert Group (appointedby the UK Government with the responsibility to assess the anticipated benefits, risks, and alternatives of new areas of research using embryos), and the House of Lords' Select Committee (appointed to consider and report on the issues connected with stem cell research and human cloning arising from the new regulations). Within their reports, several arguments can be found aimed at justifying the position that the value of the early embryo can be outweighed by research. Two of these arguments will be mentioned here: 1. early embryos lack relevant qualities ('the argument from lack of qualities'); 2. early embryos only have a potential to become humans with moral status ('the argument from potentiality').[51] Research is allowed only if its purposes include increasing knowledge about serious medical conditions, developing treatments for serious medical conditions, advancing the treatment of infertility, increasing knowledge about the causes of miscarriage, developing more effective contraception techniques, developing methods for detecting genetic or mitochondrial abnormalities in pre-implantationembryos, and increasing knowledge of embryonic development.[52]

Licensed research can only take place on embryos created in vitro, i.e., embryos that have developed from eggs fertilised outside the body. Licensed research can only take place on embryos up to 14 days. Human reproductive cloning is illegal in the UK. As a result of the *Human Reproductive Cloning Act (2001)* nobody in the UK is allowed to use cell nuclear replacement, or any other technique, to create a child.[53]

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[49]Statutory Instrument 2001 No. 188. The Human Fertilisation and Embryology (Research Purposes) Regulations 2001. Norwich. The Stationery Office Limited.

[50] Lee, D. A. (2012). Embryonic stem cells: scientific possibilities, ethical considerations, and regulation in the UK. Interdisciplinary Science Reviews, 26(2), 112–124. https://doi.org/10.1179/0308018012772542

[51]Deckers, J. (2005). Why current UK legislation on embryo research is immoral. How the argument from lack of qualities and the argument from potentiality have been applied and why they should be rejected. Bioethics, 19(3), 251–271. https://doi.org/10.1111/j.1467-8519.2005.00440.x

[52]Human Fertilization and Embryology Act (2008), 3A

[53] Ibid

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Gene editing technology is permitted in the UK. However, clinical trials need a license and ethics approval.[54]The main authority responsible for this approval is the *Human Tissue Authority (HTA)* under *the Human Tissue Act (2004)* and *Human Tissue Regulation (2007)* for tissues and cells that may be transplanted into humans.[55]

11.2.3 Russia

Legislation in Russia prohibits basic ESC research and embryo research. Specifically, it prohibits the creation of "a human embryo for the production of biomedical products" as well as "using biological materials obtained by suspension or interruption of the development of a human embryo or fetus for the development, production and use of biomedical cell products".[56] Russian law doesnot contain aprecise definition of embryo but establishes the inadmissibility of creating a human embryo for the production of biomedical cell products, the inadmissibility of using biological material obtained by suspension or interruption of the development of a human embryo or fetus for the development, production and use of biomedical cell product.[57]

Russian science recognizes the basic ethical principles that underpin the decisions of the United Nations, the United Nations Educational, Scientific and Cultural Organization, the WHO and other international organizations, as well as the provisions of the Council of Europe's Convention on Human Rights and Biomedicine. These principles will define the system of ethical expertise and inform how Russia regulates the field.[58]

11.2.4 Israel

The policy on ESC research, cloning and gene editing in Israel is formed by Law and guidelines.[59]Israel has a law banning reproductive cloning, but does not address other forms of human embryo research. ESC research is permitted and regulated by guidelines which address sources of embryo and the 14-day rule.[60]Scientists in Israel are not restricted to derive ESC lines and the Israeli government is financially supportive of this research.[61]There is an Israeli society

[54]Kirstin RW Mathews& Daniel Morali (2020), Ibid.
[55]https://www.eurostemcell.org/regulation-stem-cell-research-united-kingdom
[56]Federal Law On Biomedical Cell Products (2016) 180-FZ (2016).http://www.gratanet.com/up_files/biomedical_cell_products_russia_june2016_eng.pdf
[57] Ibid.
[58]Elena G. Grebenshchikova. (2020). Russia's stance on human genome editing.Nature, Vol 575.

[59]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf

[60]Kirstin RW Mathews& Daniel Morali (2020), ibid., p. 1907.
[61]F.Simonstein. (2007), Embryonic Stem Cells: The disagreement debate and embryonic research in Israel, Global medical ethics, p732.

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for stem cell research (the Israel Stem Cell Society) and a governmentally funded consortium of industrial and academic partners for the development of cell therapy (the Israeli Consortium for Cell Therapy, "Bereshith").[62]

The Israeli law generally prohibits "human reproductive cloning" unless authorization for it is granted by the Minister of Health based on the determination that the procedure would not harm human dignity and with the recommendation of the Superior Helsinki Committee appointed in accordance with the Public Health (Medical Experiments in Human) Regulations. [63]

There is also the Amendment Law which further amends the definition of human reproductive cloning, previously defined by the Law as either:

- the creation of an embryo by the transfer of a human cell into an egg or a fertilized egg from which the nucleus has been removed (in this Law a cloned embryo), for the purpose of creating a person who is identical from a genetic chromosomal [standpoint] to another person or embryo, living or dead;
- the insertion of a cloned embryo into a uterus or the body of a woman or into anotheruterus or into another body.[64]

Similarly, to the case of Chinese law, the Israeli law does not define the status of the embryo. However, we can refer to Jewish religious law and from there we can derive information about the spirit that governs the laws and the guidelines for hESC research.[65] This choice does not mean that the religious factor is the primary factor in the formation of the Israeli regulatory framework but it gives an idea regarding the public acceptance of research and technology advances. According to Jewish religious law the human life begins 40 days after the fusion of egg and sperm cells and only when the embryo is within the mother's womb. Therefore, the law refuses to grant full human inviolability to the unborn child from conception.It is clearly agreed that the potentiality for life must not be compromised except for the most substantial medical reasons.[66]

Regarding germline gene editing, the Israeli law states that is banned "for the purpose of creating humans"[67]and can be punishable with up to four years imprisonment or fines under the Prohibition of Genetic Intervention Law, passed in 1999 and since revisedmultiple times by

[62]A. Elstner, A. Damaschun, A. Kurtz, G. Stacey, B. Arán, A. Veiga, J. Borstlap, The changing landscape of European and international regulation on embryonic stem cell research, Stem Cell Research,Volume 2, Issue 2,2009, pp. 101-107.

[63]*SeferHahukim* (the Book of Laws of the state of Israel) 1697, 7 January 1999: 47; *SeferHahukim* (the Book of Laws of the state of Israel) 1934, 31 March 2004: 340; *SeferHahukim* (the Book of Laws of the state of Israel) 2212, 22 October 2009: 233;*SeferHahukim* (the Book of Laws of the state of Israel) 2553, 25 May 2016: 882.

[64]Ibid.

[65]Joseph G. Schenker(2008), The beginning of human life**.** Status of embryo. Perspectives in Halakha (Jewish Religious Law),25(6): 271–276. See also, Barbara Prainsack (2006), 'Negotiating Life': The Regulation of Human Cloning and Embryonic Stem Cell Research in Israel. Social Studies of Science 2006 36: 271-276

[66]Joseph G. Schenker(2008), Ibid.

[67]Law Library of Congress (2012 Global Legal Research Center LL File No. 2012-008118), p.68-73.

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the Israeli Parliament. However, the Minister of Health may give permission for germline gene editing experiments, upon the recommendation of an advisory committee.

An amendment of the Prohibition of Genetic Intervention Law[68], was passed in 2016 and in effect until 2020, upheld a ban on germline gene editing unless authorization for it is granted by the Minister of Health. Authorization must be based on the determination that the procedure would "not harm human dignity" and must be made with a recommendation of the Superior Helsinki Committee, an advisory committee for the approval of human research.[69]

11.2.5 USA

There is no federallawthat prohibits stem cell research, cloning and gene editing in the United States. Related to ESC research, eight states—California, Connecticut, Illinois, Iowa, Maryland, Massachusetts, New Jersey and New York— encourage embryonic stem cell research, while South Dakota's law, strictly forbid research on embryos regardless of their source.[70] States that specifically permit embryonic stem cell research have established guidelines for scientists such as consent requirements and approval and review proceduresfor projects.

Although, there is no federal law for prohibiting ESC research in USA, there is an Amendment (Dickey-Wicker) which prohibits federal funding for human embryo research. [71]This amendment has been passed annually within the federal budget ofthe US Department of Health and Human Services since 1995, prohibiting scientists from obtaining funding for human embryo research work inthe US. The Dickey-Wicker Amendment bans federal funding for "the creation of a human embryo or embryos for research purposes or research in which a human embryo or embryos are destroyed, discarded, or knowingly subject to risk of injury or death," including developing hESC lines[72]. The Amendment only applies to federal funding and does not affect such research funded by state or local governments or private institutions.[73]

In the same Amendment there is adefinition ofhuman embryo according to which ''the term 'human embryo or embryos' includes any organism … that is derived by fertilization,

[68]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf

[69] Law Library of Congress, ibid.

[70]Matthews KRW, Yang E. "Politics and Policies Guiding Human Embryo Research in the United States." Baker Institute Report (2019). https://doi.org/10.25613/vbe8-z426

[71]Further Consolidated Appropriation Act. H.R. 1865, 116th Cong. Sec. 508 [Dickey-Wicker Amendment] (2020). www.congress.gov/bill/116th-congress/house-bill/1865/text. See also, Hurlbut JB. Experiments in Democracy: Human Embryo Research and the Politics of Bioethics. Columbia University Press, NY, USA (2017).

[72]Further Consolidated Appropriation Act. H.R. 1865, 116th Cong. Sec. 508 [Dickey-Wicker Amendment] (2020). Ibid.

[73]A slow road for stem cells. (2018). *Nature*, 557(7705), p.279.

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parthenogenesis, cloning, or any other means from one or more human gametes (sperm or egg) or human diploid cells (cells that have two sets of chromosomes, e.g., somatic cells)''[74]

In 2005, the United State of National Academies of Sciences, Engineering, and Medicine released its Guidelines for Human Embryonic Stem Cell Research. These Guidelines were prepared to enhance the integrity of human embryonic stem cell research in the public's perception and with the intention of encouraging responsible practices in the conduct of such research.[75]The guidelines preserve two primary principles. First, that hESC research has the potential to improve our understanding of human health and discover new ways to treat illness. Second, that individuals donating embryos should do so freely, with voluntary and informed consent.[76]Currently in the U.S., regulatory bodies at universities and other research institutions adhere to the 14-day rule.[77]Regarding gene editing, we could say that USA allows it under the oversight and approval of the *Department of Health and Human services (DHSS)*. Germline gene therapy is regulated more strictly

Although the U.S. has no outright ban on ESC research, cloning and gene editing, a restrictive regulatory landscape[78] and a lack of federal support has imposed significant restrictions on researchers. Congress has banned NIH funding for research involving live human embryos, forcing researchers to either abandon these projects entirely or seek private funding with fewer restrictions.[79]

11.2.6 China

With regard to ESC research, China mainly relies on guidelines insteadon laws. The stem cell research in China follows the *Measures for Ethical Review of Biomedical Research Involving Human Subjects* [80] (National Health and Family Planning Commission, 2016) and *Ethical Guidelines for Human Embryonic Stem Cell Research* (Ministry of Health and Ministry of Science

[74] Further Consolidated Appropriation Act. H.R. 1865, 116th Cong. Sec. 508 [Dickey-Wicker Amendment] (2020). Ibid.
[75]https://www.nationalacademies.org/news/2005/04/guidelines-released-for-embryonic-stem-cell-research
[76]https://web.archive.org/web/20120502033034/http://stemcells.nih.gov/policy/2009guidelines.htm
[77]Kirstin RW Mathews& Daniel Morali (2020), ibid., p. 1907.
[78]Tracey Tomlinson(2018), A CRISPR Future for Gene-Editing Regulation: A Proposal for an Updated Biotechnology Regulatory System in an Era of Human Genomic Editing, 87 Fordham L. Rev. 437.Available at: https://ir.lawnet.fordham.edu/flr/vol87/iss1/15
[79] B. Ashok, J. Kasten (2019). Is there a responsible way forward for gene editing? Brookings, https://www.brookings.edu/blog/techtank/2019/10/29/is-there-a-responsible-way-forward-for-gene-editing/
[80]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf See also,

National Health and Family Planning Commission, 2016 National Health and Family Planning Commission Measures for Ethical Review of Biomedical Research Involving Human Subjects, No. 14, (2016)

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and Technology, 2003).[81] The Measures for Ethical Review prescribes general bioethical principles for biomedical research but without any specific guidance for stem cell research.

HESC research is based on *Ethical Guidelines for Human Embryonic Stem Cell Research*. The content of articles that are included in the*Guidelines* concerns the prohibition of human cloning, the means of deriving human embryonic stem cells (hESCs), the 14-day criterion for in vitro research, the prohibition of the implantation, the prohibition commercialization, the principle of informed consent and protection of privacy and the establishment institutional ethics committee. According to the last one, every institution which is doinghESC research is required to establish Ethics Committees which should be interdisciplinary and they should formulate their regulatory rules in compliance with *Ethical Guidelines.*[82]

Gene editing research is allowed in China.Gene editing requires approval by an ethics committee of a hospital or IVF clinic, but approval from national regulatory agencies is not required.[83]But it is also limited from the 14-day rule. China remains one of the countries with "the most unrestrictive regulatory regimes on stem cell research" [84] but with a turn in 2011 towards tighter regulation of stem cell research.

The Chinese law doesnot provide a clear definition for embryo.[85]However, in the Chinese tradition there are ethical values that determine to some extent the view of the embryo's status and possibly influence the spirit that governs the national regulation framework.[86] According to the Confucian view,[87]a person's life begins at birth, sinceonly then does the being acquire the characteristics that identify it as a person: body, psyche, and the capacity for learning and innovating.[88] As Tsai put it, "[t]he moral obligations we have for (rational, conscious) persons is clearer and stronger than those we have for human embryos".[89]In contrast to Western perspectives, the embryo in China holds a less significant legal and ethical status than the born human being. The recognition of birth as the beginning of legal personhood is common to several Western countries. Nonetheless, other jurisdictions

[81]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf See also,

Ministry of Health and Ministry of Science and Technology, 2003, Ministry of Health and Ministry of Science and Technology Ethical Guidelines for Human Embryonic Stem Cell Research, No. 460, (2003).

[82]Yao-Jin Peng, Xiaoru Huang, Qi Zhou (2020), Ethical and Policy Considerations for Human Embryo and Stem Cell Research in China, *Cell Stem Cell,* Volume 27, Issue 4, pp. 511-514.

[83] Saleem, Hafiz, Saleem, Rehman, Khaskheli, Muhammad, Bibi, Sughra 2019/02/01, Legal framework for gene editing in human genome "World's First Mutant twins by China"

[84]Law Library of Congress (2012 Global Legal Research Center LL File No. 2012-008118), p.30.

[85]Jiang, L; Rosemann, A (2018), Human Embryo Gene Editing in China: The Uncertain Legal Status of the Embryo, *BioSocieties*

[86]Tsai, D. F. C. (2005). Human embryonic stem cell research debates: A Confucian argument. *Journal of Medical Ethics*, *31*(11), 635. See also Yu, E., & Fan, R. (2007). A Confucian View of Personhood and Bioethics. Journal of Bioethical Inquiry. 4(3), 171.

[87]Ibid.

[88]Ibid

[89]Ibid

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recognize legal and ethical value to embryos and foetuses, whereas in China this is not the case.[90]

11.2.7 Japan

According to the ***International Compilation of Human Research Standards*** 2020[91], in September 2001, the Japanese government issued its Guidelines for Derivation and Utilization of Human Embryonic Stem Cells,[92] which outline the regulations that the Ministry of Education, Culture, Sports, Science, and Technology is responsible for implementing and enforcing. A number of these regulations were relaxed in 2009 by the Council for Science and Technology Policy, a cabinet office chaired by the prime minister and composed of cabinet members, academics, and industrial leaders, following recommendations from its subcommittee, the Expert Panel of Bioethics.[93]

Under the revised Guidelines, ES cells can be derived only from "spare" IVF embryos, and only if the embryos are younger than 14 days (not counting time spent frozen), were donated with informed consent, and were donated without financial compensation beyond "necessary costs."[94] The guidelines ban reproductive cloning, but research-oriented SCNT is permitted, although regulatory delays in the approval process have retarded the development of human SCNT research.

Japan limits also human embryo research to the 14 days rule and this arise from the legal definition of embryo from the Act on Regulation of Human Cloning Techniques (2000) 146 (2000).[95]According to this Act, an ''embryo is a cell or a cell group which has the potential potential to grow into an individual through the process of development in utero of a human or an animal and remains at a stage prior to placental formation''.[96] In addition, one is considered a human only after he/she is born, even though human life may have started at the moment of

[90]Raposo, V. L., & Ma, Z. (2019). An ethical evaluation of the legal status of foetuses and embryos under Chinese law. *Developing World Bioethics.*

[91]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf,Japan, p. 128.

[92]MEXT, Guidelines for the Derivation and Utilization of Human Embryonic Stem Cells, enacted September 252001, http://www.lifescience.mext.go.jp/files/pdf/32_90.pdf [English].

[93]https://www.thenewatlantis.com/publications/appendix-e-overview-of-international-human-embryonic-stem-cell-laws

[94]Japan, MEXT, *Guidelines on the Derivation and Distribution of Human Embryonic Stem Cells, Public Notice of MEXT, No. 86 of May 20, 2010, art. 6, 1, i, http://www.lifescience.mext.go.jp/files/pdf/n743_00.pdf, tentative translation; ibid., art. 6, 1, iv; ibid., art. 6, 1, ii; ibid., art. 4.*

[95]www.cas.go.jp/jp/seisaku/hourei/data/htc.pdf

[96]Japan, Ministry of Education, Culture, Sports, Science and Technology (MEXT), *Guidelines for the Derivation and Utilization of Human Embryonic Stem Cells* (*Hito-ES saibou no jyuritsuoyobisiyounikansurusisin*), enacted September 25 2001, http://www.lifescience.mext.go.jp/files/pdf/32_88.pdf [Japanese], http://www.lifescience.mext.go.jp/files/pdf/32_90.pdf [English].

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fertilization. Still, the laws admit that fertilized embryos, or human embryos, must be respected as human life.[97]

Japan's germline gene editing regulations are looser than in most of the world, but still restricted. Guidelines issued in 2018 allow for gene editing of human embryos for research to treat genetic diseases. The guidelines restrict germline gene editing for reproductive purposes and clinical testing but violations are not punishable by law. The guidelines also do not regulate doctors at private hospitals who might use gene editing for treatment; they only regulate researchers.[98]

11.2.8 Australia

Various aspects of research involving stem cells are subject to *Commonwealth of Australia (2002a) The Prohibition of Human Cloning Act (Federal Parliament of Australia, Canberra)* and territory legislation, guidelines and standards issued by the *Australian Health Ethics Committee (AHEC),* which is a Principal Committee of the National Health and Medical Research Council (NHMRC).[99]However, Australia does not currently have a comprehensive legislative scheme, or set of guidelines, regulating all research involving human embryonic cells, whether conducted by publicly funded institutions or private entities. In December 2002, the Australian Parliament passed two Acts providing a regulatory framework to prohibit certain practices including human cloning, and to regulate uses of human embryos created through assisted reproductive technology. These *Acts* set the 14 day limit[100] and establish a regulatory framework to prohibit certain practices including human cloningand to regulate uses of human embryos, including excess embryos, created through assisted reproductive technology and embryos created through processes other than fertilisation. The national legislation states that any cloning technique (reproductive or therapeutic) resulting in a human embryo or chimera of any kind in Australia carries a penalty of 15 years imprisonment (Commonwealth of Australia, 2002a, p. 7).[101]

However, after 4 years, in December 2006, this same legislation was amended, reversing the prohibition on therapeutic cloning, while retaining the ban on reproductive cloning.

[97]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf See also, S. Machino (2013), Bioethics in Japan and iPS Cells, JMAJ 56(6): 448–457

[98]David Cyranoski (2018), Japan set to allow gene editing in human embryos. Draft guidelines permit gene-editing tools for research into early human development.https://www.nature.com/articles/d41586-018-06847-7

[99]https://www.alrc.gov.au/publication/genes-and-ingenuity-gene-patenting-and-human-health-alrc-report-99/15-stem-cell-technologies/stem-cell-research-in-australia/

[100]https://www.legislation.gov.au/Details/C2016C00968

[101]Commonwealth of Australia (2002a) The Prohibition of Human Cloning Act (Federal Parliament of Australia, Canberra).

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Under the same Act, [102]gene editing is prohibited, although it is possible for research purposes. The legal definition of human embryo in Australiacontains the following: human embryo means a discrete entity that has arisen from either: (a) the first mitotic division when fertilisation of a human oocyte by a human sperm is complete; or (b) any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears; and has not yet reached 8 weeks of development sincethe first mitotic division.[103] The Australian legislation defines embryos in purely biological terms. This strictly biological definition may influence communities to view embryos as biological cells and ultimately influence acceptance of the use of embryos in research. A survey on perceptions of embryo status and embryo uses in an Australian community, showed that the majority of Australians preferred thoseembryos be used (either for research or reproduction) rather than be discarded.[104]

The table below summarizes the differences and similarities between the countries' regulatory frameworks and at the same time provides information on the policies adopted by countries regarding hESC research, cloning and gene editing. The way that the table is structured reflects the way in which the respective regulatory frameworks emerge. Thus, in the first column the question of the definition of the embryo is raised. The way that the embryo is legally defined reflects the values of each culture regarding human life and the answer to the question of when life begins. The assimilation of these values in the definition of the human embryo is directly related to whether research is permitted and to what extent or if it is prohibited.

[102]https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdfhttps://www.legislation.gov.au/Details/C2016C00968

[103]Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act (2006) 172 (2006). www.legislation.gov.au/Details/C2006A00172& Research Involving Human Embryos Act (2002, amended 2016) 145 (2002). www.legislation.gov.au/Latest/C2016C009

[104] De Lacey, S., Rogers, W., Braunack-Mayer, A., Avery, J., Smith, D., & Richards, B. (2012). Perceptions of embryo status and embryo use in an Australian community. Reproductive BioMedicine Online, 24(7), 727–744. https://doi.org/10.1016/j.rbmo.2012.01.014

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Countries	Status of embryo	14 days limit	ESC research	Cloning (SCNT)	Gene editing	Regulated by**
Austria	NA	NA	Prohibited	Prohibited	Prohibited	L
Germany	Embryo is any totipotent cell which, if the necessary conditions are met, is able to divide and develop into an individual	NA	Prohibited	Prohibited	Prohibited	L
France	NA	NA	Permitted	Prohibited	Prohibited	L
Italy	NA	NA	Prohibited	Prohibited	Prohibited	L
Spain	Embryo is the stage of embryonic development from the moment the fertilized oocyte is implanted in the uterus until the onset of organogenesis, which ends at 56 days post fertilization. Pre-embryo is an in vitro embryo from the fertilization of the oocyte through 14 days post fertilization	Adopted	Permitted	Prohibited	Prohibited	L
Sweden	NA	Adopted	Permitted	Permitted	Permitted	L
	Status of embryo	**14 days limit**	**ESC research**	**Cloning (SCNT)**	**Gene editing**	**Regulated by****

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The Netherlands	cell or a set of cells with the capacity to grow into a human	Adopted	Permitted	Prohibited	Prohibited	L
Belgium	the cell or the organic set of cells capable, as they develop, of becoming a human being	Adopted	Permitted	Prohibited	Prohibited	L
United Kingdom (UK)	Embryo means a live human embryo and does not include human admixed embryo (as defined by section 4A[6]), and references to the embryo include an egg that is in the process of fertilization or is undergoing any other process capable of resulting in an embryo	Adopted	Permitted	Permitted	Permitted	L
Russia	The Law establishes the inadmissibility of creating a human embryo for the production of	NA	Prohibited	Prohibited	Prohibited	L
Countries	**Status of embryo**	**14 days limit**	**ESC research**	**Cloning (SCNT)**	**Gene editing**	**Regulated by****

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Russia	biomedical cell products; the inadmissibility of using biological material obtained by suspension or interruption of the development of a human embryo or fetus for the development, production and use of biomedical cell products	NA	Prohibited	Prohibited	Prohibited	L
Israel	NA	Adopted	Permitted	Prohibited	Prohibited	L,G
United States of America (USA)	the term'human embryo or embryos' includes any organism that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes (sperm or egg) or human diploid cells (cells that have two sets of chromosomes, e.g., somatic cells)	Adopted *	Permitted(No federal funding)	Prohibited	Prohibited	L, G
China	NA	Adopted	Permitted	Prohibited	Permitted	L
Countries	**Status of embryo**	**14days limit**	**ESC research**	**Cloning (SCNT)**	**Gene editing**	**Regulated by****

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Japan	embryo is a cell or a cell group which has the potential to grow into an individual through the process of development in utero of a human or an animal and remains at a stage prior to placental formation	Adopted	Permitted	Permitted	Permitted	L
Australia	human embryo means a discrete entity that has arisen from either: (a) the first mitotic division when fertilisation of a human oocyte by a human sperm is complete; or (b) any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears; and has not yet reached 8 weeks of development since the first mitotic division.	Adopted	Permitted	Permitted	Permitted	L

*The US 14-day limit is not a federal policy or guideline, but was developed by a nongovernmental organization, the National Academies of Sciences, Engineering and Medicine

**Regulated by L(Law) and/or G(Guidelines)

11.3 Comparative analysis

According to the previous analysis there are a number of differences in national legislationspertainingto stem cell research and relevant technologies. Differences are due to the various traditions, history and policies of each country but also because of different cultures

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that accept or not a specific level of health innovation and its related technologies. Human life and human dignity are inviolable rights worldwide associated and grated to human subjects even to the unborn.Thus, human life and rights associated with it are respected from the very first instance that human life appears. The answer to the dilemma between limiting the use of embryos for research or medical purposes in accordance with the principles of human dignity and respect for human life, and, on the other hand, supporting scientific research to promote the health of those who are ill and the welfare of infertile couples, shapes the regulatory framework of counties. The priorities of countries lead them to adopt a liberal, restrictive or intermediate regulatory framework.

Basic research on human embryos is prohibited in four countries: Austria, Germany, Italy, and Russia. These countries have prohibitions regarding the use of embryos for non-reproductive or medical purposes. Austria's *Reproductive Medicine Act* prohibits using cells capable of development for purposes other than medically assisted procreation. Germany's *Embryo Protection Act* banns the creation of embryos (embryos created for IVF but stored and not used) and embryos created for non-reproductive purposes (e.g., for research), eliminating all potential embryo sources for research. In Italy, the Law 40/2004 state that 'any experimentation on a human embryo is prohibited'.[105]The only research allowed is for 'therapeutic and diagnostic purposes' and to protect 'the health and development of the embryo'. Russian law, *Federal Law on Biomedical Cell Products*, prohibits the use of human embryos or their products for research as they cannot be used for 'biomedical cell products'.The prohibition of basic research with ESCs excludes the potential of other types of research and technologies like cloning and gene editing.

Eight countries permit ESC and embryo research and limit it to 14 days: Australia, Belgium, China, Japan, the Netherlands, Spain, Sweden, and the UK. Arguably, the most well-known law is the UK *Human Fertilisation and Embryology Act* of 1990.[106]It permits ESC and human embryo research prior to 14 days if deemed 'necessary and desirable,' while prohibiting 'keeping or using an embryo after the appearance of the primitive streak.' [107]The *Act* allows the creation of embryos for research purposes, including through somatic cell nuclear transfer (cloning) and gene editing. Sweden's law, *Genetics Integrity Act,*[108] and Belgium's law, In vitro *Embryo Research Act,*[109] are similar to the UK's *Human Fertilisation* and *Embryology Act* and

[105]https://www.eurostemcell.org/regulation-stem-cell-research-italy

[106] Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act (2006) 172 (2006). www.legislation.gov.au/Details/C2006A00172& Research Involving Human Embryos Act (2002, amended 2016) 145 (2002). www.legislation.gov.au/Latest/C2016C009

[107] Ibid.

[108] Law on Genetic Integrity (2006, amended 2009, 2010, 2013, 2014, 2016, 2017, 2018, 2019) 351 (in English). https://www.icj.org/wp-content/uploads/2013/05/Sweden-Genetic-Integrity-Act-2006-eng.pdf

[109] https://www.hhs.gov/ohrp/sites/default/files/2020-international-compilation-of-human-research-standards.pdf

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allow for the creation of embryos for research purposes. Sweden permits "experiments for the purpose of research or treatment on fertilized eggs and eggs used for somatic cell nuclear transfer may be carried out no longer than up to and including the 14thday after fertilization or cell nuclear transfer respectively".[110]Belgium allows human embryo research to advance medical knowledge, based on latest scientific findings, and with no other alternative available. [111]Other countries have slightly more restrictive policies. Australia, Japan, the Netherlands, Spain, allow human embryo research, but only on embryos created for IVF and donated for research.[112]Australia has a 14-day limit within their laws and national guidelines. Japan's *Act on Regulation of Human Cloning Techniques* does not include a 14-day limit, but the national guidelines from the Ministry of Education, Culture, Sports, and Science have adopted this limit. China does not have a law, but instead a 14-day limit is specified within their national hESC guidelines. In Japan, the Netherlands, and Spain, the law on human embryo research contains a requirement for approval from a governmental body. For example, the Netherlands' *Embryo Act of 2002* permits research if "a positive opinion has been obtained from the central committee on the research protocol".[113] In addition, Spain's *Biomedical Research Law* prohibits creating human pre-embryos and embryos for research purposes, but it does permit SCNT. Spain's law has the only mention of a pre-embryo in the laws reviewed and refers to the stage of embryo development prior to 14 days.[114]

France and Israel belong to the countries with permissive regulatory frameworks for ESC research but they do not explicitly adopt the 14-day rule. Israel has a 1999 law banning reproductive cloning and a set of guidelines for hESC research, but it does not address or limit in vitro human embryo research.[115]French law permits the use of leftover IVF embryos for scientific research if scientifically justified.[116]

USA has an intermediatelevel of regulations. As we have mentioned in the previous section, while the USA were the first to propose the 14-day limit, the limit was never passed as a federal law. The USA prohibit federal funding for human embryo research through the *Dickey-*

[110] Law on Genetic Integrity (2006, amended 2009, 2010, 2013, 2014, 2016, 2017, 2018, 2019) 351 (in English). https://www.icj.org/wp-content/uploads/2013/05/Sweden-Genetic-Integrity-Act-2006-eng.pdf

[111]Kirstin RW Mathews& Daniel Morali (2020),ibid.

[112] Ibid.

[113]https://www.thenewatlantis.com/publications/appendix-e-overview-of-international-human-embryonic-stem-cell-laws#_ftn48. See also, van Beers, B. C., de Kluiver, C., & Maas, R. (2020). The Regulation of Human Germline Genome Modification in the Netherlands. In A. Boggio, C. Romano, & J. Almqvist (Eds.), *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies* (pp. 309-334). Cambridge University Press. https://doi.org/10.1017/9781108759083.012

[114] Law: Biomedical Research Law (2007, amended 2011) 14 (in English) (2017). https://www.isciii.es/QueHacemos/Financiacion/solicitudes/Documents/SpanishLawonBiomedicalResearchEnglish.pdf

[115]*SeferHahukim* (the Book of Laws of the state of Israel) 1697, 7 January 1999: 47; *SeferHahukim* (the Book of Laws of the state of Israel) 1934, 31 March 2004: 340; *SeferHahukim* (the Book of Laws of the state of Israel) 2212, 22 October 2009: 233; *SeferHahukim* (the Book of Laws of the state of Israel) 2553, 25 May 2016: 882.

[116]https://www.eurostemcell.org/regulation-stem-cell-research-france

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Wicker Amendment.[117]The Amendment prohibits scientists from obtaining funding for human embryo research work from the US NIH, which is one of the largest funders. Therefore,the prohibition applies only to federal funding and there are not explicit laws or guidelines related to ESC research, cloning and gene editing.

12 Expert interviews

12.1 Disclaimer

Based on the rationale, presented in Section 7, the expert interview study relevant to D3.1 and D3.2 has been informed by all 18 interviews and not as initially planned (i.e. D3.1 to be informed only by the experts working in European entities and D3.2 to be informed by experts working outside Europe). In the following section the authors present the main points of discussion derived from the 18 conducted interviews which focus on cultural differences and different research environments.

12.2 Input provided by the experts' interviews

The interviewees gave the following general description of the differences and/or similarities between research cultures, at the level of continents.

A comparison between different research cultures was possible, since a significant part of the interviewees have direct experience in working as researchers or bioethicists in different parts of the world. A common reflection is that there are differences in terms of moral compass, at the level of individual researchers, and differences in existing regulations at the organisational level of research performing organisations and with regard to national context. From the responses it is evident that there are three main categories, if someone wants to remain at the level of continents: (a) America (meaning explicitly or implicitly USA), (b) China, and (c) Europe or EU together with Australia.

In America the pressure for innovativeness to be directly connected to commercialisation (patenting, securing intellectual property rights, creating spin offs) of innovative technologies is greater than in other places in the world. In Europe and Australia, the research culture is permeated by the "*communitarian spirit*" as one bioethicist pointed out. In these two continents (Europe and Australia) research is more bound to produce positive societal than economic impact. This was quite bluntly put by a researcher in the biomedical sector: "*That's*

[117] Dickey-Wicker Amendment. (2020). www.congress.gov/bill/116th-congress/house-bill/1865/text. See also, Hurlbut JB. Experiments in Democracy: Human Embryo Research and the Politics of Bioethics. Columbia University Press, NY, USA (2017).

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not the attitude in America. They don't really care about helping people. It is not in their value set. They care about making money. It's unfortunate."

An attitude that was expressed by some of the interviewees is that it is positive to fertilise the research culture of America and China with the long-established European perspectives on the ethics of particular technologies or sciences. These researchers became more specific by pinpointing that United States and Asian countries could benefit from such a process. These researchers did not fail to mention that other perspectives should be taken into account, but they were quite adamant in insisting that "*our foundation is armed with so-called European values so, for example as you find the European Charter of Fundamental Rights, we developed really differently from what you find in the United States.*"

In other cases, the input became more nuanced, as in regard to which elements USA and European countries differ. The following excerpt is characteristic: "*The United States and the Netherlands and Europe are similar in, I think, basic liberal democratic values, but there are of course differences in accents in the United States, I think there is less of an emphasis on issues of social equality and solidarity and community and more of an emphasis on individual rights and individual person*."

In addition, differences in the research culture were highlighted at the level of regions or countries.

A bioethicist pinpointed the differences between countries of the Caribbean, which might seem as a set of homogeneous countries with regard to the approach to new technologies. Specifically, among the countries of the Caribbean, where there are 34 member states, there is a great variety with regard to their character as being secular or "*totally really just driven with its religious things*". This bioethicist mentioned that for the countries of the Caribbean with the weakest secular character it is expected that any kind of tissue, as long as it is derived from a human being, all aspects of humanity and human considerations should come to be a part of the evaluation and judgment.

Another interviewee shared the experience of drafting legislation for South Africa on the use of indigenous knowledge. In that case, where cultural perceptions had to be taken into account in defining concepts like a community or a donor, the interviewee explained that it was a challenging work; "*it is the least trivial thing I've ever had to do*" according to her/his words.

Within Europe the situation can get quite complicated. Despite the fact that the EU has a traditionally strong secular character, there was a need for a political compromise with regard to the production of embryonic stem cells primarily because of objections from the Catholic Church: the production of embryonic stem cells cannot be funded through EU. However, the use of embryonic stem cells can be funded. As a bioethicist explained: "*I call it a political*

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compromise. So, you can use stem cells derived from tissues, let's say blood stem cells, to create whatever you want to from human tissue." In addition, despite that fact that the EC is able to apply a certain extent of harmonization to such rules across its Member States, the situation also within the EU is variable.

For example, there are countries, like Germany, where any kind of experimentation with embryonic stem cells is forbidden. Such differences will be reflected also in the field of organoid research, since embryonic stem cells are the point, albeit not the only one, of derivation from which organoids are created. There are cases, where practices with some analogy to "ethics dumping"[118] could occur also within Europe. For example, in Britain a researcher could get national funding to create stem cells and then use them with European funding. By contrast, in Germany a researcher is allowed to use certain pre-defined embryonic stem cell lines, which were identified at a particular point in time and no new ones.There are cases, where the source of funding determines the content of the research. Without having to conduct "ethics dumping" a researcher can alternate her/his funder, in order to facilitate research that would have been deemed to be characterized as unethical otherwise.

According to an interviewee, with strong background in bioethics from the viewpoint of the Catholic Church, described that there are cases where scientific research inthe biomedical sector can be legitimized on the grounds of philosophical-religious traditions. This bioethicist described that there are two ways with which the research community can seek guidance: (a) one way is to have clear rules, e.g. how much time an embryo can be preserved outside a human womb for research purposes (i.e. the 14-day restriction); (b) another way is to apply philosophical arguments; as described by the interviewee: "*to go back to Aristotelian and Thomasian understanding of when pregnancy begins thus allowing the 14-day rule to proceed for a section of the American Catholic tradition; Thomas Shannon for one has written publicly and extensively on this and that allowed a compromise to go forward so human embryo research could proceed in the United States*."

A researcher in biomedical research, with strong background in bioethics, described that the research culture in Australia follows, in a sense, isolationalism. Specifically, it was mentioned that Australian research has fallen relatively behind on issues of benchmarking: "*So, sometimes they do things that have already been done* (...) *instead of looking to the experts in other places and seeing mistakes* (...) *this is a best practice, it's fascinating culturally*."

Finally, a categorization between national research environments could be made by studying whether there are single or multiple laws for specific issues that can have effect in biomedical research. According to a biomedical researcher, there is heterogeneity in the way

[118]Ethics dumping is a concept in research ethics that describes the export of unethical research practices from higher-income to lower-income settings.

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different countries apply their policy on animal welfare. In some countries, like China, there is no single law addressing animal protection, while other countries, like the UK, the EU, and Japan, have a single comprehensive framework. This can affect the arsenal of argumentation – in a specific country – in favor of organoid research, since one of the possible impacts of organoid research is the reductionof the use of animals in experiments.

In addition to geographical differences in research cultures, special reference was given to the religious context within which countries and researchers do their research.

An interviewee, historian of science and bioethicist, explained that "*when you talk about science you start talking about peoples' values. Very infrequently people talk about duties and responsibilities. They say I value life, I value good health and culturally this may be quite different*." Especially in countries where religion has a prominent place in society, issues like abortion, cloning, or the status of cells that have just been fertilized are deeply connected withnotions that were described as follows: "*And so religious society will want, once any aspect of human cells is associated with an entity, that the same moral respects should be accorded to such an entity as it would to a human being*." In contrast, more secular societies are expected to adopt a different approach that was described as "*more scientific*", meaning that an aggregate of cells that has not yet developed any humanoid features will not be considered to have the same moral status as a human being.

This discussion was made in the context on how organoid and organoid-related research can be communicated to societies with different sets of values. The interviewee was explicit in what was meant: "*But the issue is that you cannot have one communication platform that will address all cultural and philosophical meanings all around the world. It has to be tailored to the particular jurisdiction and the particular communities, which you wish to speak to at the time. How you tailor up your communication to suit for full understanding as well as if not full acceptance?*" The example of Africa was used to highlight the ways that societies "*were there are many cultures, cultural aspects with magical, religious beliefs*" perceive scientific advancements. Such considerations, according to the interviewee, must be connected to the frameworks that provide ethics guidance, in the sense that a comprehensive framework needs to have these types of input that is different in different parts of the world.

This religious perspective was pointed out by another bioethicist, in the European context: "*The human fertilized egg is considered by many, particularly from the Catholic Church, to be a fully-fledged human agent being. So, an organoid developed from a single cell, which is derived from a human particularly if it is embryonic, may have ethical implications in some traditions*." So, according to the same interviewee, a religious individual in many European countries, would consider the moral status of a single fertilized cell as that to a fully grown embryo. Britain and

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France (with less certainty) were presented as examples that the above approach would be weaker, with respect to other countries, where religion has still strong roots. This observation, according to the interviewee, is connected to the fact that Britain is about to relax the 14-day rule.

However, the criteria for deciding whether an entity is a human or an experimental block of cells still elude us. Again, in this instance the connection between the wider societal values, posed by religion, and specific decisions on how research is performed is quite straightforward: If someone comes from the "*British type of tradition which says it's a block of cells and if I say it's a block of cells then my concern is purely the scientific one. If I was in Italy, probably I would not be able to consider it's a block of cells and therefore the way I handle the cells, dispose of the cells, and so on, would have to be regulated if I was allowed to do any research with them*." This heterogeneity of approaches, according to the interviewee, is even more complex in USA. The authors would argue that this response is based on the fact that in USA there exist a plethora of religions and/or various interpretations of dogmas, more than in any place in the world. This could create more variable, more ambiguous/conflicting, and stronger societal pressures on the way research should be regulated.

Another bioethicist provided the following response, with regard to the moral status that an embryoid body will be given in the British context: "*we regard these embryos as human embryos with human capacities and so we handle them and treat them in a certain way, as if they could become human beings. And that's a very fruitful way of thinking about this, I think, because we don't know if these embryoid bodies could ever be actual beings*." What follows in the interviewer's response is that the default civic position might be to give the strongest possible moral status to embryoid bodies; they should be treated like human embryos "*because they look just like human embryos and they begin to organise just like human embryos and they just might be capable of some kind of sentience which is the dividing line*."

According to another bioethicist who touched upon, what hecalled "the peculiarities of Jewish thought" it is unclear whether an embryoid body has any moral status whatsoever. The interviewee expressed his view as follows: *"(An embryoid) might be 'like water', which is the rabbinic understanding of what the embryo at this stage of development was and therefore have no moral status and it is entirely regarded as property, technically property of the man, or a part of the body of a woman*." So, this approach is clearly different from that of the Catholic Church.

Finally, according to an expert in biomedical research an embryoid poses as a completely new type of entity, "*a genuinely new category*" that "*needs some genuinely new thinking and probably some genuinely new norms about it*". According to the same researcher, European values on justice and social solidarity are very important to inform the discussions on the moral

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status of an embryoid. In addition, the interviewee raises its concerns, since "*Americans' unfortunate tendency to veer towards personal liberty and autonomy skews many discussions in bioethics. 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*." In general, the researcher's view is that, in order to have an informed discussion of embryoids as many as possible cultural narratives must be taken into account.

Two interviewees brought to the discussion the Jewish tradition that is called the protection of life. According to one of the interviewees, the foundational concept of the Jewish tradition is that you can do anything to protect life. "*In the traditional discussion, if you have two people or three people in the desert and you have enough water for one, do you share it and both die or does one drink it and that one survives while the other dies? And if that is the second one, then who should survive? The answer is, in Jewish tradition, one drinks it, one dies, not both*." According to this, the production of organoids as long as it aims at preserving life or for therapeutic reasons "*is absolutely required, not even possible, it's much higher than that, it's required*." Consequently, to facilitate organoid research for therapeutic aims is a matter of duty.

Special (more nuanced) points

In addition to country-specific rules on biomedical research, there exist rules that pertain to the function of specific cell banks that were characterized by one interviewee as "*very curious*". In this instance, an example was provided, where a German lab was using stem cells obtained from a Danish cell bank, despite the fact that these cells could not be used outside Denmark. As put by the interviewee: "*The German scientists were breaking the law in using these [cells] because they shouldn't have them, as they could only be used in Denmark*." This is an issue that was touched upon when the interviewee was describing the lack of harmonization in rules/guidelines within the EU; but in this instance the issue is raised by a specific cell bank, i.e., what are the implications of such a breach on the use of a product that was based on these "smuggled" stem cells? In which countries can they then be used? Additional questions were raised by the interviewee: "*If that makes sense, if I get them in Denmark, do something with them in Denmark, can I then take them to France?*"

Another interesting point was made by a principal investigator in organoid-related research. The interviewee mentioned that there are specific preconceptions on the way that ethics appraisal is performed in China. As mentioned, a usual response from a European researcher, with regard to the pressures the members of a research ethics committee in China face, would be: "*But my lab's sort of intuitive feeling was like, 'yeah, but you know in China, you don't go against the Party and probably the people that had to give approval were just afraid to*

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go against a big-name researcher.'" However, as the interviewee described, they were lucky since some members of the laboratory had lived and worked in that environment and shared their critical thinking about the situation in China. These researchers were able to provide a perspective of whichEuropean researchers could not have any kind of knowledge.

What came out of this interaction was that the above mentioned "*intuitive feeling*" may be partly mistaken, since "*people that are doing ethics approvals in China are not necessarily experts in their field*." By no means has such an interpretation alleviated the responsibility of doing unethical research in China or elsewhere. What it does achieve, however, is that it pinpoints the source of the problem and provides a more truthful picture of the working ethos of Chinese researchers or of the research policy in China: the issue "*lies much deeper than just bullying into signing an approval form. It's actually sort of at the educational level, where things already go wrong*." What could be said is that China and Europe face similar issues, i.e., the lack of the appropriate expertise of the members of research ethics committees, but is seems that these issues are more serious or prevalent in China. The interviewee described this kind of knowledge in the following way: "*And so it was very useful, I found, to have a discussion like that and have a bit more nuanced insight into how things go. 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*."

13 Concluding remarks

According to the previous comparative analysis based on relevant resources, it accrues that there are differences in national legislatures, in relation to stem cell research and relevant technologies.Furthermore, we can identify differences in national understandings of what it means to protect life and citizenship.[119] All these differences are due to the various traditions, history and policies of each country but also because of different cultures that accept or not a

[119]See Jasanoff Sh. And Metzler I., Borderlands of Life: IVF Embryos and the Law in the United States, United Kingdom, and Germany, Science, Technology, & Human Values 2020, Vol. 45(6) 1001-1037, doi: 10.1177/0162243917753990, and Hurlbut J.B., Metzler I., Marelli L., and Jasanoff Sh., Bioconstitutional Imaginaries and the Comparative Politics of Genetic Self-knowledge, Science, Technology, & Human Values 2020, Vol. 45(6) 1087-1118, doi: 10.1177/0162243920921246.

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specific level of health innovation and its related technologies. Human life and human dignity are inviolable rights worldwide associated and grated to human subjects even to the unborn.Thus, in most cases, human life and rights associated with it are respected from the very first instance that human life appears. Some countries seem to weigh the risks of stem cell research against the potential benefit this research may generate and set specific grounds on when such research is allowed. Several debates within countries themselves exist with Constitutional disagreements and interpretations fueling the debates and controversies borne by the already controversial character of stem cell research.The comparison reveals distinct bioconstitutional foundations that give rise to systematicallydifferent understandings of each state's responsibilities toward human life and hence its particular treatment of claims on behalf of embryonic lives.

In the EU,stem cell research and research on embryos are regulated by law, although there are several differences among member states in their national legislations. Some countries adopt a very restrictiveline prohibiting any kind of stem cell research or research on embryos while some others provide specific preconditions for stem cell research. It appears that there are less strict regulations in countries following the common law tradition(UK, USA, Australia) as in these countries judicial decisions play a significant role in the regulatory framework. We also understand that there are even less restrictions in countries like Japan and China due to several reasons mentioned before.

International conventions and normativeinstruments that are ratified by countries play a crucial role in regulating health innovations and sensitive legal issues that surface because of them and somehow provide a basic protective framework for rights that are not weighted or questioned. Developing regulations at an international level is very important as it would provide a safe and commonly agreed ground for ethical research. As sensitive legal issues arise some scholars invite for more nuanced legal interpretations of basic notions such as the notion of "legal personhood" in the light of the recent developments in the life sciences. There is much debate surrounding these developments with opposing views that challenge legal thinking and established categories. These debates are likely to continue and puzzle scholars struggling to provide answers to demanding questions.

Respect for cultural diversity in bioethics and the transition from the local to the global perspective seems to be at issue in the case of organoid research. Cultural models ofhealth, illness, and moral reasoning are receiving increasing attention in bioethics scholarship. "The concept of culture can serve as a heuristic device at various levels of analysis. In addition to considering how participation in particular ethnic groups and religious traditions can shape moral reasoning, bioethicists need to consider processes of socialization into professional cultures, organizational cultures, national civic culture, and transnational culture. […]From the

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local world of the community clinic or oncology unit to the transnational workings of human rights agencies, attentiveness to the concept of culture can illuminate how patients, family members, and health care providers interpret illness, healing, and moral obligations."[120]

These complex matters relate, also, toorganoid research, and are set, further, in light of the conceptual framework of responsible researchand innovation, including an element of ethical research practices in the scientific experiments, within a globalised research environment that calls for cooperation and a level of agreement in values and goals of the research enterprise.

[120]Leigh Turner (2005) From the Local to the Global: Bioethics and the Concept of Culture, Journal of Medicine and Philosophy, 30:3, p. 305, DOI: 10.1080/03605310590960193. See, also, Chattopadhyay S. and De Vries R., Respect for cultural diversity in bioethics is an ethical imperative, Med Health Care Philos. 2013 November; 16(4): doi:10.1007/s11019-012-9433-5.

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Part 4: ANNEXES

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14 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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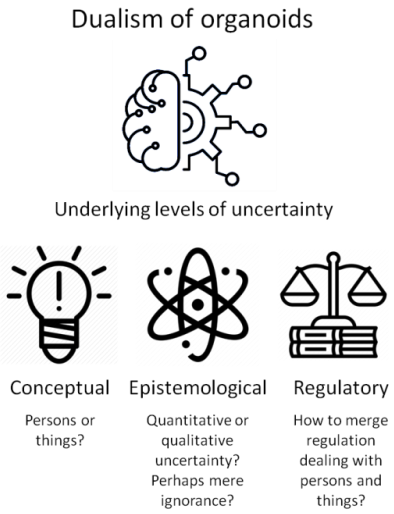
Together with the invitation, a one-page letter of information was also sent to the potential interviewee as an attachment.

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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15 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 RegulationThe ethical approval of the interview study in work package 3has been obtained from theResearch 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, anonymiseddata, 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

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minimum. This means that as soon as the interview has finished the audio recordings will be saved at 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:

[Intervieweename][Interviewer name]

Day/month/year

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16 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?

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

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 or research integrity issues. We need input on	**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?** Comments: If 'not' why? If 'yes' why?Thesewill	**3. What are the major challenges that legislation needs to address in relation to organoid research?** Comments: We have to leave room for the relevant technologies, if we know beforehand

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.	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.	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? Comments: Input on current, upcoming or	**5. What kind of help/advice/knowledge sources do you think a Bioethicist/Research Ethics Committee member needs when assessing projects related to organoid**	**6. How adequate is the information to patients/donors of tissue in current consent procedures? How could it eventually be improved?**

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needed Codes of conduct, SOPs, guidelines, advisory bodies, RECs. What is already there and what is missing?	**research?** Comments: Input on current, upcoming or needed Codes of conduct, SOPs, guidelines.	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 "everydaylanguage" supposedly to be	**7. How do you usually translate philosophical terminology or the core of ethical debates related to organoids or similar technologies**	*This cell was left intentionally blank*

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understandable by non-experts? Comments: Input on how to avoid unfounded hypedor doomsday scenarios(e.g. “mini brains”), when communicating with policy makers orwith lay people. Clarifywhat 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.	**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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17 Annex 4: Ethics approval

NTUA, as leader of WP3, obtained ethical 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 requested filled form was supplemented with the documents presented in Annexes 1 and 2. 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. For this reasonthe authors of this report translatedthe document in the English 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.

Translation of the original document of ethical approval in English:

DECISION

RESEARCH ETHICS AND DEONTOLOGY COMMITTEE (R.E.D.C.)
OF THE NATIONAL TECHNICAL UNIVERSITY OF ATHENS

FOR
APPROVAL
OF RESEARCH PROTOCOL

Title of study for which approval was requested
HYBRIDA «Embedding a comprehensive ethical dimension to organoid-based research and resulting technologies» **codenumber 63/2369**
Principal Investigator of the study
Konstantinos Charitidis (NTUA professor)
Type of suggested study
20 in-person interviews with scientists, 10 with scientists working in European Union (EU) Member States and 10 with scientists working in non-European countries (USA, Israel, China, Japan, Australia)
REDC protocol number
1405/07.01.2021
Number and date of decision of the Research Ethics and Deontology Committee (R.E.D.C.)
Session 14.01.2021, Discussion point 1.2
Decision of the Research Ethics and Deontology Committee
Approved
Comments from the Research Ethics and Ethics Committee (R.E.D.C.) on the basis of which the decision was made on the submitted application
Studying the research protocol and all relevant supporting documents / additional approvals, as submitted to the Research Ethics and Deontology Committee(R.E.D.C.),

and

taking into account the aims and expected benefits, the research methodology, the lack of conflict of interest of the researchers and the lack of potential risks to the research subjects,

the R.E.D.C.

ascertains and unanimously approves the submitted application (article 23 par. 1 law 4521)

This decision of R.E.D.C. in no case replaces the required by another competent public service, administrative body or independent administrative authority, approval or licensing of this research project / study which may additionally be required by law.

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18 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:Codesandlegislation	PRINTEGER	D3.1
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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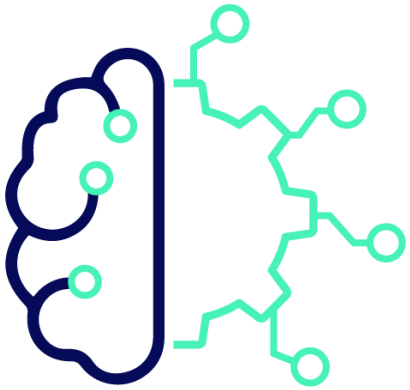

HYBRIDA

CONSORTIUM MEMBERS