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D 6.1: Regulating organoid and organoid-related activities: An analysis of the regulatory gaps and areas of over-regulation

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

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ABSTRACT:	This deliverable integrates the two maps produced in WP2 (of the organoid and organ-on-a-chip research and patent landscapes) and WP3 (of the regulatory landscape). The result is a multi-dimensional "Super Map," showing which organoid and organoid-related activities are regulated in which ways and by what agencies/actors. On the basis of the Super Map, this report identifies and details areas of activity that are currently unregulated or under-regulated ("gaps") as well as areas of activity that are over-regulated.
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WP6 Partners:

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2.	Partner	Institut National de la Santé et de la Recherche Médicale	INSERM	France
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1 Overview of the HYBRIDA project

The HYBRIDA project is a 3-year project, funded by the Horizon2020 framework programme. The main aim is to build a comprehensive ethical dimension for organoid-based research and related technologies[1].

An organoid is a self-organised cluster of cells generated *in vitro* from different kinds of stem cells (either pluripotent or derived from some types of adult tissue) through the use of 3D tissue culturing methods. By using organ-specific cell types, such entities might serve as "three-dimensional culture models" mimicking the structural and, especially, the functional properties of different organs from both humans and non-humans, such as the retina, heart, brain, intestine, kidney, pancreas, liver, inner ear and skin.

From Roman times, all entities have been categorized and regulated either as persons or as things (subjects or objects). However, organoids are entities – and organoid research and organoid-related technologies are examples of disruptive research and innovation – that challenge this conceptual, epistemological and regulatory dualism. More precisely, the dualistic normative framework pertaining to health and life science research is disrupted by three different kinds of uncertainty (***Figure 1***).

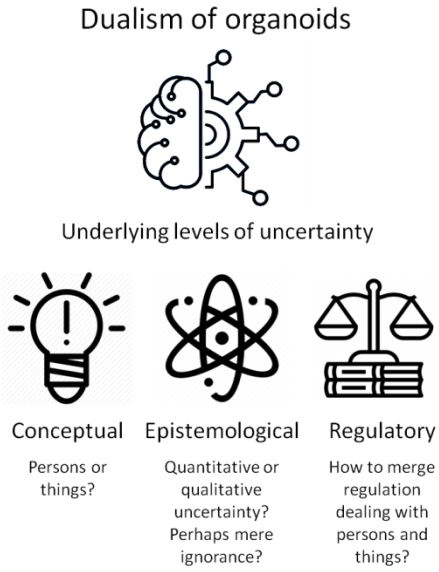

Figure 1. Levels of uncertainty stemming from the dual nature of organoids.

First, ***conceptual uncertainty* (*ontological uncertainty*)**: How should one conceive of 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

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

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is too low for randomized controlled trials or other statistically based experiments. As precision medicine and related new technologies emerge, evidence-based medicine is challenged to find new footing. Epistemological uncertainty comes in two kinds, which can be categorized as i) qualitative, or strict, uncertainty and, ii) ignorance or non-knowledge. Qualitative, or strict, uncertainty is a form of uncertainty where possible positive and negative outcomes can be identified in advance but, contrary to risk assessments, the statistical magnitude of each possible outcome cannot be estimated. By contrast, ignorance or non-knowledge represents forms of uncertainty where neither possible outcomes nor the statistical magnitude of each can be identified in advance. 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 is addressing 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.

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2 Executive Summary

WP6's aim is to contribute to existing ethical and normative frameworks involving organoid research, organoid-related research (including research involving organs-on-chips), and the clinical applications of organoids and organoid-related technologies. Since August 2021, WP6 has sought to identify gaps in existing regulatory frameworks as well as identify those instances where current frameworks lead to over-regulation of organoid and organoid-related activities.[2]

In this report, a "regulatory gap" is said to exist if organoid or organoid-related activities give rise to a practical or normative (i.e., moral or legal) consideration, question, or problem of regulatory significance that is not satisfactorily covered, addressed, answered, or overcome by existing legal instruments or legally binding definitions. Alternatively, a regulatory gap is identified if lawmakers or their representatives have decided not to deal with the potential regulatory issue in question by way of legal instruments or definitions but have not made their decision and reasons public.

An area has been identified as "over-regulated" if current regulations are such that there is uncertainty as to which laws apply, if applicable laws give rise to conflicting legal requirements, if there is a lack of appropriate regulatory harmonization across EU Member States, if regulatory requirements and standards have been recognized by the European Commission or Commission-associated groups as presenting genuine barriers to research or innovation, and/or if expert consensus is that current legally binding regulations are too restrictive.

The regulatory gaps and areas of over-regulation, as they pertain to organoid and organoid-related activities, were identified through four tasks:

1. An integration of the mapping of organoid and organ-on-a-chip research and patent landscapes produced by WP2 and the mapping of regulatory frameworks produced by WP3. The resulting multi-dimensional "Super Map" (see Appendix 1) shows how and in what ways organoid and organoid-related activities are regulated both internationally and by the European Union (EU) / European Commission (EC).
2. A "snowballing" exercise to identify pertinent regulations not captured by WP3 in its mapping exercise, including full reviews of all current Council of Europe conventions and protocols and current EU/EC regulations and directives.
3. A close reading of all regulations captured through WP3's mapping exercise and WP6's snowballing and review exercise using standard legal methods of regulatory interpretation.

[2] In this report, when we refer to "organoid activities", this should be taken to include, unless specified, organoid derivation, organoid research, organoid-based technologies, and (potential or planned) clinical translations of organoid research. When we refer to "organoid-related activities", this notably includes organ-on-a-chip derivation, research, and any potential clinical applications.

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4. A stakeholder engagement workshop organized by WP4 in Copenhagen in June 2022, during which WP6 collected the views of relevant stakeholders as they relate to the regulation of organoid and organoid-related activities. The results from the earlier 'mini-publics' conducted by WP4 were also taken into account when appropriate.

Each regulatory gap or area of over-regulation is assigned to one of three of the following main categories:

1. Informed consent, data protection, donor rights, and user rights within the context of organoids[3]
2. Open Science (OS), including the issue of benefit sharing within the context of organoids
3. Organoid research and use as a social/institutional practice, including organoid use in healthcare

For a summary of the regulatory issues, gaps, and areas of over-regulation, see Table 1.

In terms of Informed consent, data protection, donor rights, and user rights within the context of organoids, we found that:

- EU/EC regulations regarding standards of informed consent do not explicitly include (organoid or organoid-related) research that uses human tissue and cells. This has led to national differences in the formal legal requirements for the research use of human tissue, cells, and associated data.
- Genuine informed consent for the depositing and use of human biomaterials is often difficult (if not impossible) to obtain owing to unknown future organoid and organoid-related research uses and risks. This issue could be addressed by requiring blanket consent for all possible uses or very broad consent for all healthcare related uses**.** Alternatively, donors could be required to provide consent on a regular and ongoing basis for specific organoid and organoid-related research studies and/or organoid-based clinical applications.
- Current regulation of donated cells and cell lines operate on the assumption that deposited biomaterial and any derivatives are "objective" material (i.e., material that is no longer significantly part of the donor's body such that they have severely limited moral and legal claims over that material). However, as a matter of both principle and practice, organoids complicate the issue of what does and does not form part of the human body thereby calling into the question their categorization as purely "objective" material.[4] Thus, there is a question of whether the normative (i.e., legal and moral) status of organoids needs to be (re)considered at the regulatory level.

[3] Unless specified, when we refer to "organoids" in this report, this should be understood as including organs-on-chips.

[4] This claim can also be said to apply to all cultured human cells, including tumour cells and immortalized cell lines.

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- Given that regulators have not considered the ways in which organoids may be an exception to regulatory assumptions concerning the "objective" status of donated biomaterial, regulations guiding donor withdrawals only extend to the donated cells and tissues. It is not clear that a donor's right to withdraw consent extends to the organoids that have been derived from those cells. If the boundary between donor and organoid is or becomes blurred, then donors may have legitimate moral and legal claims over their organoids and, thus, may legitimately request withdrawal of their organoids. However, organoid researchers have raised pragmatic concerns regarding the feasibility of organoid withdrawal.

- According to the scientific literature and stakeholder consultation, there is, at this stage, no reason to believe, or evidence to suggest that the neural organoids that have been established resemble a fully functioning brain or integrated parts of the brain. Therefore, there is no reason to believe that such organoids possess sentience or will achieve a level of consciousness that warrants special ethical or legal concern. Nevertheless, as certain neural organoids mature and become more complex when combined with other organoids in complex neural assembloids,[5] regulatory questions regarding ownership, the normative status of these entities, and user's obligations to them may arise. Organoid researchers have stated that these questions would also arise for gonadal assembloids and organoid-derived human gametes.

- Organoid and organoid-related research often analyzes and therefore reveals the genetic make-up of donors. This leads to a potentially problematic interaction between the regulation of donated cells and cell lines intended for research and the regulation of information derived from the analysis of that material. Specifically, the legal instruments and provisions for the processing of personal data associated with donated biomaterial differ from those covering donation and subsequent research use of that material. In practice, this significantly complicates the exchange of organoids between research institutions. This is because organoids are governed by two sets of regulations: one set based on their characterization as donated biological materials; and another based on the personal information about the donor's genetics that they contain.

[5] Neural assembloids are organoids that combine multiple cell types or lineages (i.e., cells from different regions of the brain) in 3D culture or co-culture and connect several neural organoids modelling different brain regions.

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In terms of the implications of the regulation of organoids and organoid-related research for Open Science (OS), we found that:

- Organoid researchers have raised concerns regarding current regulatory standards and procedural rules relating to Material Transfer Agreements (MTAs).[6] The process of drafting and agreeing an MTA between two parties based in different jurisdictions (e.g., different research institutions or biobanks) is complex due to legal differences in states' domestic laws and the fact that domestic laws may or may not appeal to other international laws and regulations. This can lead to legal uncertainty as to the applicable legislative and regulatory requirements. The differences in domestic laws may also explain why institutional legal teams interpret the terms of the MTA differently and, thus, why organoid researchers have reported experiencing significant delays in executing MTAs.
- Although the European Commission (EC) has produced standard contractual clauses for data associated with material under a MTA, there are no such clauses covering the material component of the MTA. This is because the transfer of material is legislated by the domestic laws of individual Member States. However, given the value of these standard contractual clauses for those seeking to transfer Material Associated Data, organoid researchers have indicated that it would be useful to have MTA templates and standard clauses for human embryonic stem cells (hESCs),[7] induced pluripotent stem cells (iPSCs),[8] and organoids.
- Organoid researchers have concerns regarding the implications of Europe's patent laws for the patentability of iPSCs or their derivatives, organoids, and resulting applications. In Europe, hESCs and their derivatives cannot be patented if the hESC lines have been obtained by the prior destruction of human embryos. Given the definitions of a human embryo and a hESC used by the

[6] MTAs are legal contracts that set out the terms and conditions of the transfer and use of materials and/or data between the owner or provider (e.g., a specific research institution) and a recipient (i.e., a different research institution). They also set out any relevant legislative and/or regulatory requirements which the recipient and provider must comply with.

[7] Human embryonic stem cells (hESCs) are stem cells derived from early-stage, preimplantation embryos. They are pluripotent meaning that they are capable of differentiating into germ cells and any of the three primary layers of cells that form during embryonic development.

[8] Induced pluripotent stem cells (iPSCs) are stem cells that have been generated directly from cells that make up the body of an organism (i.e., somatic cells). Like hESCs, they are pluripotent, meaning that they are capable of differentiating into germ cells and any of the three primary layers of cells that form during embryonic development.

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European Court of Justice (CJEU) and the European Patent Office (EPO) in their respective judgments regarding the non-patentability of hESC lines and their derivatives, it is unclear whether technologies derived from (some) iPSCs, gastruloids,[9] blastoids,[10] and functioning gonadal organoids would fall under the non-patentability restrictions.[11]

In terms of the regulation of organoid and organoid-related research and the regulation of the clinical applications of such research, we found that:

- In principle, organoids could be used to develop Advanced Therapy Medicinal Products (ATMPs).[12] The European Medicines Agency (EMA) has recognized the concerns raised by researchers seeking to develop ATMPs, those applying for market authorization of ATMPs, and manufacturers of ATMPs regarding the significant levels of regulatory scrutiny, the burdens placed on applicants regarding clinical testing, and the problems applicants may face in demonstrating and providing evidence for how they have met regulatory standards for marketing authorization. In addition, where potential organoid-based medicinal products are concerned, the EMA acknowledges that correct characterization and categorization will prove to be particularly challenging, leading to significant regulatory uncertainty among those anticipating making an application for marketing authorization as to the type of ATMP under which their planned product falls, or, indeed, whether their planned product satisfies the regulatory requirements for an ATMP.

[9] Gastruloids are embryo-like structures cultured from pluripotent stem cells that recapitulate the early stages of development of post-implantation embryos. Unlike true embryos, gastruloids are devoid of the tissue ("primitive streak") that forms on day 15 of embryo development and which marks the point at which an embryo transforms from a one-dimensional layer of cells into a multidimensional cell structure ("gastrulation").

[10] Blastoids are stem-cell-derived embryo models that contain inner cell mass and embryonic and extra-embryonic cell types. They model the early pre-implantation stages of embryo development.

[11] Gonadal organoids are stem-cell-derived three-dimensional structures that model testicular or ovarian tissue, and, in principle, cell differentiation processes involved in gamete production.

[12] Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, cells, or tissue engineering.

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- The EU/EC regulatory landscape for medicinal products and medical devices is complex.[13] The Medical Device Coordination Group (MDCG)[14] has acknowledged that legally binding definitions, which determine whether a technology can be classed as a medical device or a medicinal product, lack sufficient clarity. In principle, this will generate significant regulatory uncertainty when new technologies do not clearly fall under these definitions or when they incorporate elements of both medicinal products and medical devices. Although the MDCG has sought to clarify these definitions, its guidance cannot be regarded either as reflecting the official position of the EC or as being legally binding.

- The International Society for Stem Cell Research's (ISSCR) updated guidelines illustrate that current expert consensus (i.e., by those who contributed to and approved the guidelines) is in tension with EU/EC regulation of in vitro embryonic research. For certain types of in vitro embryonic research, EU/EC regulations require a more rigorous approach to ethical review than those proposed by the ISSCR. In addition, whereas the ISSCR advises that the culturing of human embryos for research purposes and the derivation of new cell lines from human embryos are permissible (subject to specialized ethics review and oversight), EU/EC regulations exclude these types of research from funding eligibility.

- A prohibition on the funding of research that involves the creation of human embryos for research purposes is enforced by EU/EC regulations and by national laws in most EU Member States. In light of this regulatory framework, there is uncertainty as to whether certain types of organoid research (e.g., involving advanced blastoids and gastruloids, and functioning gonadal organoids) would be deemed to be creating human embryos. Consequently, organoid researchers have requested EC-approved regulatory definitions of a human embryo and whatever it is that is generated through embryo-like organoids.

[13] Medical devices are instruments, apparatuses, appliances, materials, or other articles to be used, alone or in combination, on humans for a medical purpose. Medicinal products are substances or combinations of substances to be used on humans for a medical purpose. In general, according to EU/EC regulations, what distinguishes a medical device from a medicinal product is that the former does not contain or is not derived from viable cells or tissues and does not achieve a functional or anatomical change in a patient *primarily* by pharmacological (e.g., a drug), immunological (i.e., the body's defence system), or metabolic (i.e., energy generating) means.

[14] The Medical Device Coordination Group (MDCG) is made up of representatives from Member States of the EU and is chaired by the EU Commission. It provides guidance, advice, and decisions on key issues concerning the medical devices sector as they pertain to EU/EC regulations on medical devices. This includes advice and guidance on new technologies and whether these technologies can be classed as medical devices for regulatory purposes.

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Table 1: Summary of Regulatory Issues, Gaps and Areas of Over-regulation

REGULATORY ISSUE	REGULATORY GAP OR OVER-REGULATION?	SOURCE OF REGULATORY ISSUE	IMPLICATIONS OF REGULATORY ISSUE
Informed Consent, Data Protection, Donor Rights, and User Rights			
Informed Consent for Organoid Research	Regulatory Gap	1. Regulatory standards for informed consent do not explicitly include research using human tissue and cells 2. Genuine informed consent for the depositing and use of human biomaterials is difficult to obtain owing to unknown future research uses and risks	1. National differences in the formal legal requirements for the research use of human tissue and cells 2. If valid informed consent is to be obtained, then alternative models of consent should be considered
Normative Status of Organoids	Regulatory Gap	Organoids complicate the issue of what does and does not form part of the human body and thereby seem to be an exception to regulatory assumptions concerning the "objective" status of donated biomaterial	Question of whether regulators need to reconsider the normative (i.e., legal and moral) status of organoids
Donor Withdrawals	Regulatory Gap	Regulations guiding donor withdrawals only extend to the donated cells and tissues. However, donors may have legitimate moral and legal claims over the organoids that have been derived from cells and tissues	Not clear that a donor's right to withdraw consent extends to the organoids that have been derived from donated cells
Sentient and Conscious Neural Organoids	Regulatory Gap	Extensive debates regarding the ethical permissibility of generating or using organoids with sensory, cognitive, and/or consciousness capacities. However, there is no evidence to suggest that the neural organoids that have been established resemble a fully functioning brain or integrated parts of the brain	As neural organoids mature and become more complex, regulatory questions regarding ownership, the normative status of these entities, and user's obligations to them may arise
Information Derived from the Analysis of Donated Cells	Over-regulation	Problematic interaction between the regulation of research-intended donated cells and cell lines and the regulation of information derived from the analysis of that material	Complicates the exchange of organoids between research institutions

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Open Science (OS) and Benefit Sharing			
Material Transfer Agreements (MTAs)	Over-regulation[15]	Process of drafting and agreeing an MTA between two parties based in different jurisdictions is complex because the transfer of material is legislated domestically, with substantially different provisions, standards, and requirements within different states	Substantial differences in domestic laws result in institutional legal teams interpreting the terms of the MTA differently, leading to significant delays in MTA execution being reported by organoid researchers
	Regulatory Gap	The European Commission (EC) has produced standard contractual clauses for data associated with material under an MTA. However, because material transfer is legislated domestically, there are no such clauses covering the material component of the MTA	Organoid researchers have requested MTA templates and standard clauses for human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and organoids
Patentability of Organoids	Over-regulation	In Europe, human embryonic stem cells (hESCs) and their derivatives generally cannot be patented. However, in their judgments regarding the non-patentability of hESC lines and their derivatives, the European Court of Justice (CJEU) and the European Patent Office (EPO) employed very broad definitions of a human embryo and a hESC	Organoid researchers are uncertain as to whether Europe's non-patentability restrictions would extend to (some) induced pluripotent stem cells (iPSCs) or their derivatives, organoids, and resulting applications

[15] By classifying this issue as an instance of "over-regulation", we do not suggest that there is "too much" regulation at the EU level such that the EU/EC's own requirements and standards for MTAs are legally unclear, generate legal uncertainty, or lead to contradictions. Indeed, there are no specific EU/EC legal instruments that cover the transfer of material. Rather, because material transfers are legislated domestically, we refer to this as an instance of "over-regulation" in the sense that the regulation of MTAs is not harmonized across Member States.

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Organoid Research and Use			
Classifying Organoid-based Technologies for Medical Use	Over-regulation	The European Medicines Agency (EMA) recognizes that there is substantial regulatory scrutiny of those seeking to apply for market authorization for new Advanced Therapy Medicinal Products (ATMPs)	Extremely difficult for applicants to demonstrate and provide evidence for how they have fulfilled the requirements for marketing authorization of new ATMPs
	Regulatory Gap	In Europe, legally binding definitions, which determine whether a technology can be classed as a medical device or a medicinal product, lack sufficient clarity. Some advice has been provided but it is not legally binding, nor can it be taken to reflect the official position of the EC	Significant regulatory uncertainty when new technologies do not clearly fall under the current legally binding definitions of a medicinal product or a medical device or when new technologies incorporate elements of both medicinal products and medical devices
Organoids and the Regulation of In Vitro Embryonic Research	Over-regulation[16]	For certain types of in vitro embryonic research, EU/EC regulations require a more rigorous approach to ethical review than those proposed by the International Society for Stem Cell Research. In terms of the culturing of human embryos for research purposes and the derivation of new cell lines from human embryos, the ISSCR advises that such research is permissible (subject to certain conditions and approval) whereas EU/EC regulations exclude them from research funding eligibility	Current expert consensus regarding the regulation of in vitro embryonic research (as represented in the ISSCR's updated guidelines) is in tension with EU/EC regulation of such research
	Regulatory Gap	A prohibition on the funding of research that involves the creation of human embryos for research purposes is enforced by EU/EC regulations and by national laws in most EU Member States. But an adequate definition of a human embryo is absent in these regulations	Organoid researchers are uncertain as to whether the EC would deem certain types of organoid research to be creating human embryos

[16] EU/EC regulations in this area are largely a response to the substantial differences in the domestic laws of individual Member States. Therefore, the fact that a Member State prohibits the practices recommended by the ISSCR does not imply that the there is "too much" EU regulation such that the EU/EC's legal requirements and standards for in vitro embryonic research are legally unclear, generate legal uncertainty, or lead to contradictions. Rather, relative to the recommendations put forward in the updated ISSCR guidelines, the EU's own approach to the regulation of certain forms of embryonic research is more restrictive. It is for this reason that, in this report, we refer to this aspect of the EU's approach to in vitro embryonic research as an instance of "over-regulation".

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3 Introduction to D6.1

WP6's primary aim is to contribute to existing ethical and normative frameworks involving organoid and organoid-related research (including research involving organs-on-chips) and the potential clinical applications of organoids.[17] This will be done by identifying regulatory gaps in existing normative frameworks as well as by identifying those regulatory areas where current frameworks lead to instances of over-regulation of organoid and organoid-related activities, including cell/tissue procurement, organoid derivation, modelling, experimental, preclinical, and clinical research, and medical application activities.[18] Following on from this deliverable report, the task is to develop specific proposals for addressing these gaps and areas of over-regulation.

To these ends, WP6 employs the mapping of organoid and organ-on-a-chip research activities and patents produced by WP2 and the mapping of regulatory, ethics and normative frameworks produced by WP3 as the initial basis for its work, whilst collaborating with WP4 in a two-way ongoing exchange of information relevant to stakeholder engagement, co-creation and validation.

3.1 Scope of D6.1

The two maps produced in WP2 (Task 2.1/D2.1) and WP3 (Tasks 3.2/3.3/D3.1/D3.2) have been integrated into a multi-dimensional "Super Map", showing which organoid and organoid-related activities are regulated in which ways and by what agencies/actors. The integration is based on close reading of the extant regulations using standard legal methods of statutory/regulatory interpretation. The Super Map is the basis on which this deliverable report has identified areas of activity that are, when conducted in the European Union, currently unregulated or under-regulated ("gaps") and areas of activity that are over-regulated.

[17] Unless specified, when we refer to "organoids", this should be understood as including organs-on-chips.
[18] In this report, when we refer to "organoid activities", this should be taken to include, unless specified, organoid derivation, organoid research, organoid-based technologies, and (potential or planned) clinical translations of organoid research. When we refer to "organoid-related activities", this notably includes organ-on-a-chip derivation, research, and any potential clinical applications.

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Following the outline of Tasks 6.2-6.5 contained in the Grant Agreement, the identified gaps and areas of over-regulation have been classified in terms of how they relate to the following four broad categories:

- Informed consent, data protection, donor rights, and user rights within the context of organoids
- Open Science ("OS"), including the issue of benefit sharing within the context of organoids
- Organoid research and use as a social/institutional practice, including organoid use in healthcare
- Other regulatory issues identified via the stakeholder engagement workshops conducted by WP4 (Task 4.1).

3.2 Outline of D6.1

Section 4 focuses on the integration of the two mapping exercises undertaken by WP2 and WP3 for the purposes of developing the Super Map. Here, we detail the methodological steps by which the two maps were integrated. We also provide explanations for how key organoid and organoid-related activities were categorized, details of the regulations against which these activities were mapped, and descriptions of the ways in which the maps produced by WP2 and WP3 were revised and extended in order to sufficiently cover the regulation of organoid and organoid-related activities within the European Union.

The Super Map, presented in its original form as a tabular data set, can be found in Appendix 1. As part of section 4, we provide graphic representations of key findings from the Super Map, an explanation of these maps, and a descriptive overview of these key findings, indicating which specific aspects, topics, and categories of organoid and organoid-related activities are covered, and to what degree, by current regulations. In other words, we interpret the scope of these regulations in terms of how they include, exclude, or *might*—depending on legal interpretation—include or exclude cell procurement, organoid derivation, research, and medical application activities.

Section 5 details the gaps in the regulations and areas of potential over-regulation with respect to specific organoid and organoid-related activities. These gaps and areas of over-regulation have been identified not only by analyzing the prevalence of certain organoid activities, topics, and categories within those regulations that have been mapped, but also, more importantly, through close reading of the regulations. We also identify and explain some of the ethical, legal, classificatory, and practical issues posed by certain organoid and organoid-related activities that highlight these regulatory problems. To support our analysis of these issues, gaps, and areas of over-regulation, we refer to, and make use of critical discussions relating to EU case law along with empirical evidence and normative analyses in the academic literature.

Section 6 provides a summary of the key findings in relation to the regulatory gaps and areas of over-regulation. In addition, an overview is provided of the upcoming tasks related to WP6 as it seeks to develop proposals for addressing the regulatory gaps and areas of over-regulation in organoid and organoid-related research and clinical application.

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4 Super Map

This section focuses on the development, analysis of, and key findings relating to the Super Map, which demonstrates which organoid and organoid-related activities are regulated in what ways and by which regulators and organizations.

Section 4.1 provides a brief overview of the two mapping exercises undertaken by WP2 and WP3, which were integrated to form the basis of the Super Map.

Section 4.2 details the methodological steps by which the two maps were integrated. This includes explanations for how key organoid and organoid-related activities were categorized, details of the regulations against which these activities were mapped, and descriptions of the ways in which the maps produced by WP2 and WP3 were revised and extended in order to sufficiently cover the regulation of organoid and organoid-related activities within the European Union.

Finally, section 4.3 provides graphic representations of key findings from the Super Map and a descriptive overview of these key findings, indicating which specific aspects, topics, and categories of organoid and organoid-related activities are covered, and to what degree, by current regulations.

4.1 The basis of the Super Map: WP2 and WP3 Maps

In D2.1 (“The research landscape of organoid and organ-on-a-chip models”), WP2 presented a comprehensive literature-mapping analysis of organoid and organ-on-a-chip research activities and patents relating to organoids within academia and industry, covering the period 2011 to 2022. Full details of that mapping exercise can be found in D2.1.

For the purposes of developing the Super Map, WP6 were primarily concerned with the “categories” and “terms” developed by WP2, and which WP2 employed to identify and capture important features of organoid and organ-on-a-chip research. WP2 subsumed these “categories” and associated “terms” under the following broad areas:

- Origins and types of cells and tissue
- Types of organoid and organoid-based aggregates
- Purpose of research
- Types of disease, disorders and damage investigated in organoid and organ-on-a-chip research
- Types of medical application of organoid and organ-on-a-chip research (both planned and potential translations)

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- Types of therapeutic product and medical devices incorporating organoids (both planned and potential)

These six broad areas, their categories, and the terms they contain define the broad structure and content of the Super Map (see section 4.2 for further details).

In D3.1 ("Map report of normative, research ethics and research integrity frameworks"), WP3 conducted a systematic scoping review to map the normative dimensions of research activities, as they relate to research ethics and research integrity frameworks, as well as the debates concerning the regulatory, ethical, and integrity-related dimensions of organoids and similar technologies.

As the Super Map seeks to map organoid and organoid-related activities against the relevant normative (i.e., regulatory) frameworks, WP6 were not primarily concerned with WP3's systematic scoping review as it pertains to the normative debates concerning organoids and similar technologies (though some of these debates, as we demonstrate in section 5, are important for determining the nature, scope of, and issues associated with the identified gaps in the regulations).

As part of D3.2 ("Comparative analysis"), WP3 undertook a systematic scoping review of legislation and other means of regulation (guidelines, standard operating procedures, codes of conduct) for selected families of technologies (gene editing, cloning, induced pluripotent stem cell and human embryonic stem cell technologies) and selected countries/research environments.

In seeking to map the regulatory frameworks relating to organoid and related research, WP3 included, within the scope of their reviews:

1. International Conventions that apply in and beyond the European area as well as regional legislation such as Council of Europe legislation
2. EU legislation as laid down in treaties, regulations, and directives as well as European Commission "soft law" documents that are not binding on Member States
3. Relevant opinions from established committees and professional bodies
4. Codes of conduct relating to medical ethics.

In addition, and although WP3 did not conduct a comprehensive scoping review of national regulatory frameworks, some national regulations were identified (e.g., for Germany, Great Britain, USA, Israel, Russia, China, Japan, and Australia).

Finally, WP3 did not include, within the scope of their mapping exercises, non-English texts or outdated legislation.

WP6, in developing the Super Map, identified all the regulations listed within WP3's two deliverable reports, and used them as a starting point for mapping against the organoid and organoid-related activities, categories and terms provided by WP2.

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4.2 Developing the Super Map

In its mapping exercise, WP2 developed "categories" and associated "terms" related to organoid and organ-on-a-chip research and subsumed these under the following broad areas:

- Origins and types of cells and tissue
- Types of organoid and organoid-based aggregates
- Purpose of research
- Types of disease, disorders and damage investigated in organoid and organ-on-a-chip research
- Types of medical application of organoid and organ-on-a-chip research (both planned and potential translations)
- Types of therapeutic product and medical devices incorporating organoids (both planned and potential)

For each of these six broad areas, WP2 provided categories together with more specific terms, allowing it to produce a fine-grained mapping of organoid and organ-on-a-chip activities (see Figure 2).

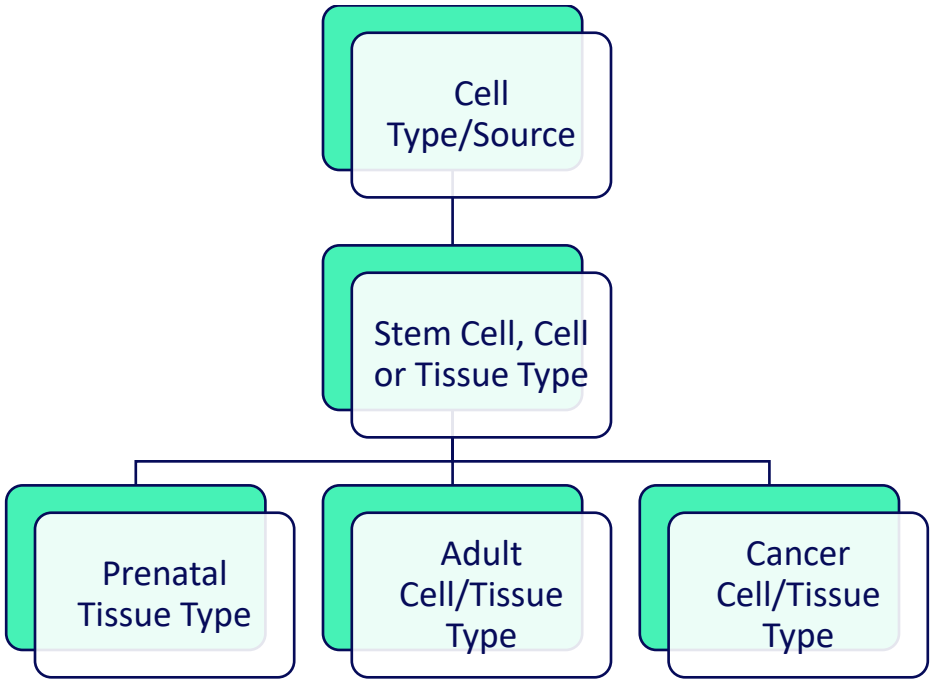

Figure 2: Example of WP2's approach to organoid and organ-on-a-chip categorization and mapping

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In developing the Super Map, WP6 adopted this hierarchical approach to organoid and organoid-related activity mapping and employed all the associated categories and terms used by WP2.

In order to rationalize the hierarchical approach adopted by WP2, WP6 developed additional higher-level categories, under which WP2's categories and sub-categories could then be subsumed. The overarching structure of the Super Map as it relates to WP2's categories is provided in Figure 4.

Each of the categories and sub-categories provided by WP2 (see Figure 4) contain a number of terms, which were employed by WP2 to map organoid and organ-on-a-chip activities. WP6 utilized the terms provided by WP2 in order to map organoid and organoid-related activities in relation to the relevant regulatory frameworks.

WP6 identified all the regulations listed within WP3's two deliverable reports and used them as a starting point for mapping against the organoid and organ-on-a-chip activities, categories, and terms provided by WP2.

Given the categories and terms provided by WP2 in its mapping exercise, WP6 identified a number of regulations (applicable to organoid and organoid-related activities within the EU) that were not included in WP3's mapping exercises but which fall within the scope of those organoid and organ-on-a-chip activities mapped by WP2 (in particular, a number of Council of Europe additional protocols, EU/EC regulations and directives, and pertinent "soft law" documents provided by the European Medicines Agency and the leading international scientific organisation in this area, the International Society for Stem Cell Research (ISSCR)).

WP6 conducted a "snowballing" exercise to identify the outstanding regulations, including full reviews of all current Council of Europe conventions and protocols and current EU/EC regulations and directives. The full list of regulations incorporated within the Super Map is provided in Table 2.

Each regulation was mapped against regulation-specific categories and associated terms, following the same hierarchical approach adopted by WP2 (see Figure 3).

A close reading of each regulation in Table 2 was conducted using a pluralist approach to legal interpretation (Greenberg, 2021). This is taken to be the most common approach to legal interpretation, and includes textual analysis, precedent-based reasoning, and forward-looking assessment of consequences. This approach was adopted because very few regulations explicitly refer to, or mention organoids, organs-on-chips, organoid or organoid-related activities. Instead, they tend to focus on the normative dimensions of more general topics, activities, or practices (e.g., procurement and donation of human tissue, clinical trials, medicinal products or devices, the legal protection of biotechnological inventions, and so on). Given the lack of explicit reference to organoids, organs-on-chips, organoid and organoid-related activities in all "hard law" regulations, the pluralist approach allowed WP6 to interpret the more general principles and provisions within these regulations to determine: 1) whether organoids

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or organoid and related activities, in principle, fall under a regulation; and 2) which organoid and organoid-related activities would, in principle, be covered by that regulation.

For each regulation in Table 2, a pluralist interpretation was employed to answer 1) and 2) in the previous paragraph. The answers to these two questions are presented in the Super Map in the form of "tags". In other words, for each regulation, we identified the relevant categories in Figure 4 that were applicable and "tagged" the regulation with the appropriate terms provided by WP2 that fall under those categories. For further details of the results generated through this tagging exercise, see section 4.3.

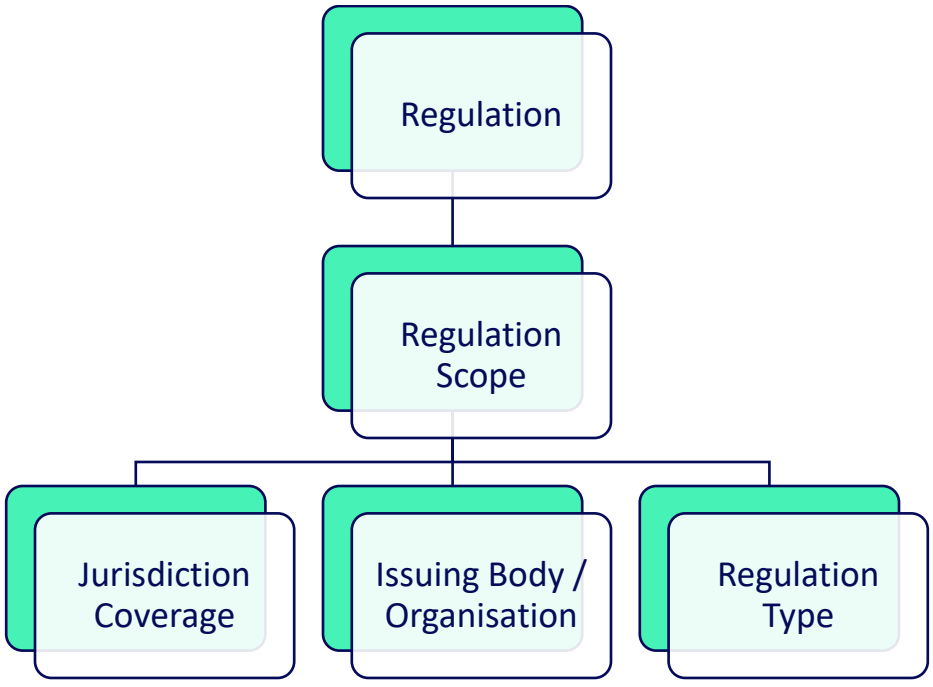

Figure 3: Hierarchy of categories for mapping regulations

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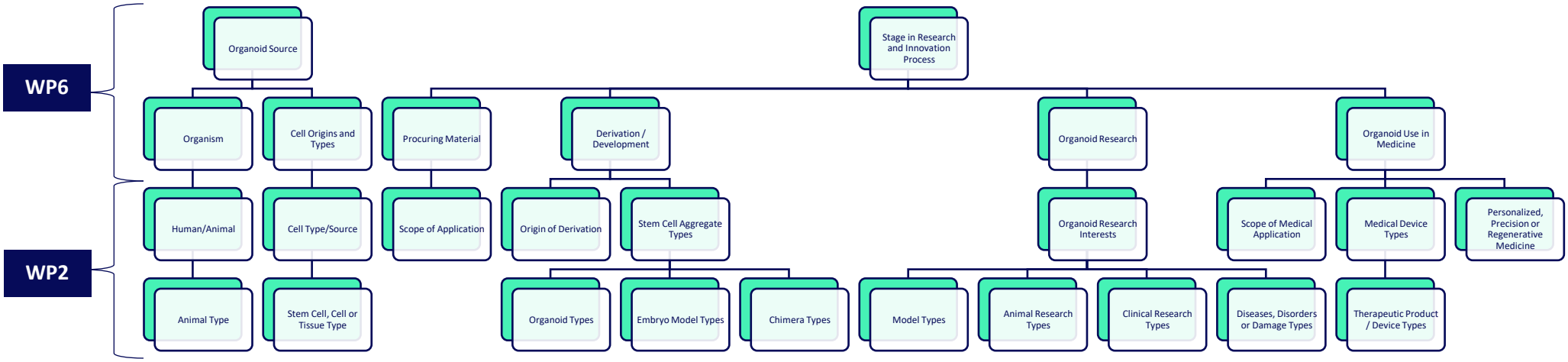

Figure 4: Structure of the Super Map for Organoid Activities

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Table 2: Full list of regulations incorporated in the Super Map

Regulation	Jurisdiction Coverage	Issuing Body/Organisation
HARD LAW		
Charter of Fundamental Rights	Multinational Union	European Union
Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC	Multinational Union	European Union
Directive 2001/20/EC on clinical trials (repealed by Regulation (EU) 536/2014)	Multinational Union	European Union
Regulation (EU) 536/2014 on clinical trials on medicinal products for human use	Multinational Union	European Union
Commission Implementing Regulation (EU) 2017/556 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014	Multinational Union	European Union
Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells	Multinational Union	European Union
Directive 2006/86/EC implementing Directive 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells	Multinational Union	European Union

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Directive 98/44/EC on the legal protection of biotechnological inventions	Multinational Union	European Union
Directive 2001/83/EC on the Community code relating to medicinal products for human use	Multinational Union	European Union
Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use	Multinational Union	European Union
Regulation (EC) 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency	Multinational Union	European Union
Regulation (EC) 141/2000 on orphan medicinal products	Multinational Union	European Union
Regulation (EC) 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004	Multinational Union	European Union
Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products	Multinational Union	European Union
Regulation (EC) 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) 726/2004	Multinational Union	European Union
Directive 93/42/EEC concerning medical devices (repealed by Regulation (EU) 2017/745)	Multinational Union	European Union
Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices (repealed by Regulation (EU) 2017/745)	Multinational Union	European Union
Regulation (EU) No 722/2012 concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin	Multinational Union	European Union

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Regulation (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Directives 90/385/EEC and 93/42/EEC	Multinational Union	European Union
Directive 98/79/EC on in vitro diagnostic medical devices (repealed by Regulation (EU) 2017/746)	Multinational Union	European Union
Regulation (EU) 2017/746 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU	Multinational Union	European Union
Directive 2009/41/EC on the contained use of genetically modified micro-organisms	Multinational Union	European Union
Directive 86/609/EEC on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes	Multinational Union	European Union

HARD LAW/SOFT LAW[19]		
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 (ETS No. 164)	Multinational Union	Council of Europe

[19] At the level of the European Court of Human Rights ("ECtHR"), if a state is a signatory to and has ratified a Council of Europe ("CoE") convention or protocol, then it is undisputedly "hard law" for that state. Relatedly, only those articles of those conventions/protocols to which a state has not entered reservations when signing/ratifying are hard law.

If a state has not signed or ratified a particular CoE convention, then it is considered to be "soft law" in the sense that the ECtHR may still explicitly appeal to it as part of its interpretation of specific articles within the European Convention on Human Rights ("ECHR").

Because the status of a particular CoE convention or protocol is, in part, dependent on whether states have signed and ratified it, we have classed the "Oviedo" convention (Convention on Human Rights and Biomedicine) and its additional protocols as both hard law and soft law.

If enough countries ratify a particular CoE convention and the ECtHR refers to it frequently, then it may attain the status of "customary international law" and will thereby be binding on all states regardless of whether they have signed and ratified it. In terms of the "Oviedo" convention, state infringements would, in principle, be infringements of Articles 3 or 8 of the ECHR. However, it is questionable whether the Oviedo convention has attained the status of customary international law. This is another reason why we have tagged this convention and its additional protocols as both hard and soft law.

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

SOFT LAW		
Universal Declaration on Bioethics and Human Rights	International	UNESCO
Universal Declaration on Human Cloning	International	United Nations
Universal Declaration on Human Genome and Human Rights	International	UNESCO
Statement on Genome Editing Technologies by the Committee on Bioethics	Multinational Union	Council of Europe
Guide to the quality and safety of tissues and cells for human application. 4th edition, 2019	Multinational Union	European Directorate
EMA Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials	Multinational Union	European Medicines Agency
EMA Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products	Multinational Union	European Medicines Agency

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EMA Guideline on human cell-based medicinal products	Multinational Union	European Medicines Agency
EMA Guideline on xenogeneic cell-based medicinal products	Multinational Union	European Medicines Agency
EMA Guideline on quality, preclinical and clinical aspects of gene therapy medicinal products	Multinational Union	European Medicines Agency
EMA Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells	Multinational Union	European Medicines Agency
EMA Reflection Paper on clinical aspects related to tissue engineered products	Multinational Union	European Medicines Agency
EMA Reflection Paper on stem cell-based medicinal products	Multinational Union	European Medicines Agency
ISSCR Guidelines for Stem Cell Research and Clinical Translation	International	International Society for Stem Cell Research

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4.3 Super Map: Key Findings

The full Super Map, in its original form as a tabular data set, is provided in Appendix 1.

In this section, we provide graphic representations of the following dimensions of the Super Map:

- Organoid Source
- Procuring Material
- Organoid derivation/development
- Organoid research
- Organoid use in healthcare

Each graph is constituted by several levels:

- One of the five categories listed above, indicating whether the graph relates to organoid source/origin, the normative issues relating to organoid cell or tissue procurement, organoid derivation and development activities, organoid research activities, or organoid use in healthcare;

- The *categories* provided by WP2, with nodes colored green, which indicate the general types of organisms, cells, tissues, diseases, disorders, models, research/research interests, and (planned or potential) medical uses involved in organoid and organoid-related activities;

- The *terms* provided by WP2, with nodes colored purple, which provide further specification of the categories associated with organoid and organoid-related activities.

For each node colored in green or purple, its size, relative to the size of the higher-level orange node in the relevant graph (representing all 42 regulations contained in the Super Map), represents the number of those regulations listed in Table 2: i) that explicitly mention these categories/terms (or semantically equivalent or conceptually related terms/categories); or ii) whose scope, in terms of its provisions, requirements, standards, or guidance, would, in principle, extend to the relevant aspects of organoid and organoid-related activities. In other words, node size reflects the prevalence of that specific aspect of organoid or organoid-related activity within the regulation set.

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4.3.1 General Findings

Most international and EU/EC regulations and relevant "soft laws" cover standards concerning (in order of prevalence):

1. Humans and/or animals as the source of biomaterial ("Human/Animal"; n=42; 100%)[20]
2. Types of cells and tissue involved in procurement, derivation, research, and medical application activities ("Cell Type/Source"; n=42; 100%)
3. Types of research/research interest ("Organoid Research Interests"; n=32; 76.2%)
4. Types of medical application of research ("Scope of Medical Application"; n=30; 71.4%)
5. Types of clinical research ("Clinical Research Types"; n=20; 47.6%)
6. Medical devices ("Medical Device Types"; n=20; 47.6%)
7. Medicinal products *and* medical devices (and types thereof) ("Therapeutic Product/Device Types"; n=18; 42.9%)

Organoids, organoid-related technologies (e.g., organs-on-chips), and organoid-based clinical applications are not explicitly mentioned in international regulations or legally binding EU regulations. When organoids are mentioned, it is within the "soft law" documents (i.e., those by the European Medicines Agency (EMA) and the International Society for Stem Cell Research (ISSCR)). Organs-on-chips are not mentioned either in legally binding international and EU regulations or in "soft law" documents.

There may be several reasons why organoids and organ-on-chip activities are not explicitly mentioned in legally binding regulations. Firstly, current international regulations and EU/EC regulations and directives are intended to cover procurement, derivation, research, and medical application activities *in general*. Where specific technologies or biomaterials and their derivatives are mentioned in these documents, this may be because they have been used for far longer than organoids and organoid-related technologies, with time to consider and account for any particular legal and ethical issues to which they give rise. By contrast, although organoid and organoid-related activities give rise to specific regulatory issues, some of which have been raised at law, in the academic literature, and by expert-constituted professional bodies such as the ISSCR, there may have not been enough time to collaborate with regulators on these issues nor to develop these academic discussions and case law judgments into legally binding provisions.

An equally plausible explanation is that organoids can be regarded as just a collection of differentiated cells of various types (though cultured in three dimensions ("3D")). Aside from the emergence of additional differentiated cell types in 3D, there are no substantial differences between 2D stem cell differentiation and the culturing of stem cells in 3D (even when extra-cellular fluid substances are introduced as part of 3D growth or drug delivery). Presumably, this is why derivation and research activities involving organoids have not, at the regulatory level, been considered separately from those activities involving differentiated stem cells in general.

[20] "N" values reflect the number of relevant regulations in the regulation set (42 regulations in total)

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Thirdly, particularly where the potential or planned clinical application of organoids is concerned, the absence of organoid-specific provisions, standards, and requirements in international and EU/EC regulations may be due to a lack of clarity regarding the specific normative issues raised by organoid applications and/or a lack of certainty regarding whether these issues are of a sufficient normative weight to warrant specific provisions, requirements, or standards. This may be warranted given that that organoid and organoid-related research is still very much at the preclinical stage (see D2.1).

Given that organoids, organoid-related technologies, and organoid-based clinical applications are not explicitly mentioned in the legally binding documents within the regulation set, our assessment of whether a regulation would extend to organoid and organoid-related topics, issues, activities, and practices is based on a pluralist interpretation of the provisions, standards, and principles associated with more general topics, activities, or practices (e.g., procurement and donation of human tissue, clinical trials, medicinal products and devices, the legal protection of biotechnological inventions, and so on) (see section 4.2). In short, the pluralist approach allows us to interpret the more general principles and provisions within these regulations and to determine whether, in principle, these rules and provisions would extend to organoid and organoid-related activities, types, and categories.

4.3.2 Organoid Source Findings: "An Absence of Cell-Specific Regulations"

See Figure 5 for a graphic representation of this dimension of the Super Map.

The key results to note are:

1. All the regulations contained in the Super Map: i) provide standards and requirements for using humans and animals as sources of biomaterial; and ii) cover the origins and uses of cells/tissue in procurement, derivation, research, or medical application activities. However, even though all regulations contained in our set address the procurement or use of cells/tissue, the majority (n=34; 81.0%) do not provide further specification as to the specific types of cells or tissue involved. Instead, they refer to more general concepts such as "human biomaterial", "human tissue", or "human cells", or just "tissue" or "cells".

2. In the Super Map, the majority of regulations (n=40; 95.2%) explicitly cover procurement, derivation, research, or medical application activities involving *human* organisms. This compares to fourteen regulations (33.3%) containing provisions concerning the use of *animals*.

3. The more specific the type of cell or tissue (e.g., "stem cell", types of stem cell, "*adult* cell/tissue", "*prenatal* tissue") the less likely it is that a regulation will contain *specific* provisions, standards, and requirements for procurement, derivation, research, or medical application activities involving those types. Where specific types are mentioned, these tend to be in more specialized regulations focused on a specific aspect of research or medical application activity.

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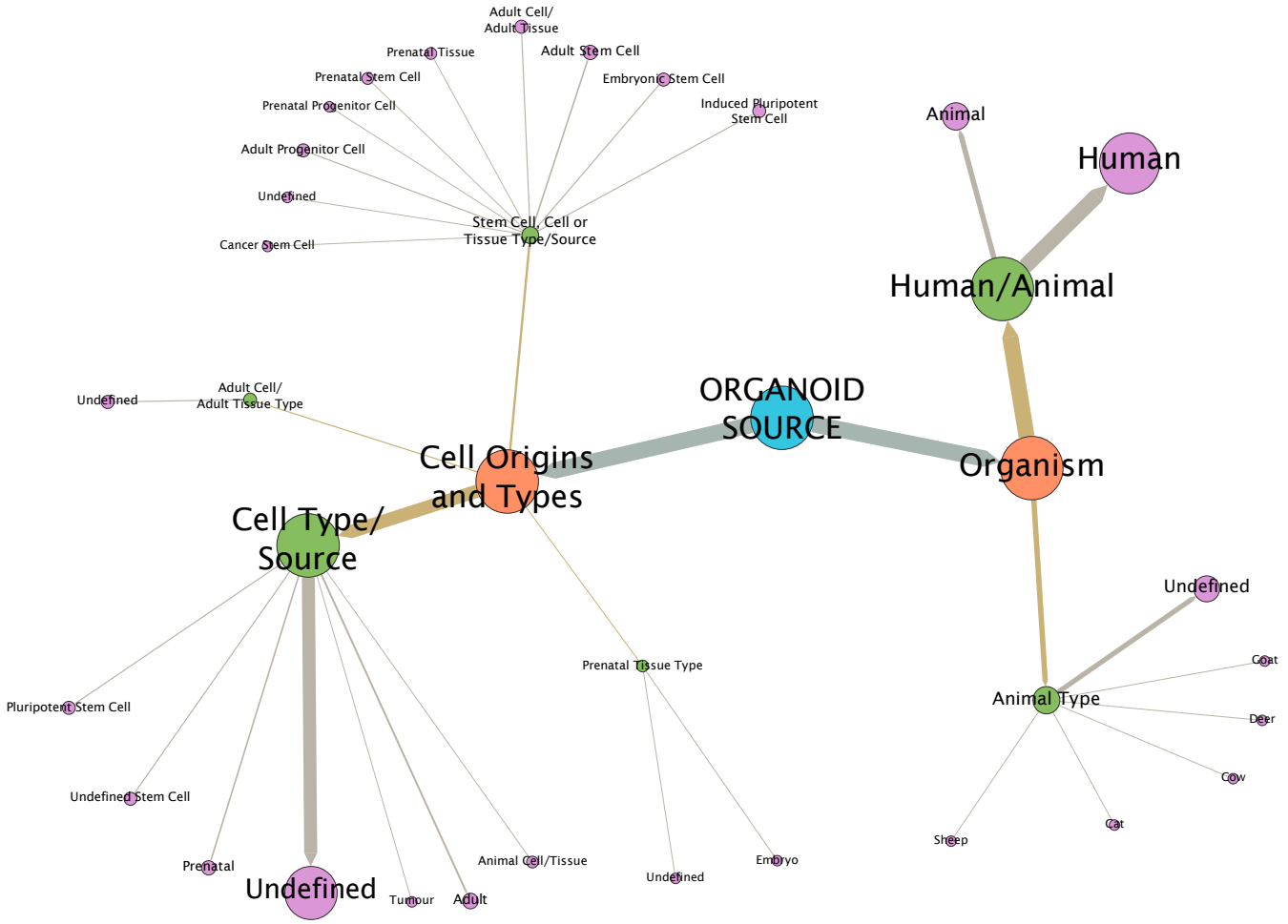

Figure 5: Graphic Representation of the Super Map (Organoid Source)

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4.3.3 *Procuring Material Findings: "Regulations Focus on Standards for Donation"*

See Figure 6 for a graphic representation of this dimension of the Super Map.

The key results to note are:

1. Fourteen regulations (33.3%) cover the procurement of biomaterial for derivation, research, or clinical application activities.
2. The provisions, standards, and requirements contained in these regulations relate to the following topics:
    - Donation (n=10)
    - Biobanking (n=7)
    - Data stewardship (including anonymization) (n=7)
    - Ethics Committee review, approval, or oversight (n=4)
    - Disclosure of health information or findings (n=4)

4.3.4 *Derivation/Development Findings: "Organoid Derivation Governed by 'Soft Laws'"*

See Figure 7 for a graphic representation of this dimension of the Super Map.

The key results to note are:

1. Of those regulations contained in the Super Map, few (n=6; 14.3%) explicitly mention or cover the derivation or development of organoids, organs-on-chips, organoid-related chimeras or embryo models. Of these six regulations (14.3%), four are EMA guidance documents; one is the ISSCR's guidelines; and one is Directive 2004/23/EC.
2. These results illustrate the point made earlier about the lack of explicit mention of organoids and organs-on-chips in international regulations or legally binding regulations within the EU. Only three documents (7.1%) cover the derivation of stem cell aggregates in general, two of which are "soft law" documents (the ISSCR's guidelines and a guidance document from the EMA). Directive 2004/23/EC also addresses standards for certain development processes involving stem cell aggregates in general.
3. Organoids are explicitly mentioned in two "soft law" documents: the ISSCR's *Guidelines for Stem Cell Research and Clinical Translation* and the EMA's *Guideline on Quality, Non-clinical and Clinical Aspects of Medicinal Products containing Genetically Modified Cells*. Organs-on-chips are not mentioned at all.

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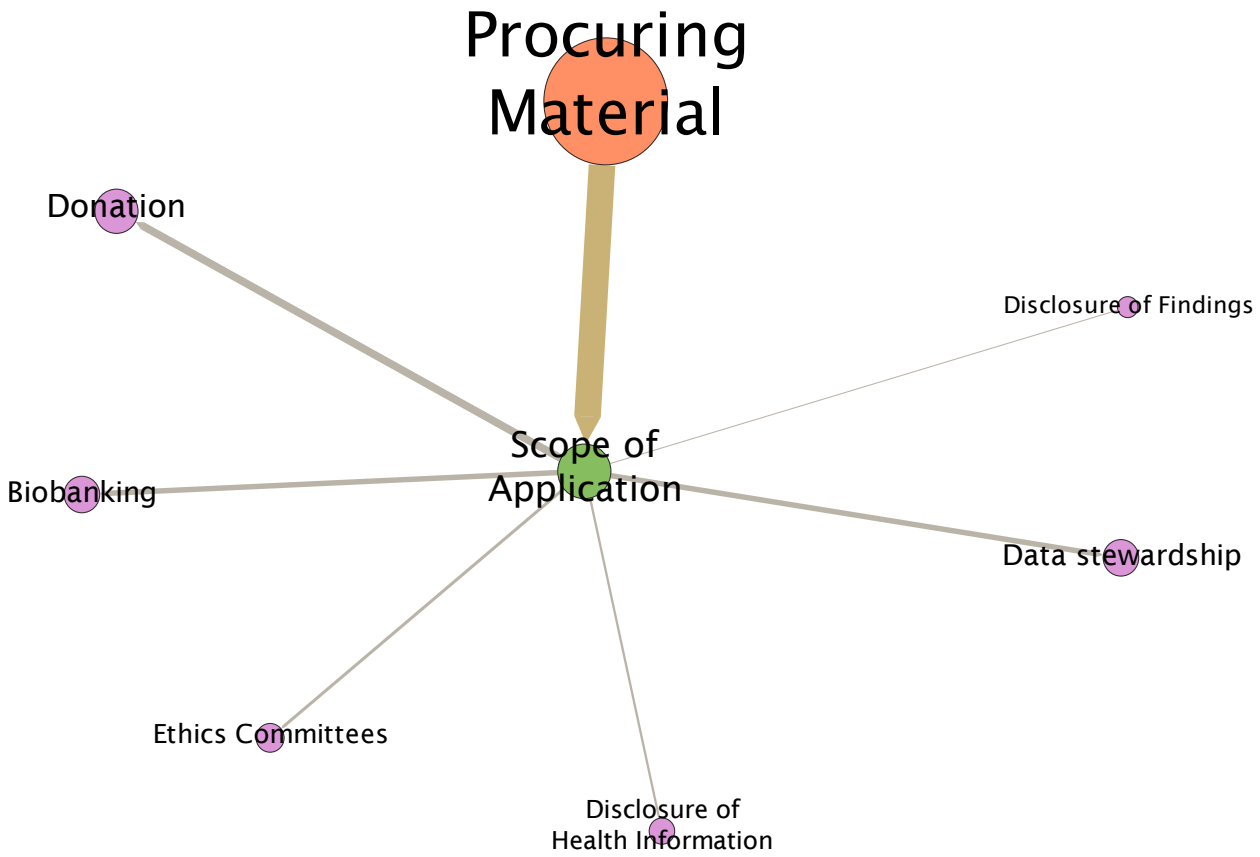

Figure 6: Graphic Representation of the Super Map (Procuring Material)

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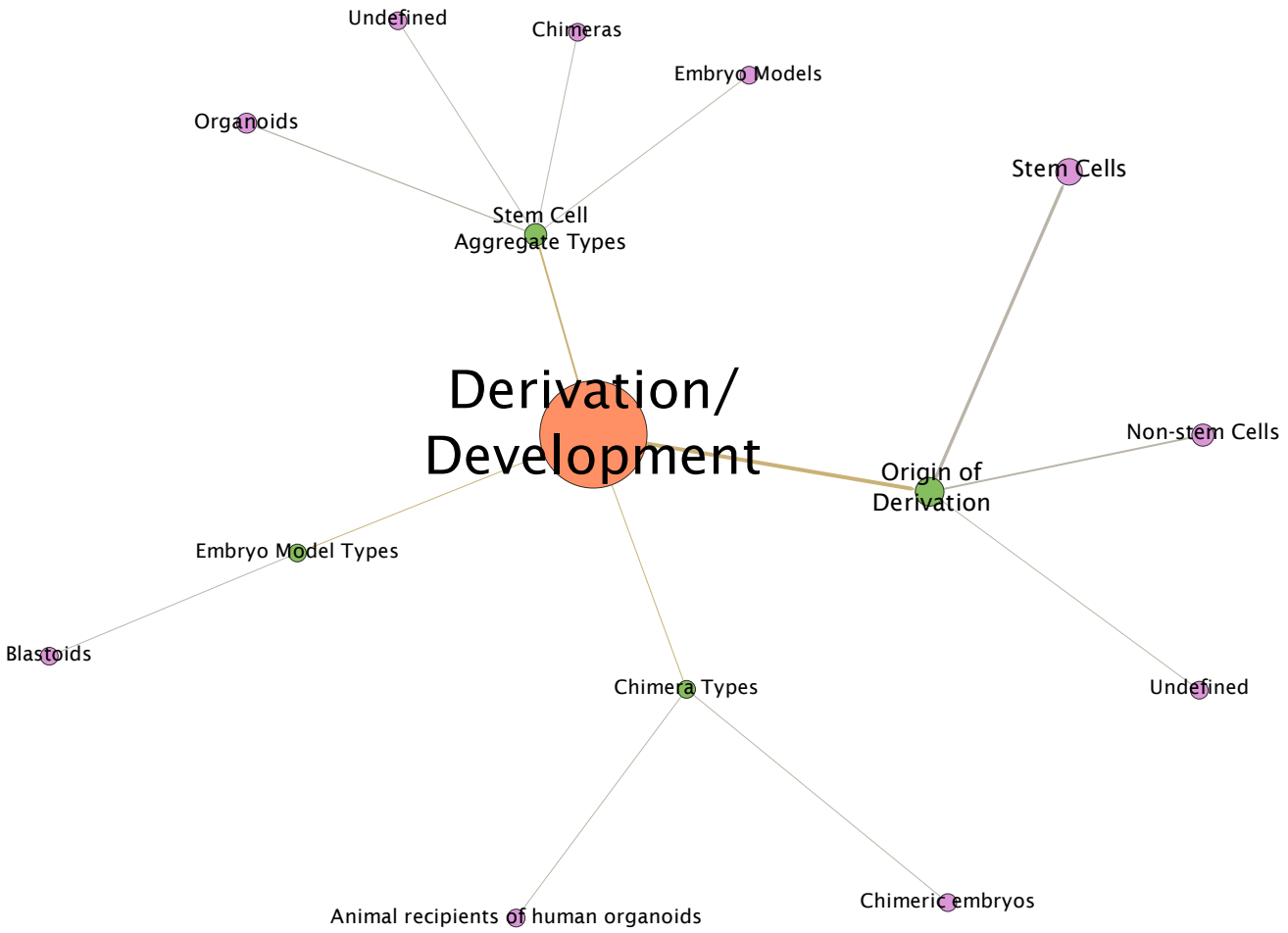

Figure 7: Graphic Representation of the Super Map (Derivation/Development)

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4.3.5 *Organoid Research Findings: "Clinical Research and Modelling are the Core Areas of Research Regulation"*

See Figure 8 for a graphic representation of this dimension of the Super Map.

The key results to note are:

1. Of the 42 regulations contained in the Super Map, 32 regulations (76.2%) explicitly cover research activities that, in principle, would extend to organoid and organoid-related research. Of these 32 regulations:
    a. 20 (62.5%) contain provisions, standards, or requirements for *clinical* research (including preclinical and experimental clinical studies)
    b. 13 (40.6%) cover the use of models in research
    c. 9 (28.1%) cover research involving animals
    d. 3 (9.4%) explicitly mention research concerning diseases, disorders, or damage
    e. 7 (21.9%) are applicable to research but do not provide specification as to the nature of that research.

1. Of the 20 regulations focused on clinical research, 14 (70.0%) provide standards and requirements for clinical trials, 7 (35.0%) cover experimental clinical research, 7 (35.0%) cover preclinical research, and 6 (30.0%) cover toxicity studies.

2. Of the 13 regulations focused on modelling, 6 (46.2%) provide standards and requirements for gene-editing or genetically modified models, 4 (30.8%) cover bioengineering models, 3 (23.1%) cover disease models, and 1 regulation (7.7%) covers immunological modelling.

3. Of the 9 regulations covering research involving animals, almost all (n=8; 88.9%) detail provisions, standards, or requirements for research involving animal models.

4. Finally, it is worth noting that of the 32 regulations that explicitly cover research activities that, in principle, would extend to organoid and organoid-related research, very few (n=3; 9.4%) explicitly mention research into diseases, disorders, or damage. Furthermore, *specific* disorders, diseases, or damage are rarely mentioned. That said, two regulations make a distinction between cancer- and non-cancer-related research.

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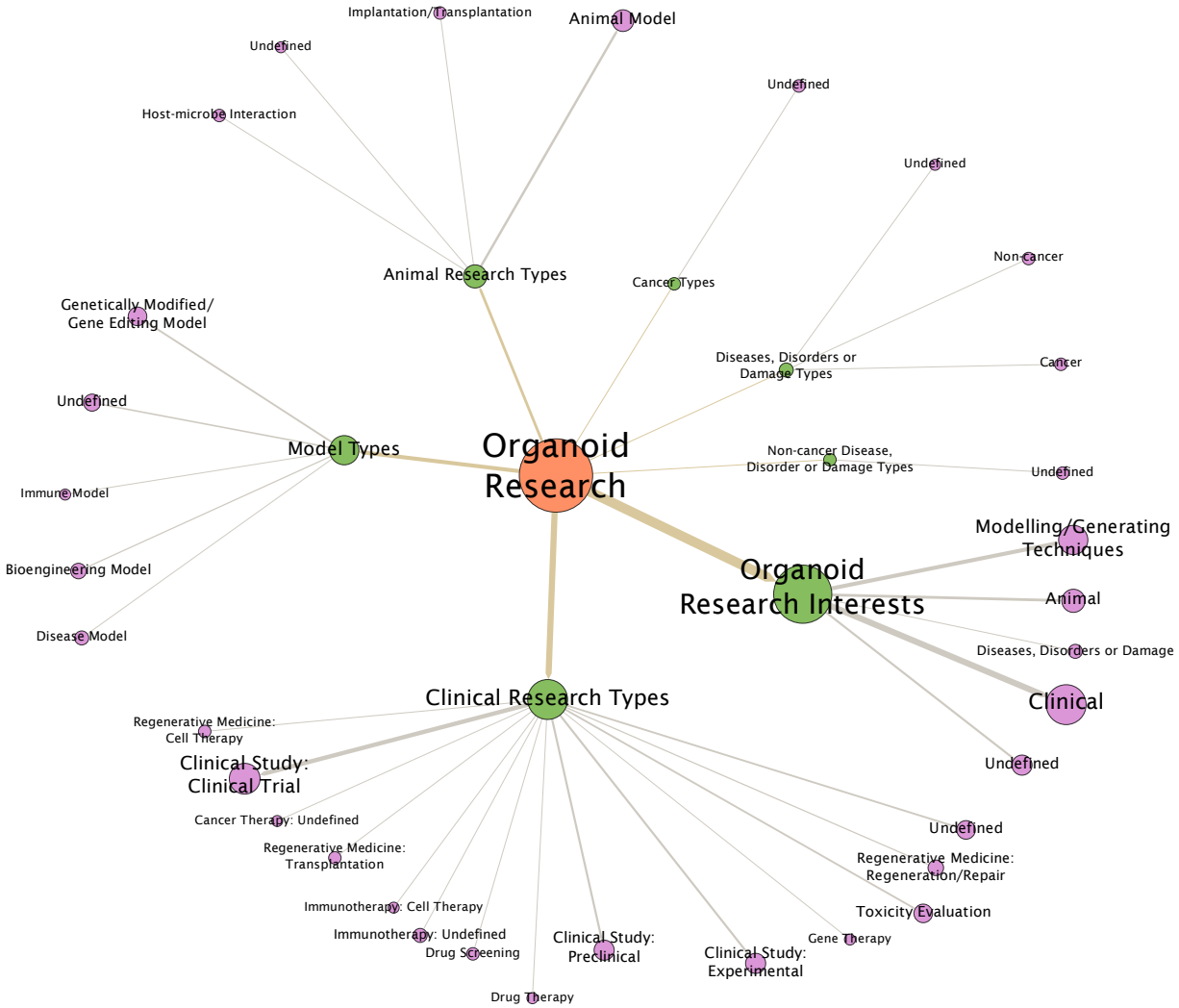

Figure 8: Graphic Representation of the Super Map (Organoid Research)

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4.3.6 *Organoid Use in Healthcare Findings: "Regulations Focus on Therapy, Medical Devices, and Medicinal Products"*

See Figure 9 for a graphic representation of this dimension of the Super Map.

1. Once again, it is worth acknowledging that given that most of the research involving organoids is still at the preclinical or experimental stage (see D2.1), the question of whether a regulation would extend to the clinical use of organoids and organoid-related technologies has been addressed by interpreting the general provisions, standards, and principles contained in the regulation. Acknowledging that, in some instances, regulations provide exceptions to these standards and requirements, if there is no reason to view the (planned or potential) clinical application of organoids as an exception, then the regulation, together with its relevant provisions, is taken to apply to organoid-based medical applications.

2. Of the 42 regulations contained in the Super Map, the majority ("Scope of Medical Application"; n=30; 71.4%) contain provisions, standards, and requirements for the medical application of research. Of these 30 regulations:

    a. 24 (80.0%) cover therapeutic applications
    b. 17 (56.7%) cover diagnostic applications
    c. 12 (40.0%) cover preventative applications
    d. 11 (36.7%) cover implantation applications
    e. 9 (30.0%) cover transplantation applications
    f. 1 (3.3%) covers prognostic applications

3. Of the 30 regulations covering the medical application of research, 20 (66.7%) contain provisions, standards, and/or requirements for medical devices ("Medical Device Types"). Of these 20, the most discussed devices are those intended for therapeutic (n=10; 50.0%) and/or implantation (n=8; 40.0%) applications. The next most common are devices intended for or associated with transplantation (n=6; 30.0%) or diagnostic (n=5; 25.0%) applications.

4. Of the 30 regulations covering the medical application of research, 18 (60.0%) mention medicinal products *and* medical devices ("Therapeutic Product/Device Types). Of these 18, 8 regulations (44.4%) contain provisions, standards, or requirements for medicinal products and medical devices *in general*, that is, without mentioning specific types of products/devices with specific characteristics, purposes, or functions. Aside from medicinal products/medical devices intended for or associated with gene therapy (n=6; 33.3%), all other types of device/product are, broadly speaking, mentioned in a similar number of regulations.

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5. Finally, of the 30 regulations covering the medical application of research, 12 (40.0%) explicitly mention, or contain provisions whose scope would, in principle, extend to, regenerative or personalized medicine applications. Precision medicine applications are not explicitly covered in any of the regulations contained in the Super Map.

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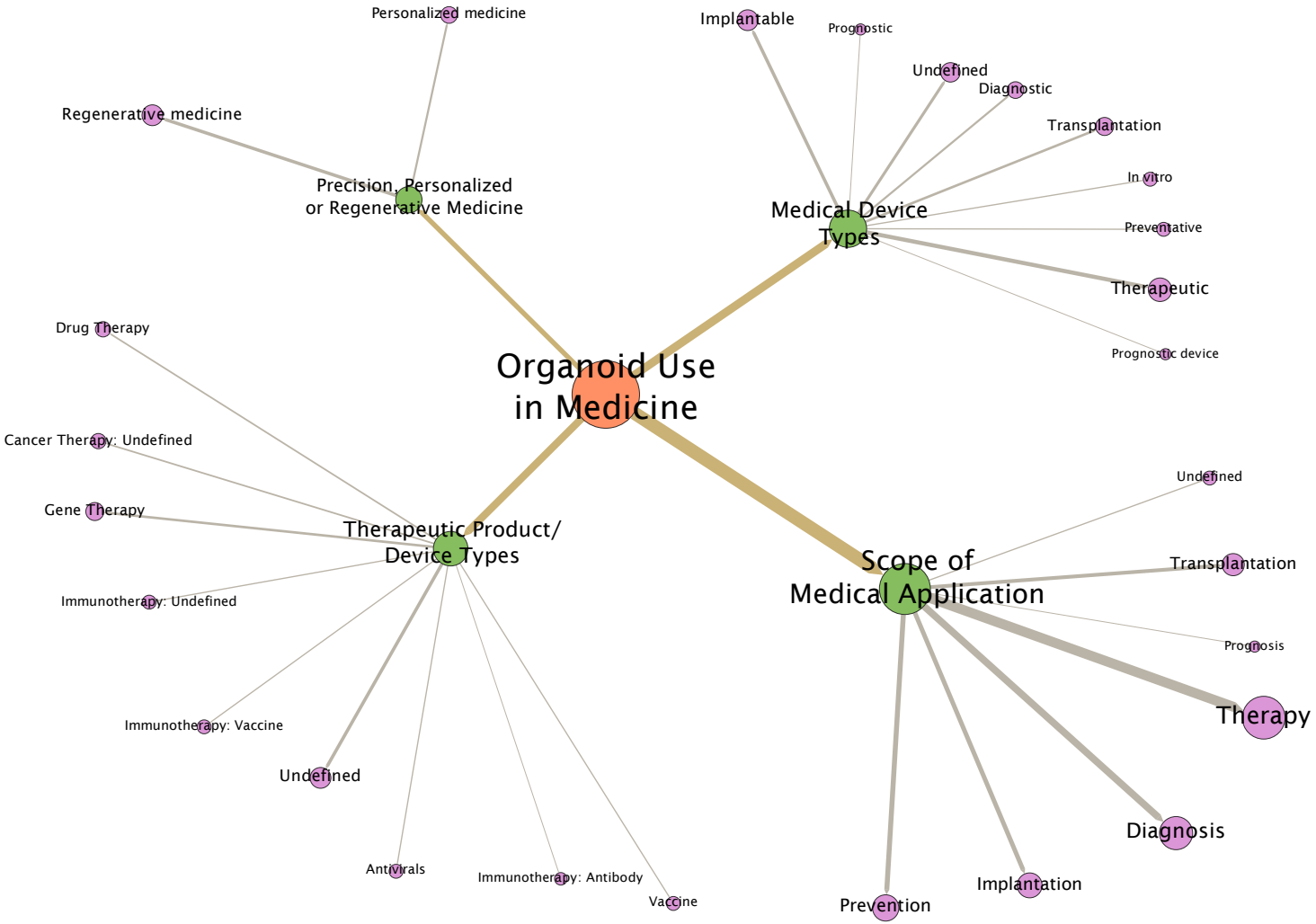

Figure 8: Graphic Representation of the Super Map (Organoid Use in Healthcare)

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5 Regulatory Gaps and Areas of Over-regulation

This section details the gaps in the regulations and areas of potential over-regulation with respect to specific organoid and organoid-related activities. These gaps and areas of over-regulation have been identified not only by analyzing the prevalence of certain organoid and organoid-related activities, topics, and categories within those regulations that have been mapped (see Table 2), but also, more importantly, through close-reading of the regulations.[21] We also identity and explain some of the ethical, legal, classificatory, and practical issues posed by certain organoid and organoid-related activities that highlight these regulatory issues/problems. To support our analysis of these issues, gaps, and areas of over-regulation, we refer to, and make use of critical discussions relating to EU case law together with empirical evidence and normative analyses in the academic literature.

Following the outline of Tasks 6.2-6.5 contained in the HYBRIDA Grant Agreement, the identified gaps and areas of over-regulation have been classified in terms of how they relate to the following four broad categories:

- Informed consent, data protection, donor rights, and user rights within the context of organoids
- Open Science ("OS"), including the issue of benefit sharing within the context of organoids
- Organoid research and use as a social/institutional practice, including organoid use in healthcare
- Other regulatory issues identified via the stakeholder engagement workshops conducted by WP4 (Task 4.1).

For an overview of these regulatory gaps and areas of over-regulation, see Section 2 and Table 1 (Executive Summary)

[21] In terms of the regulatory issues identified by stakeholders at a workshop in Copenhagen (June 2022), full details of participant selection, the views and attitudes expressed by the participants, the format, structure, and data-gathering processes, and the associated ethics assessment and approval can be found in D4.1 ("Protocol for WP4"), D4.2 ("Report on participant selection"), and D4.3 ("Report on the mini-public"). In this report, we do not directly quote individual participant views, identify individual participants or mention the capacities in which participants attended the workshop (beyond referring to some of those participants as "organoid researchers"). As a result, ethics approval was not required for this report

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5.1 Informed consent, data protection, donor rights, and user rights within the context of organoids

5.1.1 Informed Consent for Organoid Research: Regulatory Gaps

The UNESCO and United Nations Universal Declarations, several Council of Europe Conventions and Protocols and the EU's Charter of Fundamental Rights (see Table 2) detail the value and standards of informed consent. Directive 2004/23/EC (on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells) cover the standards for informed consent for the donation, procurement, and testing of human tissues and cells *intended for human applications, manufactured products, and medical devices*. This specific Directive does not cover the standards and processes for informed consent for research involving human tissues and cells (e.g., in in vitro settings or in animal models).

Given the limits of Directive 2004/23/EC, the principles and legal requirements for informed consent in terms of donation and use of donated biomaterials for research purposes have been drawn from the Clinical Trials Regulation (EU) 536/2014 (i.e., that consent must be obtained from participants before the research commences; that they have the right of withdrawal; and that all research must be reviewed by a research ethics committee prior to commencement). These legal standards reflect the longstanding international consensus expressed in the World Medical Association's Declaration of Helsinki first issued in 1964. These general standards have been applied to biobanking and organoid research that involves human tissue and cells. However, as WP2 have shown (D2.1, p. 46), although preclinical organoid research, which includes evaluation and optimization of organoid models for preclinical disease modeling as well as disease modeling using organoid models, is crucially dependent on donor- and patient-derived material, biobanking is rarely mentioned in the context of organoids, indicating the current lack of platforms for sharing biological material among researchers. Nevertheless, organoid research or future organoid biobanks dealing with donated human biological samples intended for research will be required to meet these general standards (European Commission - Directorate-General for Research and Innovation Science in Society, 2012, p. 36). Despite this, there are significant differences between preclinical organoid research and clinical trials (see D2.1, pp. 45-48). In terms of the provisions contained in Regulation (EU) 536/2014 (on clinical trials) relating to biological samples, they do not deal with the use of those samples for (organoid) research purposes.

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Directive 2004/23/EC and Regulation (EU) 536/2014 do not explicitly address standards or requirements of informed consent for the donation and use of human tissue and cells intended for research that does not involve a clinical trial (i.e., preclinical, experimental, in vitro or animal research). There is, thus, a degree of uncertainty about the legal requirements that apply to the use of cells and tissue for organoid research purposes. Relatedly, the lack of legally binding EU instruments covering the research use of human tissue has led to Member States adopting different domestic approaches (European Commission - Directorate-General for Research and Innovation Science in Society, 2012)

When it comes to an individual donating their cells and tissue for organoid research or medical applications, consent is the mechanism through which they articulate the boundaries for what they consider to be permissible use of their bodily material (Manson, 2019; Lewis and Holm, 2022). However, and as recognized by stakeholders at a WP4 workshop, one of the issues facing regulatory approaches to cell/tissue donation for organoid research or organoid-based medical applications is that an individual's consent to donate often cannot be fully informed because the very nature of biobanks is to collect samples for future research uses that may not yet be formulated and, most importantly, the risks of which are not known. Furthermore, in the case of organoid research and, more so, in future cases involving clinical trials and clinical application of organoids, there are significant epistemic limits to predicting how and in what ways a donor's cells and tissue will be used.

The risks to a donor and the nature of those risks, which, in these instances, are primarily concerned with personal data (European Commission - Directorate-General for Research and Innovation Science in Society, 2012, p. 36), are morally and legally relevant, but assessment of those risks requires specific knowledge about the ways in which biospecimens will be used in organoid research and clinical applications. If an understanding of what the research or translation involves and entails is necessary for consent in terms of determining risk, then consent—of a general and unspecified kind—to donation and subsequent use cannot be obtained (Hofmann, Solbakk and Holm, 2009, 13). In other words, if organoid researchers, biobanks, or those manufacturing clinical products or devices derived from organoids consider a donor's initial consent to extend to or entail specific uses unforeseen at the time of obtaining initial consent, then it cannot be assumed that the donor consents to those uses.

Given that this problem cannot be overcome simply by providing donors with information of current or anticipated future uses of their cells and tissue at the time of donation, **there is, in principle, reason for regulatory approaches to informed consent to specify and require blanket consent for all possible uses, very broad consent for all healthcare related uses, or more case-specific approaches to participant consent (including, for example, dynamic consent and meta-consent) for cells and tissue intended for organoid research and/or organoid-based clinical applications (see, e.g, European Commission - Directorate-General for Research and Innovation Science in Society, 2012, pp. 51-2, 57-8; Lewis and Holm, 2022). However, blanket and broad consent delineate types of material risk and benefit disclosure that fall below the appropriate standard for *genuinely* informed consent and also downplay donor autonomy to the extent that they limit downstream opportunities for donors to control which research projects and clinical applications can permissibly use their tissues, cells, and associated organoids (O'Neill, 2004; Hanson et al., 2006; Karlsen, Solbakk, and Holm, 2011; Sheehan, 2011; Lewis**

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and Holm, 2022). By contrast, critics have argued that case-specific consent, including dynamic consent and meta-consent, risks impeding the utility of research, for example, by creating delays, by diverting research resources to consent acquisition, and through the increased likelihood of donor unresponsiveness (Helgesson, 2012; Manson, 2019; Mikkelsen et al., 2019).

5.1.2 Normative Status of Organoids: Regulatory Gaps

Current regulation of donated cells and cell lines operate on the basis of biomaterial as "objective" material (Boers et al., 2018; 2019), that is, material that does not have *intrinsic* normative value yet possesses instrumental value such that it can be used in research and human applications.

In one sense, organoids seem to affirm this "object" paradigm. Although organoids are, in part, defined by their self-organising capacities (Lancaster and Knoblich, 2014), their development requires the manipulation of donated cells or tissues and considerable expertise, effort, and investment applied to those biospecimens (Boers et al., 2016; Bartfeld and Clevers, 2017). They are also instruments that serve scientific and, potentially, clinical purposes (Bartfeld and Clevers, 2017; Bredenoord, Clevers and Knoblich, 2017). In addition, patents on organoid-derivation processes, drug screening protocols, disease models, organs-on-chips, and organoid-based therapeutics have been taken out (see D2.1, section 10). Finally, if clinical translation proves to be successful, then organoid-based medicinal products and devices could become commercially available.[22]

At the same time, the relationship between a donor and organoids derived from their biospecimens can have moral value for functional, genetic, and meaning-based reasons (Boers et al., 2018; 2019; Lewis and Holm, 2022)

Firstly, as organoid researchers themselves have acknowledged, organoids relate to the bodily integrity of donors in the sense that they represent the (dys)functioning of the bodies of their donors (Lancaster and Knoblich, 2014).

[22] Some commentators have argued that if donated biomaterial is purely "objective", then it should be permissible to treat that material as a commodity that can be exchanged in the private domain (Erin and Harris, 2003; Wilkinson, 2011; Hoeyer, 2013). By contrast, current regulations operate on the principle that because donated cells and cell lines have been gifted, they should not give rise to financial gain (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, 1997, Article 21).

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Second, organoids relate to the personal identity of donors. For instance, given that sequencing techniques are routinely applied, organoid-based research is likely to reveal the donor's genetic make-up. This requires a lawful basis for data processing in addition to informed consent to research participation. Not only can genetic sequencing generate study-specific information about a donor's present medical conditions, but it can also uncover findings unrelated to the study question, such as a donor's risk of hereditary disease derived from the presence of certain genetic risk or protective factors (Boers et al., 2016; Bartfeld and Clevers, 2017).

Thirdly, the results from the analysis of donated cells and tissue and subsequent experimental and clinical research with organoids derived from those cells and tissue can shape and reshape the meanings and attitudes that donors attribute to their disorders. For that reason, organoids can be perceived to form both a literal and a symbolic representation of donors and their bodies (Boers et al., 2019; Lewis and Holm, 2022). Empirical studies have also shown that research participants perceive a value-based connection to their organoids and, more importantly, that the strength and qualitative nature of that connection depend on the type of organoid derived from their cells (e.g., stronger connections would likely exist for neural and gonadal organoids) (Boers et al., 2018; Bollinger et al., 2021; Lensink et al., 2021).

Given the current stage of organoid derivation and research, some donors may relate to organoids derived from their biospecimens only as tissue samples or living cell lines (Boers et al., 2016; Bredenoord, Clevers and Knoblich, 2017; Lewis and Holm, 2022). However, as empirical studies indicate, such relations are likely to become increasingly complicated and the boundary between organoid and body increasingly blurred when, as researchers anticipate, organoids become more mature and complex to the point that they develop into fully functioning organs or organ systems (Hyun, 2017; Boers et al., 2019).

Current regulations do not specifically address the normative (i.e., legal and moral) status of organoids. **However, as a matter of both principle and practice, organoids complicate the issue of what does and does not form part of a human body and call into the question their categorization as purely "objective" material over which those that have donated cells and tissue have severely limited moral or legal claims (Lewis and Holm, 2022).**

5.1.3 Donor Withdrawals: Regulatory Gaps

In response to the problems with obtaining genuine informed consent in organoid research contexts (see s.5.1.1), one may rightly point out that current regulations allow a donor, who does not wish for their cells and tissue to be used for specific organoid-related activities, to withdraw their samples and/or revoke their permission. **The issues are 1) that regulations guiding donor withdrawals only extend to cells and tissues (i.e., it is not clear that a cell donor's right to withdraw consent extends to the organoids that have been derived from their cells), and 2) that the 'right to withdraw' principally applies in the research context while cell lines and organoids derived from them may, over time, move into a clinical or commercial context.**

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This regulatory issue regarding withdrawal is based on an important distinction between having the right to withdraw the donated tissue, cells, or cell-lines from future use (Holm, 2006; 2011) and withdrawing a biotechnology that has been produced from the donated cells (Holm and Lewis, 2022).

As discussed in s.5.1.2, organoids possess, in part, the features of biotechnological artefacts, that is, "objective" material produced by researchers through specialized, technical processes (Parry and Gere, 2006). Organoids are not merely self-organizing entities that spontaneously arise from a collection of cells. They require manipulation of donated cells and tissues and substantial amounts of expertise, effort, and investment. Furthermore, many organoid-derivation processes, drug screening protocols, disease models, organs-on-chips, and organoid-based therapeutics will have been patented (see D2.1, section 10).

The fact that organoids are, in part, biotechnological artefacts undermines a donor's claim to exclusive control through a putative right to withdraw, Thus, in relation to organoids that have already been created from donated biomaterial, the donor's right to withdraw is either non-existent or it only applies when organoids are produced or used outside of the terms of consent (Holm and Lewis, 2022).

However, in light of the discussions concerning the normative status of organoids (s.5.1.2), were future laws and regulations to recognize the normative values that donors may attribute to mature organoids or complex assembloids derived from their cells and tissue, a donor's normative claims to their organoids may extend to a right to withdraw the biotechnological artefacts derived from their biospecimens and to some control over their future use (Holm 2006, Lewis and Holm, 2022). Nevertheless, organoid researchers have raised pragmatic concerns regarding the feasibility of organoid withdrawal (e.g., because of the level of monitoring compliance required, the logistics and costs involved in tracing samples, the capacity and resource demands associated with obtaining ongoing, case-specific donor consent, and the costs involved in destroying organoids and any organoid-based technologies). These questions regarding the ethics and practical feasibility of organoid withdrawal, as well as the question of when the right to withdrawal begins and ends, highlight a longstanding debate in bioethics regarding the tension between respecting donor autonomy and promoting scientific utility (see s.5.1.1). These questions and the regulatory implications for donation and organoid research will be discussed in greater detail in WP6's next report (D6.2).

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5.1.4 Sentient and Conscious Neural Organoids: Regulatory Gaps

In the academic literature, there has been much speculation concerning the possible sentience of cerebral organoids (i.e., their capacity for experiencing feelings such as pleasure and pain) as well as the possibility of cerebral organoids attaining consciousness. This has led to debates regarding the ethical permissibility of conducting research that may, intentionally or not, yield organoids with sensory, cognitive, and/or consciousness capacities (see, e.g., Farahany et al., 2018; Lavazza and Massimini, 2018; Sawai et al., 2019; Hyun, Scharf-Deering and Lunshof, 2020; Bollinger et al., 2021).

However, as noted by the International Society for Stem Cell Research (ISSCR) (2021) as well as organoid researchers attending the WP4 stakeholder workshop in Copenhagen, there is, at this stage, no reason to believe, or evidence to suggest that isolated neural cell organoids, brainstem, hindbrain, and choroid plexus organoids, or forebrain organoids (i.e., those neural organoids that have currently been established – see D2.1, p. 25) resemble a fully functioning brain or integrated parts of the brain. Therefore, there is no reason to believe that such organoids are sentient or will achieve a level of consciousness that warrants special ethical or legal concern.

Nevertheless, the ISSCR claims that biobanks and organoid researchers should be cognizant about the ethical issues that donors and other stakeholders may have regarding research into pleonastic organoids, particularly as they become more complex through long-term maturation (ISSCR, 2021, p. 10). Indeed, there is a major push to overcome certain limitations (e.g., the problems of oxygen and nutrient diffusion, the absence of a peripheral nervous system, and the problems of modelling interactions between different parts of the brain and understanding the neural activity of cerebral organoids) in order to generate next-generation human cerebral organoids with greater degrees of complexity and maturity (Chen et al., 2019).

In principle, as certain cerebral organoids mature and become more complex when combined with other organoids in complex neural assembloids, regulatory questions regarding ownership and normative status may arise. Organoid researchers have stated that these questions would also arise for gonadal organoids that are being cultured as assembloids as well as for organoid-derived human gametes.

In anticipation of such questions, there are extant normative considerations and principles we can adopt to shed light on the potential regulatory implications regarding the ownership and normative status of such entities. The ownership issue turns on whether a cerebral organoid/assembloid or chimeric animal transplanted with a cerebral organoid/assembloid passes the threshold for consciousness that would grant it full moral status or something approaching full moral status (for further details, see Holm and Lewis, 2022). In terms of ownership, the law currently recognizes one type of natural person only (i.e., the human being). And it is a living human being that holds full moral and, thus, legal status (though many have argued that full moral and legal status should be attributed or given to animals that have human-like

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consciousness, including self-consciousness). If an organoid were to pass the consciousness threshold for full moral status, then, in principle, it should be granted full legal status and should, therefore, not be owned (ibid.). By implication, any entity derived from organoids that fell below this consciousness threshold to an adequate, legally determined degree could still be owned. The question of who, as a matter of legal principle, would own such an entity will be addressed in WP6's next report (D6.2).

5.1.5 Information Derived from the Analysis of Donated Cells: Over-regulation

Related to the issues concerning the normative status of organoids, **there seems to be a potentially problematic interaction between the regulation of donated cells and cell lines and the regulatory frameworks governing information derived from the analysis of that material**.

As already discussed in s.5.1.1, the European Union's existing regulatory framework for biomedical research does not contain specific legally binding instruments for organoid research using human cells and tissue or for biobank-based research in general. In spite of this, the principles contained in the EU/EC's clinical trials and data protection laws provide the main standards and procedural rules for "best practice" when it comes to the protection of those participating in biobank- and organoid-based research.

Nevertheless, there are normative tensions between the Clinical Trials Regulation (EU) 536/2014 and the GDPR (EU) 2016/679 (on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC). Once tissues and cells have been donated, preclinical organoid research does not necessitate any additional direct physical intervention with donors. Unlike most clinical trials, the risks inherent in the use of the donated biomaterial for research purposes are not directly related to the donor's body, but, instead, are primarily concerned with personal data (European Commission - Directorate-General for Research and Innovation Science in society, 2012, p. 36). One of the issues here is that although the GDPR contains enough flexibility to allow for the processing of personal data, including sensitive data, for research purposes (so long as appropriate safeguards are in place), research is considered exempt from two of the fair processing principles (i.e., i) data can be kept for a longer than the original purpose; and ii) if the provision of information about secondary research purposes proves impossible, or would involve a disproportionate effort, then information about the processing does not need to be given to research participants) (ibid., pp. 37-38). **In relation to these two exemptions, concerns have been raised about the disclosure of processing information related to secondary research and the increasing risks of indirect data disclosure over time** (ibid., pp. 36-7, 52). Once again, as we observed in s.5.1.1 and s.5.1.3, this highlights a tension between the requirement to protect and support research participants—in this instance, through appropriate data protection, processing, and disclosure principles—and the need to safeguard and promote scientific research (ibid., p. 38).

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A specific problem of potential over-regulation, which complicates the exchange of cells and organoids between research institutions, is that such an exchange is an exchange of research-intended donated biomaterials predominantly governed by individual Member State laws (with standards of best practice drawn from the Clinical Trials Regulation (EU) 536/2014), and, simultaneously, an (implicit) exchange of personal information about the cell or tissue donor's genetics governed by a different set of regulations (i.e., the GDPR (EU) 2016/679). This dual nature and regulation of the exchange significantly complicates such exchanges in practice, especially exchanges between institutions where only one of the institutions is located in the EU/EEA.

As noted in s.5.1.2, given that sequencing techniques are applied in organoid research, studies can generate both study-specific information and incidental findings relating to a donor's present medical conditions and disease risks (Boers et al., 2016; Bartfeld and Clevers, 2017). By linking these biospecimen findings to a donor's health, genetic, and digital data, both study-specific and incidental information could not only impact on a donor's personal care in terms of diagnosis, prognosis, and/or treatment (Saini, 2016; Kraft et al., 2018), but also motivate prevention measures and lifestyle changes, benefit family members, and inform life planning and reproductive decisions (Burke et al., 2018; Lewis and Holm, 2022).

In addition, in the case of chronic and genetic diseases, it is in the interests of research to facilitate a two-way exchange of information, that is, from researchers to donors *and* from donors to researchers (European Commission - Directorate-General for Research and Innovation Science in society, 2012, p. 53). The point is that in order to increase the value of the donated sample and to allow for more valid and reliable correlations to be drawn between the results of research and specific disease features, clinically relevant data associated with each sample should be regularly updated. However, given the tension between the data protection, processing, and disclosure principles and the standards of biomedical research involving human tissue and cells, **there are two interrelated regulatory concerns regarding the exchange of information between researchers and participants**.

Firstly, the reporting of organoid research results challenges the existing regulatory framework that makes a distinction between the obligations of clinicians and those of researchers. As noted by a European Commission expert group, "in research projects there is no [legally binding] responsibility to return results to individuals whereas this is the main concern of a clinician" (European Commission - Directorate-General for Research and Innovation Science in society, 2012, p. 52-3). However, although the case according to EU law, this is contradicted by Council of Europe regulation.

Secondly, although not enforced via specific legal instruments at the EU/EC level, current expert consensus favours disclosing only the medically actionable findings of research to donors. Again, this is contradicted by Council of Europe law, which requires the disclosure of findings even if they are not actionable. Secondly, disclosing only the medically actionable findings is ethically problematic given that, as we observed above, there may be health-related and clinically relevant incidental findings from research using human biomaterial that, nevertheless, are not perceived to be medically actionable (Ploug and Holm, 2017).

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5.2 Open Science ("OS"), including the issue of benefit sharing within the context of organoids

5.2.1 Material Transfer Agreements (MTAs)

Material Transfer Agreements (MTAs) are a core underpinning mechanism for benefit sharing within biomedical research. An MTA is a legal contract governing the transfer of materials and any associated data between two parties. It defines the rights of the provider and the recipient with respect to the materials, derivatives, and associated data, including, in the case of biological samples, metadata, anonymized data, the clinical state of the donor, and other personal information. An MTA also defines the terms of use of the materials and any associated data processing obligations.

MTAs are required: for the export or international movement of samples and associated data; for domestic movement of samples and associated data to a separate legal entity (or, in some cases, to different parts of the same legal entity); and by larger overarching agreements, such as research protocols or bilateral agreements.

For organoid research, MTAs include the transfer of tissue, cells, cell lines, and derivatives of those materials, such as organoids, organoid-based medicinal products, and medical devices. Given that organoid-based research is based on donated human tissue and cells, including tissues and cells stored in biobanks, the transfer of organoids and the materials from which they are derived will likely include data relating to the donor of the sample. Such "Material Associated Data" extends to identification of the sample's content and pre-analytical information (e.g., name of study, owner of the study, unique identifier, sampling date, type of sample, sample volume, storage temperature). Such information may take the form of anonymized or personal data.

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5.2.1.1 Over-regulation[23]

The process of drafting and agreeing an MTA between two parties based in different jurisdictions (e.g., different research institutions or biobanks) is complex, due to legal differences in states' domestic laws and the fact that domestic laws may or may not appeal to other international laws and regulations.

Applicable national laws may be contract law, data protection law, intellectual property law, rules regarding conflicts of laws, national security law, biosafety law, national access and benefit-sharing measures, and/or regulations governing the processing, preservation, storage, and distribution of human tissues and cells (and any laws governing associated data). Applicable international laws could be instruments such as the International Health Regulations (2005) (e.g., Articles 6 and 46), the Convention on Biological Diversity (Article 15) on access to genetic resources, or the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity. Different parties may also be required to abide by international normative documents, such as the UN Recommendations of the Transport of Dangerous Goods or the WMA Helsinki Declaration.

At the WP4 stakeholder workshop in Copenhagen, organoid researchers raised concerns regarding this lack of regulatory harmonization. They reported that not only did the differences between domestic laws and the complex relationships between international and national laws generate legal uncertainty, but also institutional legal teams interpret the terms of the MTA differently, leading to significant delays in execution.

When Material Associated Data is to be transferred outside of the EEA, there is also a concern that the data-related clauses of an MTA place significant obligations on recipient parties, given that third-country data importers are required to ensure a GDPR-equivalent level of protection for personal data.

5.2.1.2 Regulatory Gaps

In terms of material transfers that include associated personal data to be processed on transfer, the MTA must be drafted and agreed in consideration of the GDPR (EU) 2016/679.

[23] By classifying this issue as an instance of "over-regulation", we do not suggest that there is "too much" regulation at the EU level such that the EU/EC's own requirements and standards for MTAs are legally unclear, generate legal uncertainty, or lead to contradictions. Indeed, there are no specific EU/EC legal instruments that cover the transfer of material. Rather, because material transfers are legislated domestically, we refer to this as an instance of "over-regulation" in the sense that the regulation of MTAs is not harmonized across Member States.

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To facilitate the transfer of personal data to countries outside of the EEA, the European Commission has enacted its powers under Article 46(2)(a) of the GDPR and adopted its Implementing Decision (EU) 2021/914. This provides standard contractual clauses for data controllers and processors to ensure that personal data transfers out of the EEA are appropriately safeguarded. These clauses are meant to ensure that personal data transferred to third countries receive a level of protection equivalent to that provided by the GDPR (as stipulated by the European Court of Justice in the *Schrems II* judgment).

For Material Associated Data transfers outside of the EEA, these standard contractual clauses are, currently, the most accessible and cost-effective means—of those available under the GDPR—to transfer personal data to third countries. Executing and applying the new clauses allow institutions and organizations to transfer personal data to third countries without the direct and immediate intervention of, or notification to, an EU supervisory authority.

Although these clauses cover data associated with any material under the MTA, there are no standard clauses produced by the European Commission that cover the material component of the MTA (because material transfers are legislated domestically). Given the generally recognized value of these standard contractual clauses for those seeking to transfer Material Associated Data, organoid researchers at the WP4 stakeholder workshop in Copenhagen stated that it would be useful to have MTA templates and standard clauses for human embryonic stem cells, induced pluripotent stem cells, and organoids.

5.2.2 Patentability of Organoids: Over-regulation

In 1999, Oliver Brüstle was granted a patent for the generation and therapeutic use of neural cells derived from human embryonic stem cells (hESCs). The patent was challenged and put before the European Court of Justice (CJEU), which ruled that inventions involving the prior destruction of human embryos cannot be patented.

Subsequently, in 2014, the Technion Research and Development Foundation applied to obtain a European patent on a cell culture comprising both human foreskin cells and hESCs as well as on methods of maintaining hESCs in an undifferentiated state. Technion appealed the European Patent Office's (EPO) decision to refuse the patent. The Technical Board of Appeal of the EPO maintained the patent's refusal on the basis that establishment of cells lines necessarily involved the prior destruction of human embryos.

The exclusion from patentability of hESC lines that have been obtained through the destruction of human embryos is now a legal certainty in Europe, having been based on two distinct legal frameworks—those of the CJEU and the EPO (Mahalatchimy et al., 2015). Such an exclusion also extends to: i) derivative products and technologies if their development requires prior destruction of human embryos; and ii) processes that require base material obtained by the destruction of human embryos (Nielen, de Vries and

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Geijsen, 2013). This is particularly important given that hESCs are employed in the design of experimental models for the development and testing of new medicinal products and devices.

Where organoid research and the clinical application of organoid and organoid-related technologies are specifically concerned, the legal maneuvering around these cases also demonstrates that the future of stem cell-based patents in Europe is unsettled. Specifically, novel technologies, products, and processes that could eliminate the use of hESCs, such as induced pluripotent stem cells (iPSCs) and organoid derivation processes, are at risk of being included under the CJEU/EPO's non-patentability rulings (Nielen, de Vries and Geijsen, 2013; Mahalatchimy et al., 2015).

Given the definitions and precedents set by the CJEU and the EPO, the most pertinent questions facing organoid researchers and manufacturers of medicinal products and devices in Europe are: i) "how far removed from embryo destruction a derived product/technology must be in order to be patentable?"; and ii) "is the product/technology or the base materials from which it is derived capable of commencing the development of a human being?"

In reaching its decision in *Brüstle*, the CJEU applied a broad definition of a human embryo as an entity that is "capable of commencing the development of a human being", and, by implication, a hESC as "any cell that is capable of commencing development into a human being". iPSCs are functionally indistinguishable from hESCs (Lancaster and Knoblich, 2014), but do not carry the same moral burden since they are derived from somatic cells of consenting donors rather than from pre-implantation embryos.

However, iPSCs offer a convenient starting cell line for differentiation protocols for most cell lineages, meaning that, in principle, iPSCs could be developed into any type of human organoid and thereby any type of tissue or organ in the human body. Given the right conditions for maturation and complexity, iPSCs may, in the future, provide a direct developmental path to oocyte- and sperm-generating organoids and, from there, to functioning human gametes. Depending on the scope of the CJEU's definition of human embryo, this may generate the same legal implications for iPSCs and gonadal organoids as for hESCs (Mahalatchimy et al., 2015). That said, in a further judgement on 18 December 2014 concerning a patent application from International Stem Cell Corporation, the CJEU stated that parthenotes, developed from unfertilized ova that have entered a process similar to embryonic development due to chemical or electrical activation, are not human embryos, as they do not possess the inherent capacity of developing into a human being. This judgment may call into question the potential non-patentability of organoid-derived human gametes. But this is a single judgment regarding a specific (non-organoid) parthenote derivative, so it is unclear whether it would extend to iPSC lines intended for organoid production, oocyte- and sperm-generating organoids, and/or functioning human gametes.

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Perhaps more pressing and legally pertinent where the question of patentability is concerned are technologies incorporating, and processes that seek to derive and develop blastoids and gastruloids, which are cultured from pluripotent stem cells and which recapitulate the organization, and early stages of development of pre- and post-implantation embryos, respectively (Pera et al., 2015; Munsie, Hyun and Sugarman, 2017; Hyun, Munsie et al., 2020; Piotrowska, 2020; Bollinger et al., 2021; Niemann and Seamark, 2021). Again, depending on the scope of the CJEU's definition of a human embryo, blastoids and gastruloids may be deemed to be "capable of commencing the development of a human being" (for the biological, technical and normative complexities around this see, for instance Denker, 2006; Holm, 2008).

For these reasons, it is unclear whether (some) iPSCs, gastruloids, blastoids, and/or gonadal organoids would fall under the same non-patentability restrictions as hESCs.

Another cause for concern for European researchers and pharmaceutical companies relates to the fact that, as demonstrated by WP2 in D2.1 (pp. 63-67), a disproportionate number of existing patents on organoid-based inventions are based in the USA and Asia. This may be associated with the legal uncertainty surrounding the patentability of pluripotent stem cell, iPSC-based, and organoid products, technologies, and derivation processes in Europe. Although the patent situation may not affect academic research in Europe directly (since academic research is not primarily concerned with generating patents), the restrictions on stem cell patents in Europe may motivate the pharmaceutical industry to prefer collaborations with academic partners in the USA and Asia. Furthermore, without patent protection, companies may be less willing to invest in the production of stem-cell- and organoid-based medicinal products and devices. Importantly, hospitals, in and of themselves, do not usually have access to the technologies, infrastructure, and expertise needed to produce a complex stem-cell- or organoid-based products for medical purposes.

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5.3 Organoid research and use as a social/institutional practice, including organoid use in healthcare

5.3.1 Classifying Organoid-based Technologies for Medical Use

At the EU level, products and devices for medical use are covered by several different regulations. Depending on how and when these technologies are/were classified, they can fall under one or more of the following:

- Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use
- Directive 2001/83/EC on the Community code relating to medicinal products for human use
- Regulation (EC) 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
  Regulation (EC) 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004
- Regulation (EC) 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) 726/2004
- Regulation (EC) 141/2000 on orphan medicinal products
- Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- Regulation (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Directives 90/385/EEC and 93/42/EEC
- Directive 93/42/EEC concerning medical devices (repealed by Regulation (EU) 2017/745)
- Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices (repealed by Regulation (EU) 2017/745)
- Regulation (EU) 2017/746 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
- Directive 98/79/EC on in vitro diagnostic medical devices (repealed by Regulation (EU) 2017/746)

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- Regulation (EU) No 722/2012 concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin
- Directive 2009/41/EC on the contained use of genetically modified micro-organisms

The following sub-sections explore the areas of over-regulation, the regulatory gaps, and the resulting regulatory issues and uncertainties that arise depending on how clinically translated organoids and organoid-related technologies are classified and which of these regulations they fall under.

5.3.1.1 Over-regulation

Given the nature and structure of, and developmental processes leading to organoids, some (perhaps most) clinically applicable organoid-based technologies will be classed as an Advanced Therapy Medicinal Product (ATMP) and thereby fall under Regulation (EC) 1394/2007. There is, then, the question of whether the organoid technology is a "Tissue Engineered Product" (TEP), a "Gene Therapy Medicinal Product (GTMP), a "Somatic Cell Therapy Medicinal Product" (SCTMP), or a "Combined Advanced Therapy Medicinal Product".

According to Article 2(1)(b) of Regulation (EC) 1394/2007, a TEP is presented as having properties for, is used in, or administered to human patients with a view to regenerating, repairing, or replacing a human tissue. A TEP may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, biomolecules, biomaterials, chemical substances, scaffolds, or matrices.

To be considered as a TEP, a product must contain cells or tissues that either i) have been subject to substantial manipulation, so that biological characteristics, physiological functions, or structural properties relevant for the intended regeneration, repair, or replacement are achieved; or ii) are not intended to be used for the same essential function or functions in the recipient as in the donor.

By contrast, according to Part IV of Annex I to Directive 2001/83/EC on the Community code relating to medicinal products for human use (as amended), a SCTMP must meet either i) or ii) for TEPs above *and* have the properties for, is used in, or administered to human beings with a view to treating, preventing, or diagnosing a disease through the pharmacological, immunological, or metabolic action of its cells or tissues. An organoid product achieving a therapeutic effect through functional integration and not by pharmacological, immunological, or metabolic action will, thus, *prima facie* not be classifiable as a SCTMP.

According to Article 2(5) of Regulation (EC) 1394/2007, a TEP or SCTMP can also be classified as a Gene Therapy Medicinal Product (GTMP) (see Part IV of Annex I to Directive 2001/83/EC, as amended), which contains recombinant nucleic acid(s) that should be directly involved in the mechanism of action as it relates to a therapeutic, prophylactic, or diagnostic effect. Alternatively, a TEP or SCTMP may employ genetically modified cells as part of the manufacturing process (e.g., to generate iPSCs that are later differentiated into organoids and subsequent SCTMPs or TEPs).

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According to the European Medicines Agency (EMA) (2014), because of the heterogenous character of ATMPs (i.e., in terms of the origin and nature of the starting material as well as the unique influences their therapeutic indication has on the risk profile), **there are concerns regarding the level of regulatory scrutiny, the burdens placed on applicants regarding the clinical testing of ATMPs, and the problems applicants may face in evidencing how they have met regulatory standards for marketing authorization**. For instance, although comparisons with similar ATMPS are possible, applicants under Regulation (EC) 1394/2007 may be required to develop/improve and validate new analytical test methods in order to investigate risks and therapeutic effects unique to a given ATMP. In addition, if an organoid-based product fulfils the criteria for an ATMP and, simultaneously, incorporates one or more medical devices as integral parts of the final product to produce a "Combined Advanced Therapy Medicinal Product" (see Article 2(1)(d) of Regulation (EC) 1394/2007), then, in the context of marketing authorization, the device part should also comply with the general safety and performance requirements laid down in Regulation (EU) 2017/745 on medical devices. Similarly, for ATMPs containing, or developed from genetically modified cells, applicants must fulfil not only the standards set in Regulation (EC) 1394/2007, but also the principles of "Good Medical Practice" and the scientific recommendations provided by the EMA.[24]

The success of applications for a new ATMP will turn on the applicant's ability to successfully characterize all the components present in the finished product, including single components (cellular and non-cellular), the combined product, and any changes to the characteristics of both the single and combined components because of the integration. **The EMA (2008) recognizes that characterization will prove particularly challenging for new products containing cells, substances, matrices, scaffolds, and medical devices. Adequate regulatory characterization is also challenged by complex interactions within an ATMP, ranging from biochemical, metabolic, or immunological actions, which are difficult to pinpoint and depend more on the functionality of the cellular components (see the next sub-section for further details), to the structural replacement of damaged tissue or (parts of) organs (ibid.).**

Ultimately, for those seeking to make an application under Regulation (EC) 1394/2007 (on ATMPs), the process for correctly categorizing and providing the required evidence for a new organoid-based medicinal product is subject to substantial regulatory requirements and, simultaneously, lacking in official EU/EC guidance. As a result, and given that organoid research is still very much at the preclinical stage (see D2.1, pp. 45-48), there is likely to be uncertainty among those anticipating making an application as to the type of ATMP under which their planned organoid-based product falls, or, indeed, whether their planned product satisfies the requirements for an ATMP.[25]

[24] Specifically, the issue here, as the EMA (2020) acknowledges, is that the early steps of deriving genetically modified cells may be affected by the availability of cell material, which, in turn, may make it difficult for an applicant to adequately qualify how they have fulfilled these standards.

[25] Further to the implementation of Article 17 (Regulation (EC) 1394/2007), potential applicants have the opportunity to obtain the scientific recommendation of the Committee for Advanced Therapies for the classification of ATMPs.

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5.3.1.2 Regulatory Gaps

The EU/EC regulatory landscape with regards to medicinal products and medical devices is complex. A number of Directives and Regulations pertain to different types of medicinal products and medical devices. **For those seeking to make an application for authorization and market approval of their technology, it can be difficult to determine the category under which the product falls and thereby which legal instruments apply**. **Traversing the regulatory terrain will likely be especially burdensome for those developing or manufacturing organoid-based medical applications given the lack of clarity relating to certain legally binding definitions, the fact that organoid research is still firmly at the preclinical stage (see D2.1), no precedents have been set in terms of the classification of organoid-based medical products or devices, and even the most recent guidelines developed by competent authorities at the EU level do not mention organoids (see, e.g., Medical Device Coordination Group, 2022).**

Directive 93/42/EEC concerning medical devices, which was subsequently, repealed by Regulation (EU) 2017/745, established the criteria for the classification of a medical device.[26]

According to this Directive, a medical device means any instrument, apparatus, appliance, material, or other article (including custom-made devices and devices for clinical investigations) to be used, whether alone or in combination, on human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment, or alleviation of disease
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap
- investigation, replacement, or modification of the anatomy or of a physiological process
- control of conception

Importantly, to be classed as a medical device, it should not contain, incorporate, or be derived from *viable* tissues or cells of human or animal origin, or consist of viable biological materials or other viable organisms, including living micro-organisms, bacteria, fungi, or viruses.

In addition, the device must not achieve its *principal* mode of action in or on the human body by pharmacological, immunological, or metabolic means, but may be assisted in its function by such means.

[26] *Active implantable devices* fell under Directive 90/385/EEC before it was repealed by Regulation (EU) 2017/745. An "active implantable device" means any medical device which: i) depends on a source of energy other than that generated by the human body or gravity for operation; and ii) is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure.
Regulation (EU) 2017/745 does not extend to *in vitro diagnostic medical devices*, which are covered by Regulation (EU) 2017/746. These are classed as tests that provide information on the predisposition to a medical condition or a disease, such as genetic tests, and tests that provide information to predict treatment response or reactions, such as companion diagnostics. (Note: this definition does not include devices that are used to monitor treatment with a medicinal product).

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This leads us to the question of the correct regulatory classification of medical devices that, when placed on the market or put into service, incorporate, as an integral part, *non-viable* tissues or cells of human origin or a *substance* (see definition in Article 1(3) of Directive 2001/83/EC), which, if used separately, would be classed as a *medicinal product*.

If a device achieves its *principal* mode of action through pharmacological, immunological, or metabolic means, then, regardless of the cells, tissues or substances it contains or from which it is derived, it will would fall under Regulation (EC) 1394/2007 (on ATMPs), the medicinal product Directives 2001/83/EC and 2004/27/EC, or Regulation (EC) 726/2004 (laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency)—note that the general safety and performance characteristics of the device part would still be governed by Regulation (EU) 2017/745.[27] However, if the non-viable cells, tissues, or substance have an action *ancillary* to that of the device, then the device shall be assessed and authorized in accordance with Regulation (EU) 2017/745.

Relatedly, if a device incorporates *viable* human or animal cells or tissues or *viable* products derived from animal or human cells or tissue, then, regardless of whether the mode of action of these cells, tissues, or products is principal or ancillary, it will fall under Regulation (EC) 1394/2007 (on ATMPs) or Directives 2001/83/EC and 2004/27/EC (on medicinal products).[28]

As this sub-section demonstrates, understanding the distinction between the definitions of medical devices and medicinal products is essential for interpretating and enforcing both sets of legislation. But, as the Medical Device Coordination Group (MDCG) (2022)—composed of competent authority representatives from Member States and chaired by the EU Commission—has recently acknowledged, this task is likely to be especially difficult for borderline cases (i.e., where it is not clear whether a technology falls under the medical device regulations or the medicinal products directive/regulations) as well as for combination technologies that incorporate elements of both medicinal products and medical devices.

[27] For an integral product to fall under Regulation (EC) 726/2004, rather than Directives 2001/83/EC and 2004/27/EC, it must contain an entirely new active substance (i.e., one that has not yet been authorized in the Community) and for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes, auto-immune diseases, other immune dysfunctions, and viral diseases. Alternatively, the applicant must show that the medicinal product constitutes a *significant therapeutic, scientific, or technical innovation* or that the granting of authorization in accordance with Regulation (EC) 726/2004 is in the interests of patients or animal health at Community level.

[28] If a device incorporates *non-viable animal* tissue or *non-viable* products derived from animal tissue, then it falls under Regulation (EU) No 722/2012 (concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin).

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In response to this issue, the MDCG endorsed a new set of guidelines in April 2022. However, these guidelines do not mention organoid-based products or devices. Furthermore, as with all MDCG guidance, it cannot be regarded either as reflecting the official position of the European Commission or as being legally binding. As we shall now demonstrate, this can generate uncertainty for those seeking to make an application for authorization and market approval of their new product or device.

The MDCG (2022, p. 4) acknowledges that there is a degree of overlap in the respective definitions of a medicinal product and a medical device. For instance, one of the two defining characteristics of a medicinal product is that it is "any substance or combination of substances *presented as having properties for treating or preventing disease in human beings*". In terms of medical devices, the definition includes those materials that are *intended by the manufacturer to be used for "diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease*". For a technology that is employed to treat or prevent disease, much, therefore, turns on the respective meanings of "presented as having properties for" and "intended by the manufacturer to be used for". Unfortunately, further specifications are not provided either in the medical device regulations/medicinal products directives/regulations or by the MDCG.

Therefore, the distinction between medicinal products and medical devices, ultimately, turns on whether the technology incorporates *viable* human/animal cells, tissues, or products or whether it has a mode of action that is achieved by pharmacological, immunological, or metabolic and whether that mode of action is principal or ancillary.

Concerns have been raised about the lack of specification regarding the meanings of "pharmacological", "immunological", and "metabolic" in the relevant directives and regulations as well as in relation to the ambiguity between "mode of action" and the connected reaction or effect (Racchi et al., 2016). After all, in terms of the latter, the body always responds with pharmacological, immunological, or metabolic means even to stimuli that are non-pharmacological.

It seems that the MDCG is aware of these concerns. Within the new guidance (MDCG, 2022, pp. 7-8), the MDCG has provided updated definitions of pharmacological, immunological, or metabolic means. Again, however, these definitions are neither legally binding nor officially endorsed by the European Commission. In addition, it is yet to be seen whether these definitions adequately resolve the issues that have been previously raised, particularly regarding future organoid-based products and devices.

Notwithstanding, given the mode of action requirements for ATMPs (including combined ATMPs that, by definition, integrate one or more medical devices) and the different regulatory specifications relating to the mode of action for different types of ATMP (i.e., pharmacological, immunological, or metabolic for SCTMPs vs. regeneration, repair, or replacement of human tissue for TEPs), the question remains about the correct classification of combination products/devices that achieve their effect primarily through functional integration.

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Furthermore, despite the revised definitions of "pharmacological", "immunological", and "metabolic", there may still be legal uncertainty for those seeking to make an application for authorization and market approval of a device that incorporates non-viable cells, tissues, or substances that have a pharmacological, immunological, or metabolic action *ancillary* to that of the device. Under Regulation (EU) 2017/745 on medical devices, these would be classified as Class III medical devices, and must be assessed on a case-by-case basis to consider the device's composition, the amount of substance, and the device's intended use. Importantly, the applicant/manufacturer must be able to justify their product's qualification, and show, based on state-of-the-art scientific data, that the substance's mode of action is, in fact, ancillary.

Relatedly, even for devices incorporating a medicinal product that does not have either a principal or ancillary mode of action, the applicant/manufacturer must also employ state-of-the-art data to show that the substance has no action on the human body, that the substance cannot leak into the body, and that the amount is such that it does not have any effect on the patient.

5.3.2 Organoids and the Regulation of In Vitro Embryonic Research

As discussed in s. 5.2.2, the CJEU's and EOP's rulings regarding the non-patentability of hESC lines, hESC-derived products, and research processes based on material obtained through the destruction of human embryos have contributed to a climate of legal uncertainty regarding European patents for (some) iPSC lines, organoids derived from iPSCs, organoids that recapitulate embryogenesis, and functioning gonadal organoids. The reason for this uncertainty is not primarily due to whether materials or processes have involved the destruction of human embryos, but, given the CJEU's definition of a hESC in *Brüstle* as "any cell that is capable of commencing development into a human being", whether research processes make use of, or generate entities that are "capable of commencing the development of a human being".

As the legal instrument for establishing the EU's most recent Framework Programme for Research and Innovation (Horizon Europe), Regulation (EU) 2021/695 explicitly excludes from funding eligibility:

- research activities aiming at human cloning for reproductive purposes
- research activities intended to modify the genetic heritage of human beings which could make such changes heritable
- research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer

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These decisions are broadly in line with international and more general multi-national regulations, including:

- UN Declaration on Human Cloning (2005)
- Council of Europe 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 ("Oviedo")
- Council of Europe Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings
- EU Charter of Fundamental Rights (2007)

However, certain activities that are excluded from the EU's Framework, notably, those involving the creation of human embryos for research purposes (within defined boundaries), are permitted by national laws within several jurisdictions in the EEA, including Belgium, Spain, Netherlands, and Denmark.

In its Statements on Regulation (EU) 2021/695 (2021/C 185/01), the European Parliament, Council, and Commission state that the EC will continue not to fund research activities which destroy human embryos, including for the procurement of stem cells.

All other research activities involving the use of hESCs or human embryos shall be subject to a specialized ethics assessment. Research involving adult stem cells (ASCs) may be financed depending on the scientific proposal and the legal framework of the Member States involved, but, as implied by Regulation (EU) 2021/695, such proposals are not automatically subject to ethics assessment.

No explicit mention is made in Regulation (EU) 2021/695 regarding research or research proposals involving iPSCs.

5.3.2.1 Over-regulation[29]

Perhaps the most straightforward and least ethically contentious issue where the interactions between organoid and embryonic research are concerned involves the use of organoids in *embryo models*. Turning

[29] EU/EC regulations in this area are largely a response to the substantial differences in the domestic laws of individual Member States. Therefore, the fact that a Member State prohibits the practices recommended by the ISSCR does not imply that the there is "too much" EU regulation such that the EU/EC's legal requirements and standards for in vitro embryonic research are legally unclear, generate legal uncertainty, or lead to contradictions. Rather, relative to the recommendations put forward in the updated ISSCR guidelines, the EU's own approach to the regulation of certain forms of embryonic research is more restrictive. It is for this reason that, in this report, we refer to this aspect of the EU's approach to in vitro embryonic research as an instance of "over-regulation".

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to the ISSCR's updated guidelines (2021) for guidance, such research, at least at first sight, seems to be permissible.

Here, the ISSCR makes a distinction between non-integrated and integrated models. In terms of organoid-based embryo models intended to recapitulate non-integrated, post-implantation embryogenesis, the ISSCR advises that such research should be reportable to the competent authority (i.e., in this case, a national authority or the EC). Even though the ISSCR suggests that such research should involve consultation between researchers and the competent body to determine categorization under the ISSCR's guidelines, **it should not normally be subject to further or ongoing specialized ethics review/oversight**. **This would include research with gastruloids** (Lovell-Badge et al., 2021)—stem cell-derived, laboratory grown decomposed embryo-like structures which, unlike true embryos, are devoid of a primitive streak that marks the start of gastrulation.

Although not legally binding, the ISSCR's guidance on non-integrated embryo models is potentially in tension with EU/EC regulations regarding embryonic research. The ISSCR suggests that such research should not normally be subject to specialized ethics review. However, if gastruloids are to be derived from hESCs, then, according to Regulation (EU) 2021/695, those applying under the Horizon 2020 Framework would be required to obtain specialized ethics approval.

In terms of the culturing of human embryos, the ISSCR advises that such research should be subject to specialized ethics review by the competent body, coordinated with other relevant oversight, such as that provided by human subjects and animal research review committees and in vitro fertilization (IVF) clinic oversight bodies. Furthermore, the research should use the minimum number of embryos necessary to achieve the scientific objective. Where the use of organoids is concerned, the ISSCR states that these requirements may extend to:

1. Research that generates human gametes from any progenitor cell type in vitro, when this entails performing studies of fertilization that produce human zygotes and embryos. The gametes may be derived from human pluripotent stem cells, oogonia, or spermatogonial stem cells that have been maintained in vitro, and they may be genetically modified or not. Any human embryos obtained from such gametes must only be studied in vitro, or be used to derive stem cell lines, such as embryonic stem cells;
2. Research involving the genetic alteration of human embryos or gametes used to make embryos in vitro;
3. Derivation of new cell lines from human embryos (not confined to pluripotent cell lines).

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4. Research involving the in vitro culture of human embryos where embryos are maintained in culture until the formation of the primitive streak or 14 days from fertilization, whichever occurs first.[30]

Once again, the ISSCR's guidance is potentially in tension with the EU/EC regulations regarding embryonic research. Firstly, where 1), 2), 4) are concerned, Regulation (EU) 2021/695 explicitly excludes from funding eligibility the creation of human embryos solely for research purposes. Furthermore, where 3) is concerned, whilst the ISSCR advises that derivation of new cell lines from human embryos is permissible (albeit subject to specialized ethics oversight), Regulation (EU) 2021/695 explicitly excludes from funding eligibility the creation of human embryos for the purposes of stem cell procurement.

5.3.2.2 Regulatory Gaps

As was discussed in s. 5.2.2, the CJEU's and EPO's non-patentability rulings may have downstream effects on the manufacture and use of organoid-based products and technologies within the EEA. Up to now, the EU's regulation of in vitro embryonic research hasn't explicitly relied on a definition of a human embryo as something "capable of commencing the development of a human being". **Nevertheless, as we shall discuss in detail below, an official EU/EC definition of a human embryo may be needed for the regulation of certain types of organoid research, particularly because, as acknowledged by organoid researchers at WP4's stakeholder workshop in Copenhagen, the regulatory implications for future European organoid research are primarily dependent on whether the EU/EC would determine that such activities lead to the creation human embryos.**

Research involving gastruloids is becoming increasingly advanced, with human and animal gastruloids being developed to model increasingly later stages of embryogenesis where: i) somitogenesis occurs (van den Brink et al., 2020); ii) the heart field starts to develop at early stages of cardiac primordia (Rossi et al., 2021); and iii) extra-embryonic structures develop in vitro (Mackinlay et al., 2021). **Given that these advances are pushing the boundaries of what has traditionally been thought to be the nature of gastruloids, regulatory clarity may be required as to the distinction between these advanced embryo models and a human embryo.**

[30] According to the ISSCR, these requirements also extend to the procurement and use of IVF human embryos for research in vitro and the procurement of human gametes to create research embryos in vitro. However, organoid research is unlikely to require the procurement of human embryos or human gametes. Rather, such research would be more likely to generate embryo-like entities and human gametes

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In terms of stem cell-based embryo models that represent the integrated development of the entire embryo, including its extraembryonic membranes, the ISSCR advises that such research should be subject to specialized ethics review and oversight. Furthermore, the ISSCR states that these integrated stem cell-based embryo models should be maintained in culture for the *minimum* time necessary to achieve the scientific objective. **Such integrated models include blastoids** (Lovell-Badge et al., 2021)—stem-cell-derived, blastocyst-like structures that contain inner cell mass and relevant embryonic and extra-embryonic cell types (Niemann and Seamark, 2021).

The issue here is that blastoids could potentially achieve the complexity by which they might realistically undergo further integrated development if cultured for additional time in appropriate conditions, or, theoretically, if transferred to a uterus (Lovell-Badge et al., 2021). **Despite experts having claimed that blastoids are unlikely to satisfy the conditions for viable embryogenesis—even though they closely resemble human embryos (ibid.)—regulatory clarity may be required as to the definition of a human embryo, and, thus, what distinguishes the latter from blastoids that could, in principle, undergo advanced embryogenesis.**

A prohibition on the funding of research that involves the creation of human embryos for research purposes is enforced by EU/EC regulations and by national laws in most EU Member States (though not currently or planned in Belgium, Spain, Netherlands, and Denmark), there may be, as suggested by organoid researchers at WP4's stakeholder workshop in Copenhagen, uncertainty as to whether certain types of organoid research, which could produce, for example, increasingly advanced blastoids and gastruloids, and functioning gonadal organoids, are deemed to be creating human embryos.

In light of these issues, organoid researchers at the WP4 stakeholder workshop requested both an EC-approved regulatory definition of a human embryo and an EC-approved regulatory definition of whatever it is that is generated through embryo-like organoids.

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5.4 Other regulatory issues identified via the stakeholder engagement workshops conducted by WP4

As detailed in the HYBRIDA Grant Agreement, regulatory gaps and areas of over-regulation identified through the stakeholder engagement in WP4 will be analysed. If the gaps/area of over-regulation can be categorized as falling within the scope of the following categories, then they will be allocated to those categories:

- Informed consent, data protection, donor rights, and user rights within the context of organoids
- Open Science ("OS"), including the issue of benefit sharing within the context of organoids
- Organoid research and use as a social/institutional practice, including organoid use in healthcare

All of the views pertaining to the regulation of organoid activities raised by stakeholders at the WP4 stakeholder workshop fell under one of these categories. As a result, there are no additional regulatory concerns to address here.

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6 Conclusions and Next Steps

Organoids, organoid-related technologies (including organs-on-chips), and organoid-based clinical applications are not explicitly mentioned in international regulations or legally binding regulations within the EU. Though they are sometimes mentioned in "soft law" documents provided by, for instance, the EMA and the ISSCR.

As a matter of principle, current EU/EC regulations and directives would extend to cell procurement, organoid derivation, research, and medical application activities *in general*. However, organoid and organoid-related activities also reveal gaps in existing EU/EC regulations, which, if such regulations are to be enforced across the EEA either now or in the future, may need to be filled. At the same time, common practices associated with organoid and organoid-related research and translation highlight areas of potential "over-regulation" in the sense that there is uncertainty as to the laws that apply, conflicting legal requirements, a lack of regulatory harmonization across Member States, "too much" regulatory scrutiny, and/or substantive tension between EU/EC regulations and current expert consensus. These can create challenges for those conducting research, sharing the benefits of research, and seeking approval and authorization for future medicinal products and medical devices. Such issues are particularly pronounced where the patentability of organoids, organoid-related technologies, organoid derivation processes, and the exchange of cells, organoids, and associated data between research institutions are concerned.

For a summary of the regulatory issues, gaps, and areas of over-regulation identified and discussed in this report, see Section 2 and Table 1 (Executive Summary).

This report has also identified regulatory issues that require specific EC-approved definitions, legally binding clauses, or legal advice. In D6.2 ("Specific proposals for addressing gaps"), WP6 will explore potential procedural mechanisms, structures and/or processes through which these issues might be addressed. However, attending to these issues in a substantive way, that is, by developing definitions or contractual clauses or providing legal advice, is beyond the remit of WP6 and the HYBRIDA project in general. The issues we refer to are:

1. The provision of legal advice to resolve conflicting interpretations of the terms and provisions within Material Transfer Agreements (MTAs);
2. The preparation of MTA templates and standard clauses for human embryonic stem cells, induced pluripotent stem cells, and organoids;
3. The delivery of an EC-approved regulatory definition of a human embryo and an EC-approved regulatory definition of whatever it is that is generated through embryo-like organoids.

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Following this report, the next step for WP6 involves the preparation of specific proposals and the identification of appropriate regulatory agencies and actors to address the regulatory gaps and uncertainties discussed in this report (Task 6.6/D6.2). Once again, where questions regarding the regulatory gaps or uncertainties require substantive answers (i.e., in the form of legal advice, official, legally binding definitions or statutory provisions, or terms and conditions within legal documents), WP6 will limit itself to identifying procedural mechanisms, structures and/or processes through which substantive proposals can then be developed.

To these ends, and in collaboration with WP3, WP5, and WP8, an inventory will be produced of current regulatory agencies and actors involved in regulating organoid and organoid-related activities, their areas of responsibility, and their main mode of regulation. Potential regulatory actors (i.e., those that could play an active role in the regulation of organoid and organoid-related activities through involvement in the development of ethics and normative frameworks, but do not currently play such a role) will also be identified. Based on this inventory and the gaps and uncertainties identified in this report, specific proposals for action will be produced for the agencies or actors best positioned to address each gap or uncertainty. In order to inform the deliberations of regulatory actors and agencies, WP6 will also identify common arguments and considerations that have been employed within the relevant ethical and legal literature to address these regulatory gaps and uncertainties. Finally, together with WP4, WP6 will collaborate with HYBRIDA's stakeholders to develop and validate each of the proposals.

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8 Appendix 1

The Super Map, in its original form as tabular data set, is too large to be included in this report. It is available on Open Access via *Zenodo*.

To access the Super Map, use this DOI: 10.5281/zenodo.6985217

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