HYBRIDA

D5.1: Operational guidelines for the field of organoids and organoid-related technologies

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

Project acronym: HYBRIDA

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1 INTRODUCTION

1.1 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 resulting technologies[1].

As for any emerging technology and emerging novel object of research, a precise and consensual definition of organoids remains to be elaborated. We chose here to define organoids as "stem or progenitor cell-derived 3D structures that, on much smaller scales, re-create important aspects of the 3D anatomy and multicellular repertoire of their physiological counterparts and that can recapitulate basic tissue-level functions." Organoids are produced and studied in several contexts: 1/ development: finding conditions allowing to observe the initiation and growth of a given organ in vitro; 2/ physiology/physiopathology: mimicking a given function of an organ to understand its physiology/physiopathology; 3/ production: mimicking a given function of an organ to produce a molecule of therapeutic interest; 4/ therapy: producing a living structure able to replace a defective organ in the context of regenerative medicine. Architecture and function(s) are therefore essential features of an organoid as research and/or clinical counterpart of its related organ.

Organoid research comes with ambitious promises of revolutionising biomedical research in the future and with it our view of the human organism and life itself. As such a train leaves the station, it is vital that ethics do not simply follow, but are having an active role in shaping the journey as it takes place.

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

Following Roman times, all entities have been categorised and regulated either as persons or as things (subjects or objects). Organoids, however, are entities, and organoid research and organoid-related technologies are examples of disruptive research and innovation that challenge this conceptual, epistemological and regulatory dualism. That is, the dualistic normative framework pertaining to health and life science research is disrupted by three different kinds of uncertainty.

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

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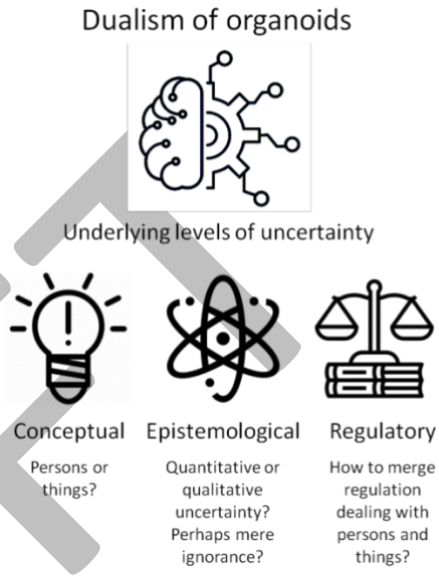
First, ***conceptual uncertainty*** **(*ontological uncertainty*)**: How should one conceive of entities that cannot be categorised as either persons or things? What *are* they? How do we *know* the characteristics of these entities called organoids?



Second, ***epistemological and methodological uncertainty*****:** How do we address forms of uncertainty that cannot be evaluated through the use of statistical methods, i.e. risk assessment? This is particularly pertinent where organoids are intended for personalised or precision medicine, where the number of research subjects with a certain characteristic is too low for randomised controlled trials or other statistically based experiments. As precision medicine and new technologies emerge, evidence-based medicine is challenged to find a new footing. Epistemological uncertainty comes in two kinds, which can be categorised as qualitative, or strict, uncertainty and ignorance or non-knowledge. Qualitative, or strict, uncertainty is a form of uncertainty where possible positive and negative outcomes can be identified in advance but, contrary to risk assessments, the statistical magnitude of each possible outcome cannot be estimated. By contrast, ignorance or non-knowledge represents forms of uncertainty where neither possible outcomes nor the statistical magnitude of each can be identified in advance. In order to develop ethically and socially robust ways of assessing the effects of organoid research and related technologies, there is a need to include these additional forms of uncertainty in the Health Technology Assessment (HTA).

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

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

1.2 WP5

WP5 is coordinated by members of the Ethics Committee of INSERM, the only public research organization in France entirely dedicated to human health, and involving contributions from all HYBRIDA partners. To develop the WP5 coordination team, first were gathered a team of seven interdisciplinary profiles, including a full-time dedicated program manager (Ioana Andreescu). Within the HYBRIDA project

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framework, WP5 is in charge of conceiving two landmark documents for the ethics of organoids: 1) an Operational Guidelines for the field; 2) a European Code of Conduct for Research Integrity for Organoids and Related Technologies, in both academia and industry, in addition, and only if needed, WP5 in collaboration with WP6 should write a supplement to the European Code of Conduct for Research Integrity (ECoC).

To begin with, the Operational Guidelines for the field of organoids and organoid-related technologies are designed to streamline certain working procedures according to best practices[2]. These recommendations should be open to a certain degree of interpretation and should provide flexibility for unforeseen circumstances. More information about this deliverable is to be found in the executive summary section of this document. Further, the HYBRIDA Code of Responsible Conduct for Researchers (CoRC or the Code) provides ethical standards of good practice to guide researchers in the organoid and organoid-related technologies field, in compliance with the principles of the ECoC: Accountability, Honesty, Reliability and Respect. Both these documents are meant to enhance the existing ethics and normative frameworks: they represent the normative bedrock of the organoid and organoid-related technologies field, should reflect HYBRIDA's objectives and convey the amount of risk and forms of uncertainty society is willing to accept.

The last document, the Supplement to the ECoC, is foreseen to provide an add-on to the ECoC in the form of a set of criteria for proper research practices and self-regulation in the field of organoids. The HYBRIDA consortium will decide together if such a document is needed.

1.3 Executive Summary

The Operational Guidelines are the first recommendations document produced by WP5. Within the HYBRIDA project, recommendations aim to ensure reliable research, development and production work on organoids and related technologies. Similarly, the guidelines will support the work of research ethics committees and associated integrity bodies, and address concerns and challenges of participants being part of organoid research studies. Ongoing progress of knowledge on organoids will require periodic updates of the document. In this sense the current Guidelines clarify and propose a general framework for the nomenclature of organoids and related technologies, having the aim of "facilitating progress and improving communication with the scientific community and the public"[3], which is supposed to be updated every 3 to 5 years at the most.

[2] Taking into consideration the complexity of the field, related technologies (such as chimeras, cloning, organ-on-chips and organoid-on-chips, etc.) will be approached in the future versions of this document.

[3] For further details, please access the article *A nomenclature consensus for nervous system organoids and assembloids*, 28 September 2022, at: https://doi.org/10.1038/s41586-022-05219-6.

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The underlying methodology is that of ***ethics by design***[4], which is strongly recommended during the construction phase of any organoid research project. WP5 has equally adopted this methodology in building these recommendations, being nevertheless aware of the fast-changing landscape of the organoid field and uncertainties related its rapid evolution. The ethics by design method places values and principles at the very core of the project development, preventing or foreseeing eventual issues and problems that could further emerge during the development and implementation of the research project. This method should be regularly re-evaluated, in order to prove its efficiency and reliability for the organoid field.

The construction of a ***Minimal Information about Organoid and its Use for Researchers*** **(MIAOU)** is a further aim of this document**.** In a nutshell, the MIAOU addresses the following concerns: assessment of concerns regarding the origin of biological material (including informed consent from donors), efficacy/reproducibility, quality of results (size, morphogenesis, cell composition), reliability, minimization of communication errors (accurate and documented description of materials and methods), compliance with safety, security and RI (research integrity) rules, prevention of research misconduct and miscommunication to the lay public. A protocol model is equally foreseen. In this document the MIAOU addresses the core requirements for scientifically robust design, characterization and use of organoids.

In order to develop the MIAOU content, this report first focuses on the characteristics and use of organoids, as well as on open questions that the field of organoids raises today. Facing the impossibility to find a unified and consensual single definition for organoids, WP5 agreed that more important than searching for a single definition is to analyse organoids' functions, their potential use (from the fundamental research to the clinical treatment), to evaluate their degree of ethical complexity. Considering the last-mentioned aspect, the current deliverable uses the ***three research review categories*** deployed by the 2021 ISSCR Guidelines for Stem Cell Research and Clinical Translation.

Another section is dedicated to the evaluation process and is entitled ***Evaluator Checklist for Organoid Ethical Studies*** **(EChOES)**; it is a significant document for Research Ethics Committees (RECs) and Research Integrity Offices (RIOs). The high-quality, well founded, and reproducible research outcomes that will result from implementing these proposed standards will undoubtedly elevate the ability of the organoid research community to strengthen public trust in the development pipeline from basic research to the translation of new and advanced patient therapies. Therefore, the Evaluator checklist for organoid ethical studies aims at implementing transparency in this pipeline and to anticipate ethical issues that can be encountered in the generation of complex organoids, or when using inappropriate or misleading semantics to name them (i.e. synthetic brain instead of cerebroid).

[4] According to All European Academics, ethics by design means bringing "ethical and societal values into the design and development of technology from the very beginning of the process". Accessible at https://allea.org/techethos-future-technology-ethics/?cn-reloaded=1.

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The benefits of adopting the MIAOU and ECHOES checklists are manifold: long-term efficiencies are realized as waste and time lost to irreproducible experiments are reduced; publications based on suitably characterized organoids provide more accurate data that enables and accelerates progress toward potential therapeutics, precision medicine, and optimized bioproducts. Reproducibility issues in basic, preclinical, clinical (translational) research and bioproduction can hinder progress and erode trust among scientific community and between scientists and society. When systematically implemented, the deployment of a quality management, including good reporting, driven by rigor and standardization, facilitates the reproducibility and accuracy of experimental outputs.

WP5 has also given a thorough reflection to the Participant Consent form, proposing recommendations on the provided content, on better communication strategies between researchers and participants, on withdrawal possibilities, on governance of research developed on organoids that suggest to set-up an intermediary independent body to represents donors' rights and interests. This section brings into discussion the ethical and legal issues of a *broad consent vs a dynamic consent vs Consent for Governance model*, a hypothetical model that facilitates the participants tasks in terms of dealing with ethical risks of organoid research projects and propose a clear decision tree at least for the collection of informed consent in the field of organoids. Some conclusive remarks are drawn at the end, as well as a Recommendation Check-list for Organoid Researchers[5].

Finally we are full aware that some open questions remain to be more deeply investigated in the future steps of the HYBRIDA project. Because of uncertainties and speed of development of the field, some of these questions may even remain open in the final document.

1.4 WP5 activity

1.4.1 HYBRIDA interactions

WP5 is a highly interactive working group, in charge of delivering several HYBRIDA's products (the Operational Guidelines for researchers in the field, the Code of Responsible Conduct for Researchers and eventually the Supplement to the ECoC. In order to achieve these goals, WP5 liaised with both HYBRIDA partners and with external experts. To begin with, WP5 organized several meetings and exchanges with WP1. Drafts and written materials circulated regularly: exchanges between WP5 and WP1 resulted in the What is behind the "ethics by design" requirement? document (Annex 2). We also thoroughly considered the ten conceptual uncertainties pointed by WP1 and how they may inform our operational guideline and code of conduct. Following the WP1 Brussels workshop on the 30th of March 2022, WP5 also provided comments and proofreading on the D1.4 deliverable.

[5] The Recommendation Check-list for Organoid Researchers is foreseen in V2.

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Furthermore, the systematic mappings performed in WP2 and WP3, and the identification of existing gaps in WP6 support the drafting of the Operational Guidelines and of the Code of Conduct. WP5 program manager (Ioana Andreescu) has been part of the WP2 Amended Working Group and participated to the discussions and drafting of WP2 documents. Further, INSERM, in the context of WP3, conducted experts' interviews for the mapping of the normative, REI (research ethics and integrity) framework of organoid and related technologies; these interviews were coded and analyzed by WP3. WP5 organized a bilateral meeting with WP6 in order to establish how exchanges and interactions will nourish the writing of the Guidelines and of the Code.

To continue with, the cooperation between WP5 and WP4 has as a result the joint organization of two Co-creation workshops, one in Paris on the 19 May 2022 and the second one in Copenhagen, on the 23 of June 2022 (for further details, please check WP4 Deliverables).

The organization of the Kick-off Meeting of the WP5 moved forward discussions of the ethics of organoids, planning the future steps in the drafting of the Operational Guidelines together with the HYBRIDA partners. The Kick-off Meeting took place on the 19th of January 2022 in Paris and was equally accessible via Zoom, featuring lectures by Christine Mummery, François Hirsch and Alexei Grinbaum (representing the H2020 Swafs29 program TechEthos), and gathering more than 30 HYBRIDA collaborators for discussions. Finally, the general plan (with the table of contents) of the Operational Guidelines was presented and discussed at the annual General Assembly of HYBRIDA in Athens, 27-28th of May 2022.

1.4.1 Experts' consultations

WP5 developed several expert exchanges and organized several bi-lateral meetings with experts from the field, focusing among others on GMP, ethics-by-design, ethical principles in organoid research, benchmarking, building up protocols, etc.

One of the consulted experts is Dr. Tenneille Ludwig, Senior Scientist and the Director of the WiCell Stem Cell Bank (Wisconsin, USA). The meeting took place on the 4th of February 2022 and was dedicated to the opportunities of collaboration in the field of stem culture conditions considering the working group she animates in the framework of future ISSCR recommendations. For ISSCR, Dr. Ludwig's ongoing work focuses on updating standards for stem cells banking, characterization, distribution for research and cGMP grade materials. Since the beginning of 2022, ISSCR has been working on an updated version of the ISSCR Standards for Basic Stem Cell Research and Dr. Hervé Chneiweiss was one of the reviewers of the document (review sent in August 2022).

Another meeting was organised with Dr. Alexei Grinbaum, researcher working on ethics of new technologies within CEA (Atomic & Alternative Energies Commission, a French industrial and commercial public establishment) and involved in several EU projects, such as TechEthos, the SwafS29 project dedicated to prioritising ethics and societal values in the design, development and deployment of new

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and emerging technologies (2021-2024) or *RRI-Practice: Responsible Research and Innovation in Practice* (2016-2019). The meeting with Dr. Grinbaum was very important in terms of building up an efficient ethics by design methodology, as well as for adding a chapter dedicated to organoid project evaluators and to the evaluation process.

Several organoid researchers took part in three working sessions dedicated to planning the content of two main sections of the Operational Guidelines: the *Minimum Information About an Organoid and its Use* (MIAOU) (Annex 5 and 6) and *Evaluator Checklist for Organoid Ethical Studies* (ECHOES), described in Annex 7.

1.5 Timeline of WP5 activities

Based on the mappings in WP2 and 3 and the 1st stage of HYBRIDA Engagement Process (HEP) version 1.0 of Operational Guidelines and the European Code of Conduct for Research Integrity for Organoids and Related Technologies were drafted and sent to the EC in October 2022. Version 2.0 of both products will be drafted by taking into account the results of the 2nd stage of the HEP. The final version (Version 3.0) will be elaborated and delivered based on consultation with experts and professional stakeholders involved in the 3rd stage of HEP[6].

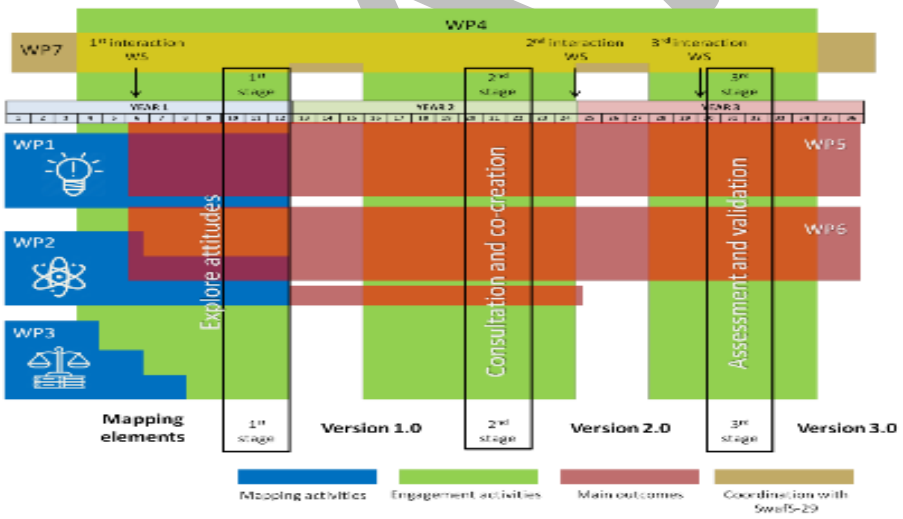

Figure 2: Flow chart and a timeline of HYBRIDA's streamlined activities.

[6] From the HYBRIDA Project, p.36.

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1.6 Inputs from other work packages

From WP1: Identification of different forms of conceptual uncertainty (ontological, moral and legal) relating to organoids; development of a socially robust typology for artificial biological entities and analysis of the ethics-by-design concept.

From WP2: Performing a traditional HTA of organoids by applying existing evidence for efficacy, effectiveness, safety, and cost-effectiveness; definition of basic concepts and perspectives for modifying HTA to assess organoids, and applying the amended HTA methodology to assess organoids as health technology.

From WP3: Mapping of ethical dimensions and concerns that have been raised in the past within the context of technologies or families of technologies comparable to organoid research; comparison of relevant regulatory frameworks in Europe and beyond.

From WP4: Carrying out three deliberative (mini-public) workshops with 15-20 participants in each, including representatives of the general public, patients, donors and CSOs. Organization of two co-creation stakeholder workshops in Paris and Copenhagen with 15-20 participants, including researchers (academic and industrial), members of RECs and RIOs, policy makers, legal experts, patient organizations and biobanks, to explore stakeholder views on initial and collective elements of the HYBRIDA Operational Guidelines and Code of Responsible Conduct.

From WP6: Analysis of existing, applicable ethics and normative frameworks in Europe and beyond and identification of assessment gaps in relation to donors, patients, civil society, Open Science (OS), in relation to organoid generation as a social practice, (c) Assessment of gaps identified through stakeholder engagement.

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2 METHODOLOGY

2.1 Concepts and Values

To address ethical issues in a scientific field, in our case organoids and related technologies, it is useful to define a number of concepts. Each concept will have to be further discussed.

Our discussions and the drafting of the present Operational Guideline and the future Code of Responsible Conduct for Researchers stem from three statements formulated by the French philosopher Paul Ricœur[7]. These three statements are related to scientific integrity, research ethics and professional conduct respectively:

1) (The desire to) conduct honest and reliable research
2) Loyalty to oneself and to the others
3) Fairness and institutions (which develop governance that promotes honest, upright, fair and accountable research)

We thus have three compasses to help define our behaviour as actors in a scientific field (here organoids and related technologies) in a given context (cultural, social, individual). These compasses are associated with a set of values that we can or want to render operational in the form of decision-making procedures (principles) or commandments to follow (standards).

We raised the following questions:

1) How do we choose the set of values (standards) that will form the basis of the ethical behaviour for researchers in the field of organoids and related technologies? Are these values universal or contextual? How will these values allow us to be a "good researcher and a good person" in order to build a "good society"? This last question constitutes the foundations of ethics of virtues[8], a reflection that can be traced back to Aristotle. Very schematically, collective and individual reflections are distinguished in order to guide our behaviour and in order to build a good society. All of these questions come under the heading of research on ethics (the field of meta-ethics).

2) How can these values be made operational?
    a. A top-down approach by minimizing the contextualization of our behaviours by establishing universal norms based on values,

[7] Paul Ricœur, *Soi-même comme un autre* **[***Self as another***]**, Editions Seuils, Paris, 1990.
[8] Louisa Yousfi, *L'éthique des vertus selon Aristote*, Nicolas Journet éd., La Morale. Éthique et sciences humaines. Éditions Sciences Humaines, 2012, pp. 96-99. Available at: https://www.cairn.info/la-morale--9782361060312-page-96.htm.

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b. A bottom-up approach by maximizing the context and keeping the values to make them the safeguards of decision-making procedures or by transforming them into principles that will be the heuristics of our behaviour.

We can thus distinguish two axes of ethical reflection:

- ✓ Deontological ethics and teleological (or consequentialist)[9] ethics
- ✓ A top-down ethics (normative) and a bottom-up ethics (ethics of practices[10], ethics of care).

2.2 Ethics by design: from ethics principles to practical solutions

Ethics by design is an approach that implies the need to effectively anticipate and reflect upon ethical issues that will arise with new technologies. According to the artificial intelligence (AI) European Project, the 'aim of Ethics by design is to incorporate ethical principles into the development process allowing that ethical issues are addressed as early as possible and followed up closely during research activities'[11]. The EU SIENNA deliverable defines ethics by design as the 'systematic inclusion of ethical values, principles, requirements and procedures in design and development processes.'[12]

Following this methodology, developers of new technologies must take into consideration ethical challenges at the stage of their design process, and thus to embed societal values in the project idea, then within the prototype, the pilot and finally during the scale up process of the emerging technology.

If initially the main field of application of ethics by design is artificial intelligence[13], currently the ethics by design approach refers to a broader perspective on the ethics of new technologies that could be applied to many emerging technologies, including biotechnologies and thus the field of organoids and related technologies.

[9] Ethique téléologique | philosophie, 10 October 2020, Available at : https://delphipages.live/fr/divers/teleological-ethics.
For further information regarding the difference on values, principles and norms, please check Annex 2.

[10] *Ethical Place. Ile de France Region.* [Espace éthique. Région Île-de-France]. Available at: https://www.espace-ethique.org/ressources/article/de-lethique-vers-la-pratique

[11] Ethics and Research Integrity Sector, DG R&I, European Commission, *Ethics By Design and Ethics of Use Approaches for Artificial Intelligence*. 25 November 2021. Available at: https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/ethics-by-design-and-ethics-of-use-approaches-for-artificial-intelligence_he_en.pdf

[12] Brey, Philip, Brandt Dainow, Yasemin J. Erden, Amal Matar, Philip Jansen, Rowena Rodrigues, Nicole Santiago, et al. 2021. *SIENNA D6.3: Methods for Translating Ethical Analysis into Instruments for the Ethical Development and Deployment of Emerging Technologies*, p.53.Available at: https://doi.org/10.5281/zenodo.5541539.

[13] See the other document for a longer review. This is especially the case of the SwafS projects SIENNA and SHERPA.

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2.3 Methodological Steps for Ethics by design

According to the SIENNA project, as well as to related biography, which provides methodological guidance for building ethical guidelines in general, there is a 5-layer Model of Ethics by Design[14]:

I. **Principles**: Reach consensus on the key moral values and principles that apply to the technology field and that we want to respect. Establishing a list of values and principles that should guide the development process.
II. **Ethical Requirements**: Translating general values into ethical requisites.
III. **Methodologies**: Translate the ethical requisites into actionable methodological guidelines. The ethics guidelines identify the specific steps in the development process where ethical assessment/intervention should take place. Guidelines are proposed to ensure that the requisites are taken into consideration during the development of the product.
IV. **Ethics by Design Guidelines:** Choose and describe an established design methodology.
V. **Tools & Methods**: Develop tools and assessment methods to address specific issues, consider special topics.

It is possible to envisage the understanding of Ethics by design in terms of methodological requisites, that could be summarized such as:

a) **anticipation** of all the consequences of the emerging technology under scrutiny

b) the attention of the **evolution** of the technology through a life cycle (ethics is not just a green light at the beginning of the research project, it should cover all aspects of the technology, as distinct issues might arise at distinct stages of technology development)

c) **inclusion** of all stakeholders potentially concerned when dealing with ethical issues

d) **interdisciplinarity** (one cannot reach all stakeholders and examine all potential ethical issues without support from the social sciences and the humanities)

e) **responsibility** of technology developers (at the end, they are responsible for the integration of the ethical requisites into the data/software/technology) and, symmetrically, ethics by design as a form of **democratic control** over technology development

If in specific contexts the Ethics by design approach might not be internalised enough for the research community, it might be supplemented by external audits, by IRBs or RECs, specifically oriented to scrutinize the different steps of the research in question and fulfil the existent gaps.

[14] Brey, Philip, Brandt Dainow, Yasemin J. Erden, Amal Matar, Philip Jansen, Rowena Rodrigues, Nicole Santiago, et al. 2021. *SIENNA D6.3: Methods for Translating Ethical Analysis into Instruments for the Ethical Development and Deployment of Emerging Technologies*, p.53. https://doi.org/10.5281/zenodo.5541539.

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2.4 World Health Organization: Choosing ethical values and principles

In the framework of its *Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing*, the World Health Organisation recommends the implementation of two ongoing processes when selecting values and principles applicable to emerging technologies in life sciences and health. These two processes are both related to decision making: social values and principles take the lead for *how* decisions are made and for *what* decisions are made[15]. Inspired by this identification of universal values for the genome editing, WP5 drew this work near to the field of organoids and related technologies.

2.4.1 To inform how decisions are made

1. **Openness, transparency, honesty and accountability**

A commitment to openness that invites collaborative ambition and work, as well as a commitment to use transparent, honest and accountable processes in order to generate and share evidence-informed, accessible and timely information about: (i) best available data (including information about sources of funding, access and outcomes); (ii) guiding ethical values and principles; and (iii) actionable policy options for organoids and related technologies.

2. **Responsible regulatory stewardship**

A commitment to support and promote legitimate, evidence-informed: (i) law and regulation; (ii) programme management and measurement; (iii) data collection, storage, processing, distribution and destruction in accordance with established privacy constraints; (iv) research training and capacity-building; and (v) public awareness about the potential benefits, harms and limitations of organoids and related technologies in ways that balance competing influences and demands.

3. **Responsible stewardship of science**

A commitment to: (i) pursue rigorous, evidence-informed basic and applied research with appropriate caution for uncertainty and risk; (ii) follow established ethical practices for research involving humans with particular attention to issues of integrity and conflict of interest; (iii) maximize the potential benefits of research while minimizing the potential harms; and (iv) respect research ethics guidelines and applicable legislation. More particularly, a commitment to align the processes and outcomes of organoids

[15] World Health Organization. *WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing*, p 27-28. https://www.who.int/teams/health-ethics-governance/emerging-technologies/expert-advisory-committee-on-developing-global-standards-for-governance-and-oversight-of-human-genome-editing.

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and related technologies research with the values, needs and expectations of society, as identified through participatory approaches involving various publics.

4. **Responsible stewardship of research resources**

A commitment to use finite research resources responsibly when choosing between research options for organoids and related technologies. This requires careful attention to scientific value and validity, as well as social value and validity. Finite research resources include: (i) biological materials; (ii) research skills; and (iii) research funding.

2.4.2 To inform what decisions are made

1. **Inclusiveness**

A commitment to carefully consider knowledge and perspectives on organoids and related technologies informed by different social, cultural and religious beliefs and moral values, as well as different skill sets. In addition, a commitment to ensure that organoid research (basic and applied) and clinical care are representative of global human diversity and are globally accessible.

2. **Caution**

A commitment to exercise appropriate caution given existing uncertainty and risk. This uncertainty and the balance of potential harms and benefits will be substantial in organoids and related technologies trials[16].

3. **Fairness**

A commitment to fair dealings in the pursuit of organoids and related technologies research and clinical care with individuals, organizations, nations and publics, in support of collective well-being and the common good. A special commitment to benefit sharing that includes giving back to participants and communities whose samples and data are used for research, such as co-research opportunities, sharing of skills and research capacity and priority access to the benefits of research.

4. **Social justice**

A commitment to develop organoids and related technologies in ways that: (i) promote human health, collective well-being and the common good; (ii) look after the needs of communities experiencing greater health burdens; (iii) reduce socioeconomic inequality; and (iv) avoid discrimination. In consultation with relevant communities, efforts should be made to ensure access to adequate resources, skills training and capacity-building for researchers, clinicians, policymakers, counsellors and others as needed.

5. **Non-discrimination**

[16] For further organoid conceptual distinctions, please check Annex 1.

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A commitment to celebrate and promote diversity by rejecting concepts of eugenics and patterns of discrimination based on personal or group characteristics including race, ethnicity, colour, religion, sex, gender, sexual orientation, age, and mental or physical ability.

6. Equal moral worth

A commitment to recognize and treat all people as having equal moral worth and their interests as deserving of equal moral consideration, with a particular need to recognize and protect the interests of persons with disabilities and of future generations.

7. Respect for persons

A commitment to respect the wishes of competent individuals regarding the most intimate aspects of their lives, including their health and their reproductive options. In addition, a commitment to promote the best interests of individuals who are not competent to make decisions for themselves.

8. Solidarity

A commitment to live and work in harmony, grounded in the recognition of the interdependence of humans. In addition, a commitment to share the benefits and burdens of research and clinical care among all people, to minimize the risk of exploitation and to promote the common good.

9. Global health justice

A commitment to equitable access to opportunities and potentially beneficial outcomes from organoids and related technologies for all people, particularly those living in low- and middle-income countries. This includes equitable access to support for health research and for the development of health interventions that are appropriate and affordable for the widest possible range of populations with a view to reducing socioeconomic inequality. It also includes equitable protection from potential coercion, exploitation and other harms.

2.5 Design of the guidelines for responsible research on organoids and related technologies for researchers and evaluators

To build a guide:

We must position ourselves in the ethical landscape in order to reach a dialogue and construct consensual guides that can be used at least in all European countries. The work consists in putting these questions into debate and making this debate alive without closing it, as is done for the construction of biomedical[17] ethics.

[17] Tom Beauchamp, James Childress, *Les principes de l'éthique biomédicale*, Médecine & Sciences humaines, Les Belles Lettres, Paris, 2008.

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We can try to build a landscape of ethics to position ourselves (proposal below to be hammered) and a glossary/thesaurus (see below the Glossary section) to avoid linguistic uncertainties.

	Why be ethical?	**How to be ethical?**	**How do we get communities to behave ethically?**
Doing reliable research	Building certified knowledge (through the peer review process)	Three minimal principles of honest research: 1) Reproducibility 2) Replicability 3) Rationality	Establish professional standards and access to information for honest and reliable research
Doing fair research	Build laboratory leadership and mentorship that promotes scientific integrity and responsible research	The four principles of fair and responsible research: Accountability, honesty, reliability and respect	Establish a code of conduct for responsible research
Doing responsible research	Building trust within society	Define the principles that enable these relationships of trust to be built	To set up a Code of Professional Conduct taking into account the consolidation of trust between scientists and citizens (to deliver certified knowledge, not opinions or beliefs)

The Operational Guidelines aim at building trust between researchers, evaluators and more generally in society at large. They will thus comprise two parts:

a) A description of reliable, honest and transparent organoid design, fabrication, characterization, functionality and uses under the title: MIAOU (Minimal Information About an Organoid and its Use)

b) A list of criteria for fair, transparent, respectful and responsible evaluation of studies involving organoids under the title: EChOES (Evaluator Checklist for Organoid Ethical Studies) comprising two documents, one for scientific evaluation and the other for ethical reviewing

EU or single countries or scientific institutions should promote the scientific dissemination of new findings in the organoid field and provide the tools through which citizens can express their views and possible concerns.

	Researcher	**Evaluator**	**institution**	**Citizen/patient**
Researcher / physician	Reliability Honesty Transparency	Honesty Reliability Transparency Respect responsibility	Honesty Reliability Transparency Respect responsibility	Physical, moral and social well-being Respect for privacy honesty
evaluator	equity (fairness) Transparency Respect Responsibility	**shared principles for evaluation** Benevolence Non-malevolence Autonomy justice	Transparence Responsabilité respect	honesrty
institution	**Engagement de l'institution** Transparence honnêteté Responsabilité	Respect Responsabilité transparence	openness	Physical, moral and social well-being honesty
citizen/patient	consent	consent	consent	Consent honesty

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3 ORGANOIDS AND SPECIFIC ETHICAL ISSUES

Building on the above values and principles, in this section specific issues related to organoids and associated technologies are tackled.

3.1 Organoid: an evolving concept

Taking into consideration their novelty and hybridity, organoids are not easy to define. Considering their characteristics, organoids are cell-derived 3D structures that self-organise, spontaneously, resulting in an architecture mimicking some aspects of a given organ and that perform certain functions of specific organs.

Following a recent Note of the INSERM Ethics Committee[18], organoids have been defined as follows:

> "Stem or progenitor cell-derived 3D structures that, on much smaller scales, re-create important aspects of the 3D anatomy and multicellular repertoire of their physiological counterparts and that can recapitulate basic tissue-level functions."[19]

However, current state of the art allows to anticipate that wider definitions will be required to describe, among other, patient explant derived organoids, guided assemblies of complex organoid performing sophisticated natural or artificial functions, as well as hybridization between organoids and non-biological devices.

3.2 Use of Organoids: the identification of 4 categories

Depending on the complexity of the organoids and of their possible use, constraints will be more or less stringent. Different objectives of organoid usage are here considered to establish an outline of the future guidelines: 1) for research, 2) for bioproduction, 3) for preclinical use, 4) for clinical use.

[18] Bernard Baertschi, Henri Atlan, Mylène Botbol-Baum, Bertrand Bed'hom, Hélène Combrisson, et al. 2020. inserm-03117706

[19] G. Rossi & al., "Progress and Potential in Organoid Research", *Nature Reviews*, 2018, vol. 19, p. 671. This definition is used in the *Organoids Research: What are the ethical issues?* Memo

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3.2.1 For research

Most of the present production and use of organoids and related technologies pertains to the research field. The organoids' fundamental research field is dedicated to seize how organoids can be produced and how they can deliver information on the development of the related organ. The acquisition of functions contributes to the understanding of organ's physiology and pathologies.

Good laboratory practices are established so that scientists receiving an organoid can rely on the data describing and characterizing the organoid (structural data: omics; morphological data: imaging and functional data). Also, the researcher must comply with all regulatory aspects before receiving the organoid, i.e. MTA (Material transfer agreement) with provisions for the use of the organoid, prior verification of signed patient consents, authorization from regulatory agencies for organoid constituted from patient cells, declaration of a collection if applicable).

What is the process for reliable and reproducible production of an organoid that a researcher can trustworthy share with other scientists? It is therefore necessary to associate a minimum of information (metadata) to each batch of organoids? In order to answer these questions, the researcher needs access to the description of sources, procurement protocols, validation and conservation of raw material protocols and data base, as well as culture protocols and quality control criteria for each level of organization, as well as for biobanking modalities and differentiation procedures. Please find a detailed description in the MIAOU section (see Section 4).

3.2.2 For bioproduction

Definition: An organoid for production is an organoid that is developed with the intent of deploying a function that is not its original one. For the production of viruses, it would be appropriate to call it production line or "factoroid" (latest term adopted in the current document). This activity concerns all the improvements for production purposes (directed evolution to optimize a precise production).

Work must be carried out according to GMP (good manufacturing practice) standards in laboratories approved by regulatory agencies and with clinical grade production processes. The quality controls involve:

- Quality control of raw materials, starting products, reagents... up to the final product
- Analysis: with all germ-free tests, functionality tests, impurity testing and environmental controls
- Validation of the batch according to GMP procedures

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3.2.3 For preclinical use

The preclinical stage concerns research and development of therapies upfront from clinical phases I, II, III and IV (Do not confound care and research). For example, this relates to understanding the mode of action of the Advanced Therapy Medical Product (ATMP), testing efficacy and toxicity before administration to humans.

There are different objectives:

1. The organoid as a drug development tool (classical-chemistry, biologics, ITD-innovative treatment)
2. The organoid as an innovative drug (MTI definition to be specified)
3. Personalization of a treatment within the framework of personalized medicine and more generally, in view of the establishment of a care protocol
4. the organoid as a medical device (Theranostic) (to be defined precisely the difference with an ITD)

A description of the level of predictability is required as well as the items of a toolbox for trial design and interpretation, and for toxicology and pharmacology studies. More generally, efficacy studies, pharmacovigilance (toxicity studies), pharmacodynamics (studies of active substance-target interactions) and pharmacokinetics (the fate of substances administered to a living organism).

3.2.4 For clinical use

GMP and medical ethics requirements should be fulfilled. All the regulatory aspects must be considered to obtain the validation of the MTI clinical grade.

3.3 Organoids and specific ethical issues

This section was inspired by the three research review categories proposed by the 2021 ISSCR Guidelines for Stem Cell Research and Clinical Translation.

Applied to our specific field, two main areas are considered as priorities as they may be subject to measures related to the precautionary principle, i) organoids associated with the dissemination of genetic

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material in the offspring and ii) organoids in which higher order brain functions such as consciousness or suffering may emerge.

It results from these classifications 4 ethical categories:

Cat. 1a: no need for specific ethical review: "simple" approach for organoids (kidney, liver, etc.). But obviously all legal and ethical reviews associated with human cell collection should be respected.

Cat. 1b: ethical consideration is recommended to the researcher and some declarations are due to the authorities: "complex" organoids such as cerebroids (not connected to sensory systems), sexual reproduction organoids, “simple” assembloids (interconnected organoids not reaching high order brain functions) and gastruloids.

Cat. 2: where approval by an ethics committee is required: blastoids, complex assembloids. By complex assembloid one may understand cerebroid connected to sensory and possibly motor systems. In these systems, nociception might become treated by the brain to become suffering, and different degrees of consciousness might emerge from complex neural networks. However, there is currently no obvious consensus on how to objectivate consciousness or suffering.

Cat. 3: prohibited organoïd because lacks compelling scientific rationale and/or is ethically concerning: gestating human stem cell-based embryo models, transferring human-animal chimeric embryos to a human or non-human primate uterus. For instance, today, any research that would allow to break the gap between germen and soma.

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4 MINIMAL INFORMATION ABOUT AN ORGANOID AND ITS USE (MIAOU) FOR RESEARCHERS

This work is in line with the more general definition given by the European Medicines Agency (EMA) on guidelines, which should 'reflect a harmonized approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives'[20]. Therefore, the central question of this rapport is the following: ***What is the process for reliable and reproducible production of an organoid that a researcher can trustworthy share with other scientists?*** The answer given by WP5 is building up a minimum information check-list (metadata) to each batch of organoids, that describes the following aspects:

- describe the sources, procurement protocols, validation and conservation of raw material protocols
- describe culture protocols and quality control criteria for each level of organization, as well as for biobanking modalities
- describe differentiation procedures

The Minimal Information About Organoids and their Use (MIAOU) presented here for basic, preclinical and clinical research as well as bioproduction, are built on a bottom-up approach from a network of scientists working in the domain for the design, characterization and usage of organoids to improve the reproducibility, replicability and rationality of research within the laboratory, between laboratories, and from organoid to organoid. The MIAOU will be harmonized with the operational guidelines worked out by the ISSCR in the next versions of the Operational Guidelines.

Critical elements for a MIAOU (Minimum Information About an Organoid and its Use):

1. Stem cell metadata (Based on ATCC model) (batch, structural, morphological and functional data, maintenance and preservation protocols)

2. Differentiation and organoid procurement protocol (Tables of differentiation factors, differentiation timeline, culture protocol, structural, morphological and functional data,

[20] European Medicines Agency. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/quality-guidelines.

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differentiation rates, purification protocols, if necessary, maintenance and preservation protocols-master organoid bank working organoid bank)

3. Monitoring of the possible drift of organoids (genetic, protein, metabolomic, other biomarkers)

4. Regulatory data and medical ethics if necessary (Restriction of use according to donor consent)

The MIAOU is used to identify the information presented (Yes (please describe) /No answer) and to evaluate the quality of their description for **reproducibility.** To increase reproducibility the following elements are of specific importance[21]:

- the integrity of datasets;
- the availability of data and the transparency of data collection methods (what was not reported, what was not used, why). An organoid CAT (Characteristics and Transfer) file should be provided for sharing information and precise the transfer details.
- the coherence of the approach (pre-registration of method/protocol);
- the analysis plan and the methodology and tools of analysis;
- and verification (both to validate and to check for mistakes in data, methods, code and results).

4.1 Source material

Information and consent appropriate to the purpose of the research	Yes/No If no, explain why
Collection declaration (declaration or authorization of activities for the conservation and preparation for scientific purposes of human body elements), mandatory for human samples	Yes/No If yes, specify references & number
Biopsy requirements: gender, age, anatomical region, diagnosis, viral status,	Yes/No
For patients: clinical data	Yes/No

4.1.1 Project title

[21] According to Baker, L., Cristea, I., Errington, T., et al, *Reproducibility of scientific results in the EU: scoping report*, European Commission, Directorate-General for Research and Innovation, Luxembourg: Publications Office of the European Union, 2020, p.5-6.

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Project title (or acronym)	
Name of the organoid (see list appendix XXX)	

4.1.2 Starting cell line (indifferent origin, ATCC, IPSC, ESC …

Genetic identity at arrival (example: DNA sequence, SNPs, digital PCR, STR, CGH array)	Yes/No If yes, please specify
Genetic quality control (example: karyotype, STR, digital PCR)	Yes/No If yes, please specify
Functional quality (example: differentiation test for pluripotency of IPSCs, permeability tests for intestinal epithelial cells)	Yes/No If yes, please specify
Cell identity after X passages	Yes/No If yes, please specify X
Cell type marker (example: marker name, detection method, target value)	Yes/No If yes, please specify
Number of passages at arrival	Yes/No If yes, please specify
Number of possible or required passages before genesis of organoids	Yes/No If yes, please specify
Storage conditions Preservation protocol	Yes/No If yes please specify (culture, freezing, thawing protocol, storage modalities)
Mutations if genetic disease	Yes/No If yes, please specify
contamination tests (mycoplasma, bacteriological, fungal)	Yes/No If yes, please specify

4.1.3 Primary cell of patient (and healthy subjects) and tumours

Genetic identity at arrival (example: DNA sequence, SNPs, digital PCR , STR, CGH array)	Yes/No If yes, please specify
Genetic quality control (example: Karyotype, STR, digital PCR)	Yes/No If yes, which one
functional quality (example: differentiation test for pluripotency of IPSCs, permeability tests for intestinal epithelial cells...)	Yes/No If yes, which one
Cell identity after X passages	Yes/No

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	If yes, please specify X
Cell type marker (example: marker name, detection method, target value)	Yes/No If yes, please specify
Number of passages at arrival	Yes/No If yes, please specify
number of possible or required passages before genesis of organoids	Yes/No If yes, please specify
Storage conditions preservation protocol	Yes/No If yes, please specify (culture, freezing, thawing protocol, storage modalities)
Mutations if genetic disease	Yes/No
contamination tests (mycoplasma, bacteriological, fungal)	Yes/No If yes, please specify
method of tissue dissociation (Production of single-cell material or tissue substructures - example: intestinal crypt)	Yes/No If yes, please specify

4.1.4 Culture conditions of cells

Composition of culture media, nature, origin and quantities of supplements used (e.g. glucose, serum, antibiotics, growth factors etc.)	Yes/No If yes, please provide extensive description
Nature and treatment of the supports	Yes/No If yes, which one
Seeding conditions	Yes/No If yes, which one
Frequency of media changes	Yes/No If yes, which one
CO2 / O2 Concentration	Yes/No If yes, which one

4.1.5 Storage conditions of the lines or cells

Master banks, (description of protocols, drift control)	Yes/No If yes, please specify
Daughter banks (description of protocols, drift control)	Yes/No If yes, please specify
Storage: freezing and thawing protocol	Yes/No

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	If yes, please specify
Storage modalities	Yes/No If yes, please specify

4.2 Manufacturing of the Organoid

4.2.1 Differentiation conditions (2D)

Composition of culture media, nature, origin and quantities of supplements used (e.g. glucose, serum, antibiotics, growth factors etc.)	Yes/No/Not applicable (N.A.)
Sequence and duration of treatments	Yes/No/ N.A. If yes, please specify
Nature and treatment of the supports	Yes/No/ N.A. If yes, please specify
Seeding conditions	Yes/No/N.A. If yes, please specify
Frequency of media changes	Yes/No/N.A. If yes, please specify
CO2 / O2 concentration	Yes/No/N.A. If yes, please specify
Quality control of differentiation process (e.g. morphology, mat homogeneity, max and min confluence, proliferation, functional test, monitoring of markers, possibly sorting, mortality rate)	Yes/No/N.A. If yes, please specify

4.2.2 Generation of organoids (3D): in general

Composition of culture media, nature, origin and quantities of supplements used (e.g. glucose, serum, antibiotics, growth factors etc.)	Yes/No/N.A. If yes, please specify
Sequence and duration of treatments	Yes/No/N.A. If yes, please specify
Nature and treatment of the supports	Yes/No/N.A. If yes, please specify

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Seeding conditions	Yes/No/N.A. If yes, please specify
Frequency of media changes	Yes/No/N.A. If yes, please specify
Quality control of differentiation process (e.g. morphology, mat homogeneity, max and min confluence, proliferation, functional test, monitoring of markers, possibly sorting, mortality rate)	Yes/No/N.A. If yes, please specify

4.2.3 Generation of organoids (3D): specificities

Matrix culture

Nature of the matrix (matrigel, hydrogels, hyaluronic acid, human decellularized matrix etc.)	Yes/No/N.A. If yes, please specify
Matrix concentration	Yes/No/N.A. If yes, please specify
Preparation method (temperature, polymerization time, drop or layer structure, etc.)	Yes/No/N.A. If yes, please specify
Seeding density per matrix volume unit	Yes/No/N.A. If yes, please specify
Volume and number of drops of matrix per unit area in the culture medium	Yes/No/N.A. If yes, please specify
Amount of medium depending on the size of the well	Yes/No/N.A. If yes, please specify
Matrix dissociation method for organoid recovery	Yes/No/N.A. If yes, please specify
Method of dissociation of organoids for their expansion	Yes/No/N.A. If yes, please specify

Culture on solid 3D support (example: mineral support for bones, support for liquid-gas interfaces)

Preparation method of the 3D solid support (composition of the medium to be freeze-dried, freeze-drying conditions)	Yes/No/N.A. If yes, please specify
Seeding method	Yes/No/N.A. If yes, please specify

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nature of biocompatible materials (PDMS, COC, Silicon, etc.)	Yes/No/N.A. If yes, please specify
Chip design (provide a map)	Yes/No/N.A. If yes, please specify
Physical characteristics	Yes/No/N.A. If yes, please specify

Suspension culture (self-organization)

Type of container	Yes/No/N.A. If yes, please specify
The nature and protocol of the agitation	Yes/No/N.A. If yes, please specify
Nature and concentration of matrices	Yes/No/N.A. If yes, please specify

Culture including multiple cell types

Sequence of co-culturing and adaptation of co-culture media	Yes/No/N.A. If yes, please specify
Proportion of cell types	Yes/No/N.A. If yes, please specify

4.3 Organoid characterization

The detailed characterization is project dependent; however, some standards emerge:

Morphology/structure	
Appearance, size, shape [circularity, tubularity, regularity of contour (budding)	Yes/No/N.A. If yes, please provide description
Opacity/ refringency	Yes/No/N.A.
Intra and inter-organoid homogeneity	Yes/No/N.A.
Expected morphological, architectural and ultrastructural features, organization of cell types (identity, proportions, distribution)	Yes/No/N.A.

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Molecular Characterization	
Elements of genomics, transcriptomics, metabolomics, proteomics,	Yes/No. If yes, please specify
Expected specific molecular markers, epigenetic characteristics	Yes/No/N.A. If yes, please specify

Function	Specific to each organoid
Qualitative and (if possible) quantitative functional characteristic	Yes/No If yes, please specify
Response to treatments (pharmacological, chemical, physical, hormonal, etc.) the treatment protocol, and evaluation (quantitative or qualitative) of the response are described	Yes/No/N.A. If yes, please specify

Traceability, organoid drift	
Traceability of components (batches, suppliers etc., environments, complements)	Yes/No If yes, please specify
Traceability of conditioned media (drift of cells used for conditioning, control of lines as for those at the origin of the organoid), control of at least one of the growth factors)	Yes/No/N.A. If yes, please specify
Drift criteria (morphological, structural, functional, molecular, etc.) specific to each organoid. Specify indices if applicable	Yes/No/N.A. If yes, please specify
Robustness criterion (same starting cells, same organoid). Specify indices if applicable	Yes/No/N.A. If yes, please specify

Traceability, organoid drift	
Traceability of components (batches, suppliers, environments, complements, etc.)	Yes/No If yes, please specify
Traceability of conditioned media (drift of cells used for conditioning, control of lines as for those at the origin of the organoid), control of at least one of the growth factors)	Yes/No/N.A. If yes, please specify
Drift criteria (morphological, structural, functional, molecular, etc.) specific to each organoid. Specify indices if applicable	Yes/No/N.A. If yes, please specify

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Robustness criterion (same starting cells, same organoid). Specify indices if applicable	Yes/No/N.A. If yes, please specify

4.4 Use of Organoids

Organoid for basic research

Bioproduction of organoids: in addition to the above, required GLP (good laboratory practice), approval number)	Yes/No/N.A.

Organoids for bioproduction

In addition to the above, GMP (good manufactory practice)	Yes/No/N.A. Specify and describe

Organoid in preclinical research (pharmacology, toxicology, ...)

Functional similarity criterion between the organoid and the mimicked organ (battery of controls to be performed with target values)	Yes/No/N.A. If yes, please specify
Number of usable passages Applicable for: Preclinical development of a drug candidate (IND file) using organoids	Yes/No/N.A. If yes, please specify
Number of usable passages Applicable for: Definition of predictive signatures of responses (companion test)	Yes/No/N.A. If yes, please specify
Number of usable passages Applicable for: Validation of a care protocol (specific patient) on a cohort: choice of a therapy	Yes/No/N.A. If yes, please specify

Organoid in clinic (personalized, predictive and regenerative medicine, transplantation)

GMP certification, total traceability of the components, qualification of the components for Domain 1: Care protocol (specific patient) (validation of the protocol of use of the organoid for the orientation of the therapeutic choice)	Yes/No/N.A. If yes, please specify

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Criterion of similarity between the organoid and the biopsy	
GMP certification, total traceability of components, qualification of components for Domain 2: Use in regenerative medicine (same as cell and tissue therapies)	Yes/No/N.A. If yes, please specify
Functionality criteria, safety (Derivation of biological material and evaluation of the risk of cancer)	Yes/No/N.A. If yes, please specify

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5 Evaluation Checklist for Organoid Ethical Studies (EChOES)

The Evaluator Checklist for Organoid Ethical Studies (EChOES) is a list of criteria for fair, transparent, respectful and responsible evaluation of studies involving organoids. **It comprises two documents, one for scientific evaluation and the other for ethical reviewing by international review boards namely research integrity organization (RIO) and research ethic committee (REC).**

5.1 Critical elements of the EChOES

The MIAOU (see above) is used to identify the information presented (Yes/No answer) and to evaluate the quality of their description for **reproducibility, replicability and rationality of organoid research**. To assess the quality of an application, the elements depicted in red are mandatory to allow the scientific evaluation process, while the ones in black are optional (depending on the call requirements and project deployment) but useful for the full evaluation of the project. It will remain for the evaluators to judge if the response yes or no is acceptable for a given project.

A) SOURCE MATERIAL

Informed Consent for proposed research	Yes/No Mandatory for human materials
Authorization to import and/or export human body products for scientific purposes	Yes/No/N.A. Please specify
Biopsy requirements: gender, age, anatomical region, diagnosis, viral status, etc.	Yes/No/ If applicable please specify
For patients: clinical board	Yes/No If applicable please specify

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Starting cell line (indifferent origin, ATCC, IPSC, ESC, etc.)

Genetic identity at arrival (example: DNA sequence, snips, digital PCR, STR, CGH array)	Yes/No If yes, please specify
Genetic quality control (example: karyotype, STR, digital PCR)	Quality control procedure and traceability Add short description/reference
functional quality (example: differentiation test for pluripotency of IPSCs, permeability tests for intestinal epithelial cells, etc.)	Yes/No Please specify
Cell identity after X passages	Quality control procedure and traceability Add short description/reference
Cell type marker (example: marker name, detection method, target value)	Quality control procedure and traceability Add short description/reference
Number of passages at arrival	Quality control procedure and traceability Add short description/reference
Number of possible or required passages before genesis of organoids	Quality control procedure and traceability Add short description/reference
Storage conditions	Quality control procedure and traceability Add short description/reference
Mutations if genetic disease	Yes/No Please specify
Contamination tests (mycoplasma, bacteriological, fungal)	Quality control procedure and traceability Add short description/reference

Primary cell of patient (and healthy subjects) and tumors

Genetic identity at arrival (example: DNA sequence, snips, digital PCR, STR, CGH array)	Quality control procedure and traceability Add short description/reference
Genetic quality control (example: Karyotype, STR, digital PCR)	Quality control procedure and traceability Add short description/reference
Functional quality (example: differentiation test for pluripotency of IPSCs, permeability tests for intestinal epithelial cells, etc.)	Yes/No Please specify
Cell identity after X passages	Quality control procedure and traceability Add short description/reference
Cell type marker (example: marker name, detection method, target value)	Yes/No If yes, please specify
Number of passages at arrival	Quality control procedure and traceability Add short description/reference

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Number of possible or required passages before genesis of organoids	Quality control procedure and traceability Add short description/reference
Storage conditions	Quality control procedure and traceability Add short description/reference
Mutations if genetic disease	Yes/No Please specify
contamination tests (mycoplasma, bacteriological, fungal)	Quality control procedure and traceability Add short description/reference
Method of tissue dissociation (production of single-cell material or tissue substructures - example: intestinal crypt)	Yes/No Please specify

Culture conditions of cells

Composition of culture media, nature, origin and quantities of supplements used (e.g. glucose, serum, antibiotics, growth factors etc. .....)	Yes/No If yes, which one
Nature and treatment of the supports	Yes/No If yes, which one
Seeding conditions	Yes/No If yes, which one
Frequency of media changes	Yes/No If yes, which one
CO2 / O2 Concentration	Yes/No If yes, which one

Storage conditions of the lines or cells

Master banks, (description of protocols, drift control)	Quality control procedure and traceability Add short description/reference
working banks (description of protocols, drift control)	Quality control procedure and traceability Add short description/reference
Storage: freezing and thawing protocol	Quality control procedure and traceability Add short description/reference
Storage modalities	Quality control procedure and traceability

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	Add short description/reference

B) **MANUFACTURING OF THE ORGANOID**

Differentiation conditions (2D)

If required, the cells can be differentiated before entering 3D culture

Composition of culture media, nature, origin and quantities of supplements used (e.g. glucose, serum, antibiotics, growth factors, etc.)	Schematic description of differentiation protocols and control procedures
sequence and duration of treatments	Schematic description of differentiation protocols and control procedures
Nature and treatment of the supports	Schematic description of differentiation protocols and control procedures
Seeding conditions	Schematic description of differentiation protocols and control procedures
Frequency of media changes	Schematic description of differentiation protocols and control procedures
CO2 / O2 concentration	Schematic description of differentiation protocols and control procedures
Quality control of differentiation process (e.g. morphology, mat homogeneity, max and min confluence, proliferation, functional test, monitoring of markers, possibly sorting, mortality rate)	Schematic description of differentiation protocols and control procedures

Generation of organoids (3D): in general

Composition of culture media, nature, origin and quantities of supplements used (e.g. glucose, serum, antibiotics, growth factors etc.)	Schematic description of differentiation protocols and control procedures
Sequence and duration of treatments	Schematic description of differentiation protocols and control procedures
Nature and treatment of the supports	Schematic description of differentiation protocols and control procedures
Seeding conditions	Schematic description of differentiation protocols and control procedures

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Frequency of media changes	Schematic description of differentiation protocols and control procedures
Quality control of differentiation process (e.g. morphology, mat homogeneity, max and min confluence, proliferation, functional test, monitoring of markers, possibly sorting, mortality rate)	Schematic description of differentiation protocols and control procedures

Generation of organoids (3D): specificities

Matrix culture

Nature of the matrix (matrigel, hydrogels, hyaluronic acid, human decellularized matrix etc.)	Schematic description of differentiation protocols and control procedures
Matrix concentration	Schematic description of differentiation protocols and control procedures
Preparation method (temperature, polymerization time, drop or layer structure, etc.)	Yes/No/N.A.
Seeding density per matrix volume unit	Yes/No/N.A.
Volume and number of drops of matrix per unit area in the culture medium	Yes/No/N.A.
Amount of medium depending on the size of the well	Yes/No/N.A.
Matrix dissociation method for organoid recovery	Yes/No/N.A.
Method of dissociation of organoids for their expansion	Yes/No/N.A.

Culture on solid 3D support

Preparation method of the 3D solid support	Schematic description of differentiation/culture protocols and control procedures
Seeding method	Schematic description of differentiation/culture protocols and control procedures
Nature of biocompatible materials for scaffold or biochip	Schematic description of differentiation/culture protocols and control procedures

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Chip or bioreactor design (provide a map), if applicable	Schematic description of differentiation/culture protocols and control procedures
Physical and chemical characteristics	Schematic description of differentiation/culture protocols and control procedures
Perfusion, technique and control	Schematic description of differentiation/culture protocols and control procedures

Dynamic culture

Type of container / Bioreactor	Schematic description of culture protocols and control procedures
if applicable, the nature and protocol of the dynamic culture	Schematic description of culture protocols and control procedures
nature and concentration of matrices (if applicable)	Schematic description of culture protocols and control procedures

Culture involving multiple cell types

Sequence of co-culturing and adaptation of co-culture media	Schematic description of culture protocols and control procedures
Proportion of cell types	Schematic description of culture protocols and control procedures

C) ORGANOID CHARACTERIZATION

The detailed characterization is project dependent, however some standards emerge

Morphology/structure	Schematic description of characterization protocols and control procedures
Appearance, size, shape [circularity, tubularity, regularity of contour (budding)],	Yes/No/N.A.
Opacity/refringency	Yes/No/N.A.

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Intra and inter-organoid homogeneity,	Yes/No/N.A.
Expected morphological, architectural and ultrastructural features, organization of cell types (identity, proportions, distribution).	Yes/No/N.A.

Molecular Characterization	Schematic description of characterization protocols and control procedures
Elements of genomics, transcriptomics, metabolomics, proteomics	Yes/No
Expected specific molecular markers, epigenetic characteristics	Yes/No/N.A.

Function	Schematic description of characterization protocols and control procedures Specific to each organoid type
Qualitative and (if possible) quantitative functional characteristic	Yes/No
Response to treatments (pharmacological, chemical, physical, hormonal, etc.) the treatment protocol, and evaluation (quantitative or qualitative) of the response are described	Yes/No/N.A.

Traceability, organoid drift	Description of traceability and control procedures
Traceability of components (batches, suppliers etc., environments, complements)	Yes/No
Traceability of conditioned media (drift of cells used for conditioning, control of lines as for those at the origin of the organoid), control of at least one of the growth factors)	Yes/No/N.A.
Drift criteria (morphological, structural, functional, molecular....) specific to each organoid. Specify indices if applicable	Yes/No/N.A.
Robustness criterion (same starting cells, same organoid). Specify indices if applicable	Yes/No/N.A.

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Methods of organoids cryopreservation	Schematic description of cryopreservation protocols and control procedures, if applicable, otherwise see cell storage.
Preparation method (dissociation/harvesting) of the cells/organoids to be cryopreserved	Yes/No/N.A.
Cryopreservation media (composition, volume per number of cells)	Yes/No/N.A.
Freezing procedure (possible successive temperatures, duration at each temperature, final storage temperature)	Yes/No/N.A.
Quantity of cells per vial and at which passage	Yes/No/N.A.
Thawing procedures	Yes/No/N.A.

D) USE OF ORGANOIDS

Organoid for basic research

Bioproduction of organoids: in addition to the above, GLP required, approval number)	Yes/No/N.A.

Organoids for bioproduction

In addition to the above, Technical Specifications (GMP)	Yes/No/N.A.

Organoid in preclinical research (pharmacology, toxicology…)

Functional similarity criterion between the organoid and the mimicked organ (battery of controls to be performed with target values)	Yes/No/N.A.
Number of usable passages Applicable for: Preclinical development of a drug candidate (IND file or ATMP registration) using organoids	Yes/No/N.A.
Number of usable passages Applicable for: Definition of predictive signatures of responses (companion test)	Yes/No/N.A.
Number of usable passages	Yes/No/N.A.

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Applicable for: Validation of a care protocol (specific patient) on a cohort: choice of a therapy	

Organoid in clinic (personalized, predictive and regenerative medicine, transplantation)

GMP certification, total traceability of the components, qualification of the components for Domain 1(IVD-MD): Care protocol (specific patient) (validation of the protocol of use of the organoid for the orientation of the therapeutic choice)	Yes/No
GMP certification, total traceability of components, qualification of components for Domain 2 (ATMP): Use in regenerative medicine (same as cell and tissue therapies)	Yes/No

5.2 EChOES for International Review Boards (Research Ethics Committee, Research Integrity Organizations)

Project title		
Global purpose of the project		Summarize
Are there ethical issues raised by your expected results?	Yes/No	Explain

Section 1: HUMAN EMBRYOS / FOETUSES		Yes/No
Does your research involve the use of human embryos?		Yes/No
If yes	Provide origin of the embryos.	
	Provide details of the recruitment, of the inclusion and exclusion criteria, of the procedure for obtaining informed consent.	
	Confirm that oral information has been provided and that informed consent has been obtained.	
	Will the research lead to the destruction of the embryo?	

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Does your research involve the use of human fetal tissues/cells?		Yes/No
If yes	Provide the origin of human fetal tissues/cells.	
	Provide details of the procedure for obtaining informed consent.	
	Confirm that oral information has been provided and that informed consent has been obtained.	
Compliance: brief description of compliance procedures, upload requested documents.		
Sections 2: HUMAN SUBJECTS		Yes/No
Does your research involve human subjects?		Yes/No
If yes	Are they volunteers for social or human sciences research?	
	Are they healthy volunteers for medical studies?	
	Are they patients?	
	Are they vulnerable individuals or groups?	
	Are they persons unable to give informed consent?	
	Are they children/minors?	
	Provide details of the procedure for obtaining informed consent.	
	Confirm that oral information has been provided and that informed consent has been obtained.	
Does the research involve physical interventions on the study participants?		Yes/No
If yes	Does it involve invasive techniques?	
	Does it involve collection of biological samples?	
	Please describe risk assessment for each technique and overall.	
	What type of samples will be collected?	
	What are the procedures for collecting samples?	
	Please add copies of ethics approval.	
Compliance: brief description of compliance procedures, upload requested documents.		
Section 3: HUMAN CELLS/TISSUES/ORGANOIDS		Yes/No
Does the research involve human cells or tissues or organoids (other than from human embryos/fetuses, i.e. section above)?		Yes/No
If yes	Provide details of the cells, tissue type	
	Provide copies of relevant ethics approval	
	Provide accreditation/designation/authorization/licensing for using cells or tissues (if required).	
	Are they available commercially?	Yes/No
If yes	Details of the provider.	
	Are they obtained within this project?	Yes/No

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If yes	Copies of import license.	
	Details on the source of material and procedure of collection.	
	Details on the duration of storage and of what you will do with the material at the end of the project.	
	Confirm that oral information has been provided and that informed consent has been obtained.	
	Are they obtained from another project, laboratory, institution or biobank?	Yes/No
If yes	Country where the material is stored.	
	Details of the legislation under which material is stored.	
	Details on the duration of storage and of what you will do with the material at the end of the project.	
	Name and country of the laboratory/institution/biobank.	
	Confirmation that the material is anonymized.	
	Confirmation that a secondary use is obtained in the consent.	
Compliance: brief description of compliance procedures, upload requested documents.		
Section 4: PERSONAL DATA		Yes/No
Does the research involve personal data collection and/or processing?		Yes/No
If yes	Details on the technical organizational measures to safeguard the rights of the research participants (protection policy).	
	Details of the procedure for obtaining informed consent.	
	Confirm that oral information has been provided and that informed consent has been obtained.	
	Details of the security measures to prevent unauthorized access to personal data.	
	How is the processed data relevant and limited to the purposes of the project (data minimization principle)?	
	Details of the anonymization/pseudonymization techniques.	
	Justification if research data will not be anonymized/pseudonymized (if relevant).	
	Details or data transfers and countries to which they are transferred.	
Does the research involve further processing of previously collected personal data (secondary use)?		Yes/No
If yes	Details of the database used or source of data.	
	Details of the data processing operations.	
	How will the rights of the participants be safeguarded? Please explain.	
	How is the processed data relevant and limited to the purposes of the project (data minimization principle)?	

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	Justification if the research data will not be anonymized/pseudonymized (if relevant).	
Compliance: brief description of compliance procedures, upload requested documents.		
Section 5: ANIMALS/CHIMERAS		Yes/No
Does the research involve animals?		Yes/No
If yes	Details of the species and rationale for their use, number of animals, nature of the experiments, procedures and techniques.	
	Justification of animal use (including the kind of animals) and why alternatives cannot be used.	
Are the animal vertebrates?		Yes/No
Are they non-human primates (NHP)?		Yes/No
If yes	Why are the NHPs the only research subjects suitable for achieving the scientific objectives?	
	What is the purpose of the animal testing? Please give details	
	Where do the animals come from?	
Are they genetically modified or cloned animals?		Yes/No
If yes	Details of the phenotype and any inherent suffering expected.	
	What scientific justification is there for producing such animals?	
	What measurement will you take to minimize suffering in breeding, maintaining colonies and using the GOMs?	
Are they endangered species?		Yes/No
If yes	Why is there no alternative to using this species?	
	What is the purpose of the research?	
Does the research involve chimeras?		Yes/No
Are the chimera human-animal?		Yes/No
If yes	What scientific justifications are there for producing such chimeric animals?	
Are the recipient non-human primates?		Yes/No
If yes	Why are the NHPs the only research subjects suitable for achieving the scientific objectives?	
Are the recipient genetically modified or cloned animals?		Yes/No
If yes	What scientific justification is there for producing such animals?	
Are the recipient endangered species?		Yes/No
Compliance: brief description of compliance procedures, upload requested documents.		
Section 6: DUAL USE		Yes/No
Does the research involve dual use items in the sense of regulation 428/2009, or other items for which au authorization is required?		Yes/No
If yes	What goods and information used and produced in the research will need export license?	

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	How exactly will you ensure compliance?	
	How exactly will you avoid negative implications?	
Compliance: brief description of compliance procedures, upload requested documents.		
Section 7: THIRD COUNTRIES		Yes/No
In case of non-EU countries are involved, do the research-related activities undertaken in these countries raise potential ethics issues?		Yes/No
If yes	Risk-benefit analysis?	
	What activities are carried out in non-EU countries?	
Are local resources planned to be used (animals, tissue samples, genetic material, endangered fauna)?		Yes/No
If yes	What type of local resources will be used and how exactly?	
Do you plan to import any material -including personal data- from non-EU countries?		
If yes	What type of materials will you import?	Yes/No
Do you plan to export any material -including personal data- from EU-contries to non-EU countries?		Yes/No
In case the research involves low- or middle-income countries, are any benefits-sharing actions planed?		Yes/No
Could the situation in the country put the individuals taking part in the research at risk?		Yes/No
Compliance: brief description of compliance procedures, upload requested documents.		
Section 8: EXCLUSIVE FOCUS ON CIVIL APPLICATIONS		
Could the research raise concerns regarding the exclusive focus on civil applications?		Yes/No
Section 9: MISUSE		
Does the research have the potential for misuse of research results?		Yes/No
	Risk assessment	
	Details of the applicable legal requirements	
	Details of the measures to prevent misuse	
Compliance: brief description of compliance procedures, upload requested documents.		
Section 1: OTHER ETHICS ISSUES		
Are there any other ethics issues that should be taken into consideration? Please specify.		Yes/No
Compliance: brief description of compliance procedures, upload requested documents.		

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I confirm that I have taken into account all ethics issues described above and that, if any ethics issues apply, I will complete the ethics self-assessment and attach the required documents.

This document was conceived following the model of *How to Complete your Ethics Self-Assessment*[22].

[22] Horizon 2020 Programme, *Guidance: How to complete your ethics self-assessment*, 2019. Accessible at: https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-self-assess_en.pdf.

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6 ORGANOIDS AND INFORMED CONSENT*

As stated in section 3.3 specific ethical considerations should be foreseen before starting a research project involving the generation of organoids, especially if they are to include human cells. The first point to consider is the information and consent of the donor of cells or tissues. Indeed, informed consent is a basic fundamental pre-requisite of any kind of research involving human subjects, including through the collection of tissues or cells. The Nuremberg Code underscores consent and is at the origin of the concept that participation in research is a voluntary activity. The Declaration of Helsinki also enshrines consent as a main guarantee (WMA, 2013). Article 6 of the Universal Declaration on Bioethics and Human Rights (UDBHR) provides that any preventive, diagnostic and therapeutic medical intervention as well as scientific research should only be carried out 'with the prior, free, express and informed consent of the person concerned'[23]. According to the mini-deliberative workshop conducted by HYBRIDA (D4.3) in Denmark, participants were particularly sensitive to the information given beforehand, the consent form and follow-up: "informed consent and information to patients and citizens should be clear, and procedures for informing patients and getting consent should be simple and understandable for the patients. The participants suggest allocating funds for this specific purpose, e.g. to secure there is sufficient time and resources for information". Finally, as part of informed consent it is also necessary to provide donors about how they will be informed of the progress of research using their donation.

For all of the following, the general conditions for the information of donors and collection of their consent must be respected.

6.1 Legal capacity to consent

In all cases, the prior, free and informed consent of the person concerned must be obtained.

Where a person is not capable of giving consent, permission must be obtained from the legal representative in accordance with applicable law. The legal representative must consider the best interests of the person concerned[24]. There are three different types of participants commonly identified

* This chapter was drafted in collaboration with Christine Dosquet, President of the Inserm Ethics Review Committee.

[23] UNESCO, *Universal Declaration on Bioethics and Human Rights*, Article 6 – Consent, 2005. Accessible at: http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html

[24] UNESCO, *International Declaration on Human Genetic Data*, 2003. Available at: https://unesdoc.unesco.org/ark:/48223/pf0000136112.

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who do not have full capacity to consent: mentally incompetent adults, adults in emergency care and children.

For adult with disability, the informed consent should be obtained with the assistance of an expert patient in addition to the legal representative.

For the collection of samples from minors, the informed consent of both parents or the legal representative should be obtained after the minor's assent when possible. The information provided must be adapted to the age and degree of maturity of the minor (vocabulary, cartoon support, etc.).

In the particular case of the use of cells from an IVF embryo, information will be provided and informed consent will be sought from both parents or, where appropriate, the legal representative of both parents.

6.2 Pseudonymisation or anonymization of biological samples and associated data

Whatever the context of the collection of biological human samples and associated data, the rights and freedom of donors must be respected. The General Data Protection Regulation (GDPR) defines personal data as "any information relating to an identified or identifiable natural person" (art. 4.1). Further, the same document implies that giving consent 'means any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her.'[25]

Pseudonymization is the processing of personal data in such a way that it is no longer possible to attribute the data to a natural person without additional information. In practice, pseudonymization consists of replacing directly identifying data (surname, first name, etc.) in a dataset with indirectly identifying data (alias, sequential number, etc.).

The GPDR requires pseudonymization of data for scientific research. Pseudonymization is presented as an inherent safeguard for the processing of personal data for scientific research purposes as long as it is compatible with the purpose of the processing (art. 89).

The GPDR encourages researchers to use this minimization measure because it is a good compromise between the needs of the research and the safeguarding of the interests of the participants by limiting the severity of the potential impacts for the research participants, in particular in the event of a breach of confidentiality of the data.

[25] General Data Protection Regulation (GDPR). Article 4 (11). Accessible at: https://gdpr-info.eu/art-4-gdpr/.

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The anonymization process aims to eliminate any possibility of re-identification, so future use of the data is limited to certain types of use. These constraints must be taken into account at the beginning of the project.

The GDPR does not include a general obligation of anonymization. It is one solution, among others, to be able to use personal data in the respect of people's rights and freedoms.

The choice between anonymization and pseudonymization, which must be carefully considered by the researcher before the project, is conditioned by the need to re-use and exploit personal data without infringing on the privacy of individuals. It also makes it possible to keep data beyond their retention period

6.3 In what contexts does the collection of biological samples take place?

For researchers having the project to build an organoid made of human cells, the provision of these cells necessarily involves a very controlled process of collecting biological samples and the data associated with the sample. This process can be done in different contexts (see the tree describing the different contexts):

1) From a patient as part of his or her medical care or follow-up,
2) From a volunteer in the context of clinical research or
3) From a public or commercial biobank.

6.3.1 Collection of samples in the context of medical care (treatment, follow-up, consulting) or clinical research

- If the collection of biological sample and associated data, necessary to establish a diagnosis or to choose a treatment, is intended to be used for research or stored for future use, oral and written information to the patient on the research purpose or the reason for the conservation and the future of his or her biological samples and associated data is mandatory. if the patient agrees, he/she must give consent for the use/re-use of the biological samples and associated data and for the way in which they will be secured. The researcher who will be using these samples should ensure that this entire procedure has been rigorously followed and that the patient has consented to the storage and re-use of their biological samples for research purposes before seeking the advice of the REC before the research project starts.

- If the collection is done in the context of a donation of biological samples and associated data to research, it is essential that the donor be provided with oral and written information about the research project and conditions and duration of the retention of his/her donation, prior to the collection of consent. In the case where biological samples and associated data are retained for secondary use, the patient must be given further oral and written information, prior to consent, about the re-use of their biological samples and any derivatives, and associated data. this could be implemented through the research project website in a dedicated donor area. In addition, the donor must be informed of the possible non-commercial use

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or commercialization of his samples. It is the responsibility of the researcher to ensure that appropriate consent is in place and to submit the research project to a REC for advice, which is required before the research project begins.

In all cases, a withdrawal procedure assures to the donor the possibility of withdrawing his or her consent at any time, without prejudice to him/her (see Chapter 6.6 below for details).

6.3.2 Collection from a public or private biobank

When a researcher wants to obtain biological samples and associated data from a public or private biobank, the biobank should release the sample(s) only after review and validation by a scientific board of the research project and the accordance with the informed consent of the donor. Consequently, we recommend that each biobank constitutes a scientific board composed of scientists, clinicians, ethicists and representatives of patient organisations to fulfil this critical mission. Furthermore, if the dynamic consent has been adopted (cf. paragraph 6.7), the biobank must inform the donor of the arrival of the various requests from researchers and their projects (by sending an email or an SMS inviting the donor to visit an interactive online site, for example). Ideally, information should be provided via a dedicated website. By putting it online, information and exchanges for donors would be accelerated by dynamic electronic consent/refusal. In addition, this website would in turn allow donors to be informed about the progress of research using their donation, which they also request as indicated above.

For his/her part, the researcher must ensure that the donor's information and consent procedure has been followed and must seek the advice of a REC before starting the project.

6.3.3 Collection from a commercial supplier

Remain to be discussed in V2 and V3. When buying cells from a commercial provider, scientists have little if any information about the origins of cells and the process of initial informed consent.

6.4 Providing prior information and what to consider during the consent process

According to the Italian deliberative workshop conducted by WP4, "participants point to rigorous consent procedures and ethics committees as two avenues for control. Despite inconclusiveness in terms of governance responsibilities, unanimity exist to the position that **ethical use of cell donations must be guaranteed through strict governance structures, control and ethical oversight procedures** to ensure ethically responsible, transparent and safe storage and use of cells, tissues or organoids in biobanks".

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Taking this into consideration, there are 4 principles to be considered for sound informed consent:

1. The donor is able to understand the information delivered orally and in writing by the physician or medical advisor and to restitute it, including the withdrawal procedure and its consequences for the safeguarding of his/her biological samples and personal data.

2. The donor has the capacity to make the decision to allow the storage and use of his/her biological material and personal data.

3. Consent is voluntary, and no manipulation, incitation or promises are made in any way. No financial inducement or other personal benefit, except for financial compensation for travel expenses, should be offered to research participants. Consent must be prior, free and informed, and must be obtained for the collection of biological samples and associated data of any kind, whether by invasive or non-invasive procedures, and their subsequent processing, use and storage.

4. The physician or medical advisor must "provide information on the treatment to be followed and on the course of the study, including the expected personal benefits and risks", and the likelihood of the benefits and risks (and their severity and/or frequency) occurring.

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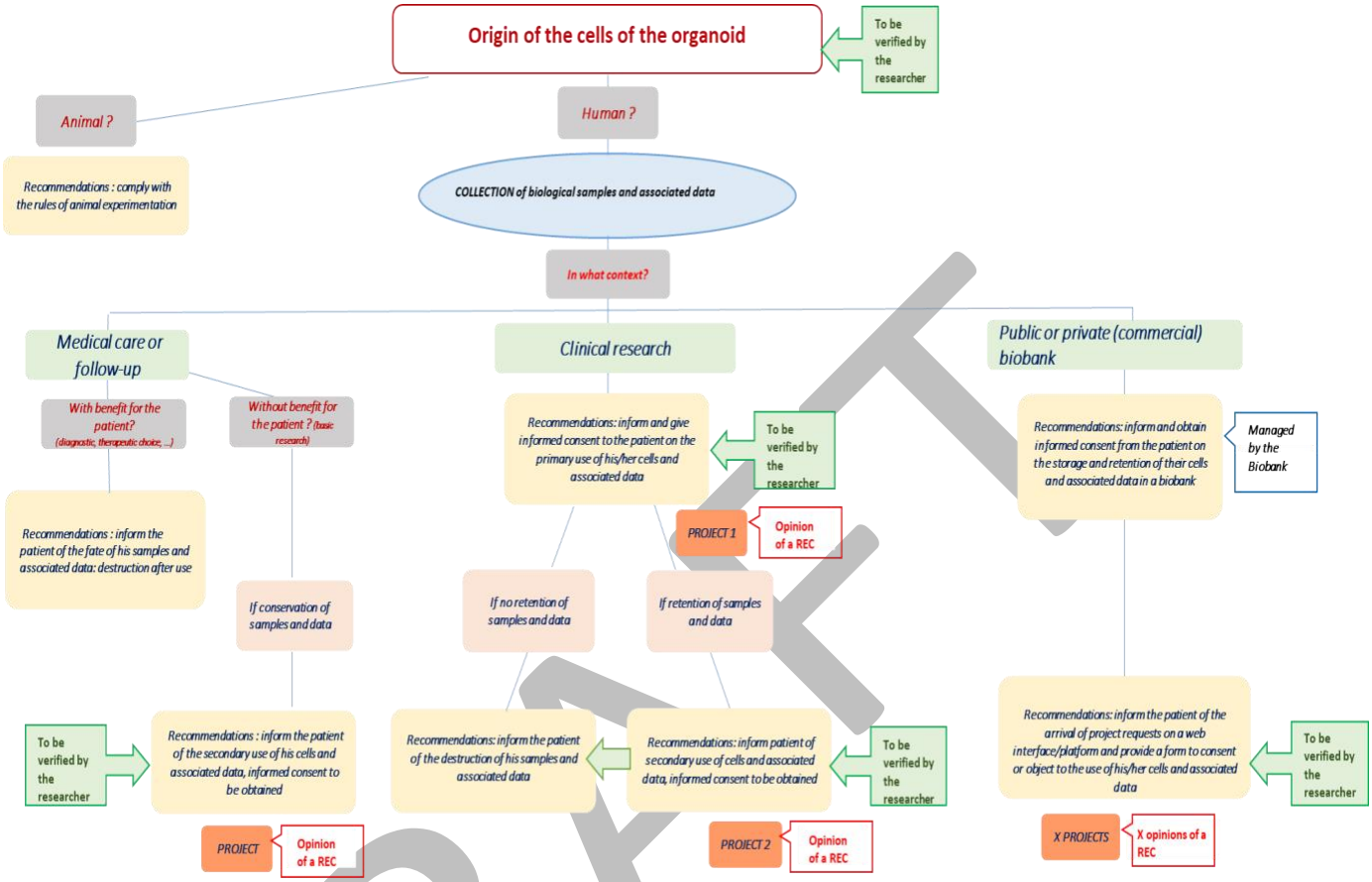

Diagram on the different contexts of the collection of biological samples and associated data

6.5 Construction and use of organoids

Specific aspects of the consent considering the future use of the organoids are addressed in this the following sections.

Organoids are simplified models of organs, composed of specific cell types which, when placed in suitable culture and environmental conditions, self-organise in three dimensions. The origin of the cells needed to construct an organoid is diverse, depending on whether they are derived from, or are pluripotent or adult stem cells from various organs. Embryonic pluripotent stem cells (ESCs) or induced pluripotent stem cells (iPSCs) have the particularity of being able to give rise to more than 200 cell types representative of all the tissues of the body. Multipotent stem cells, as are adult stem cells are derived from foetal or adult tissues with the particularity of giving rise to one or more cell types. In grafts, they ensure tissue renewal. Tumoroids are formed from tumour stem cells contained in biopsies or surgical removal of tumours.

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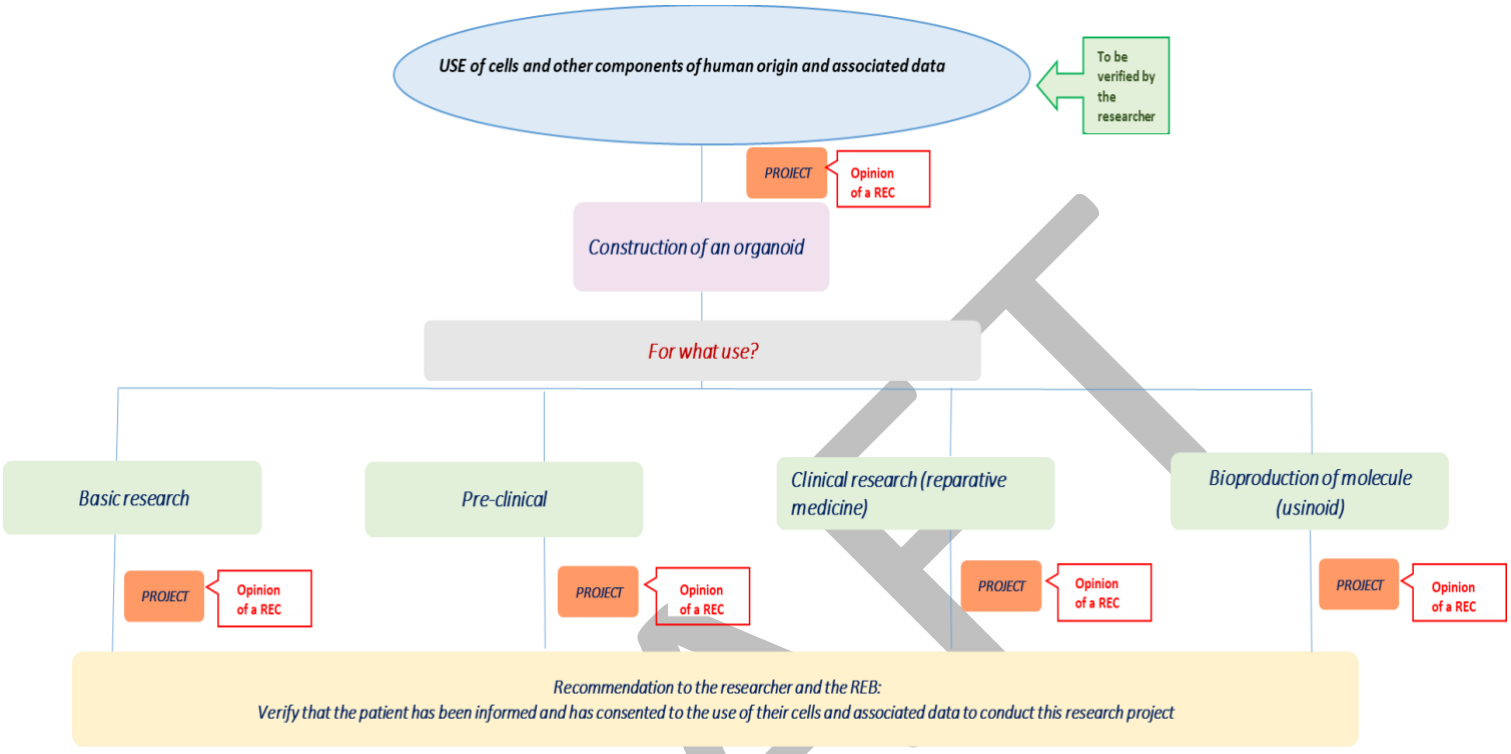

Diagram on the different uses of an organoid

6.5.1 Checklist on the type of information to be provided to donors: 3 cases depending on the use of the organoids

1. In the context of basic research or pre-clinical research	**2. In the context of clinical research or clinical use**	**3. In the context of industrial and/or commercial bioproduction of organoids, molecules, proteins, ...**
A statement that the study involves the collection of biological samples and associated data, an explanation of the general framework in which they will be used to construct an organoid.	A statement that the study involves the collection of biological samples and associated data, an explanation of the general framework in which they will be used to construct an organoid, and an explanation	A statement that the study involves the collection of biological samples and associated data and an explanation of the general framework in which they will be used/commercialised to build an organoid/factoroids and an

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	of the objectives of the study or the clinical use of the constructed organoid.	explanation of the objectives of the study or use.
Precise information on the storage of biological samples: where, how and under whose responsibility. additional information will be provided on the pseudo-anonymisation of samples with the possibility of destruction or anonymisation (no destruction)	idem	idem
The expected duration of participation: o active (at the time of sampling with a description of the modalities) o duration of storage (samples and data) o of the organoid construction project o duration of organoid storage	idem	idem
A description of any reasonably foreseeable risks, discomforts or inconveniences associated with the collection of cells/tissues prior to the construction of an organoid.	A description of any reasonably foreseeable risks, discomfort or inconvenience associated with the clinical trial	A description of any reasonably foreseeable risks, discomforts or inconveniences associated with cell/tissue harvesting prior to the construction of an organoid/factoroid.
A statement describing the procedures adopted to ensure the protection/confidentiality of privacy and data (personal, health, genetic biological...).	idem	idem
A statement that participation is free and voluntary with no impact on medical follow-up in case of refusal.	idem	idem
A statement giving the subject the opportunity to ask questions, to be informed about the use of the organoid and to be able to object to it without any consequences.	idem	idem
Information about the possibility of withdrawing consent at any time without any consequence for the donor, with an explanation of the material financial and moral consequences of such withdrawal for the research, the clinical trial, the various uses undertaken or planned	idem	idem

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Information on the persons and/or organisations organising and financing the storage and/or investigation.	idem	idem
A description of the expected benefits of this research.	idem	idem
A description of any planned genetic testing.	idem	idem
The contact details of the referring doctor who can be contacted to obtain relevant answers to the participant's questions.	idem	idem
	For investigations involving risk, an explanation of the availability of treatment or compensation for harm. The insurance cover, taken out by the sponsor, must be mentioned as well as the contact details of the person to contact in case of injury or adverse reaction	
An explanation of what will happen to the data/samples and the constructed organoid at the end of the research period and whether the data/organoid will be kept or sent/sold to a third party in France or abroad for further research	idem	idem
Information on what will happen to the results of the research and under what conditions donors could access this information.	idem	idem
Information indicating the possibility of future re-use of the biological samples, organoid and associated data in new projects.	idem	idem
Special case of organoid biobanks: Indicate the FP or website set up to inform the patient in real time of new projects.	idem	idem

6.5.2 Differential checklist that could be included in the consent form

Following the information, given as recommended above, to the donor on the future use of the organoids, the consent form should include a questionnaire with checkboxes to consent or not to the different uses of the cells, tissue and organoids to be generated.

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Do you consent to:

Genomic studies - on your cells limited to your mutation			yes	no
- on your whole genome			yes	no
Generating iPSC from your cells			yes	no
Generating organoids from your cells (list of organs to be mimicked with checkboxes, with special mention to embryonic models, cerebroids and reproductive tracts and open space to specify which organ must not be mimicked).				
Transfer your cells, tissue, organoids to other laboratories				
in your country	similar research purposes	academic laboratories	yes	no
		private research laboratories	yes	no
	other research purposes	academic laboratories	yes	no
		private research laboratories	yes	no
abroad	similar research purposes	academic laboratories	yes	no
		private research laboratories	yes	no
	other research purposes	academic laboratories	yes	no
		private research laboratories	yes	no
Commercialisation			yes	no
Sample storage duration with data:	5 years ☐	10 years ☐	Unlimited ☐	

6.6 Need for new consent

If significant changes are to be made to the ongoing study, whether it is basic research, pre-clinical and clinical studies or production, the investigator or the biobank should inform the donors of the new issues and ask them for a new informed consent. In long-term studies, it must be ensured that each participant has consented to the use of organoids derived from their cells until the end of the study (unless it is a broad consent as defined below). Refer also to the Chapter 6.8 “Typology of consent” below.

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6.7 Withdrawal of consent

Where biological samples are taken for the construction of an organoid for medical and scientific research purposes, consent may be withdrawn by the donor. In case of withdrawal, the biological samples which were used for the construction of the organoids, shall be destroyed and the personal data shall be deleted. The withdrawal of consent must not result in any inconvenience to the donor.

Nevertheless, the International Society for Stem Cell Research guidelines point that many researchers and institutes use Informed Consent documents that allow donor withdrawal only until the moment that the cells enter processing, for example in the case of hiPSC generation, until the moment the cells are thawed for reprogramming. Once the cells transformed, reprogrammed or used to generate organoids, the costs and number of samples derived from the initial tissue grows exponentially, multiple banks with various (genetic) modifications may have been generated and the cells widely distributed to users under MTAs that have been approved and signed in good faith by research institutions or biobanks.

Indeed, if a donor withdrew after several years while the project is still ongoing, the task of tracking down all the biological (sub)samples for destruction would be extremely costly and highly unlikely. The recommendation that could be made to avoid this difficulty would be to propose a possible withdrawal until the cells are thawed and cultured.

The information on the duration of secondary research to be brought to the donor is complex insofar as the lines are immortal and can be distributed by a biobank (see paragraph 6.1.3). For example, the original hESC lines have now been in use for almost 25 years. There are often reasons to return to archived samples after many years, for example to check for genetic drift or to study a rare disease.
In the situation where the donor has agreed to the use of his or her samples for secondary studies for which there is not yet clear visibility, differential storage with options ranging from 5 years, 10 years, and lifetime for which the donor would give notice would be recommended. If compliance were to be a major issue with the proposed operational guidelines, this could jeopardize their adoption.

To combine our commitment to informed consent and to respect of research conditions, an anticipation of the potential uses (see the checklist above) and a follow-up procedure (third party in charge of representing the donor's interests) should be developed.

6.8 Typology of consent

The consent that must be signed by the donor of cells or tissue after clear and honest information is mandatory to protect the rights of the donor regarding his/her biological material and personal information but it has also to facilitate research, not hinder it. With these two requirements in mind, four types of informed consent can be considered:

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1. Consent can be defined as traditional and specific when it is a clear project with no intended re-use of biological samples and derived organoids

2. Consent can be defined as broad, when the consent for a research project foresees a re-use of biological samples. In this context, the consent must include a clear description of the research areas and future directions of the research (for example to perform genetic analysis), as well as the possibility or commercialisation and/or exportation of the organoids if it is pertinent, so that the donor can consent.

In the specific case of the donation of biological samples to research, consent is broad for any purpose provided that the samples are anonymised.

In case cell lines, primary cells and organoids associated with personal data are distributed by commercial companies, the broad consent could be incorporated in a kind of passport accompanying the transfer of biological samples.

3. Consent can be defined as dynamic, when the scope or purpose of the project changes over time and a two-way communication is established between the donor and the user via a biobank. In the specific case of organoids, where research is rapidly evolving, it is difficult, if not impossible, for donors to keep up with all the innovative technologies and implicit organoid models and designs. Therefore, a dynamic, multi-option procedure with initial consent from the patient for the initial collection and storage of their samples/tissues and associated data in a biobank would be appropriate. The biobank would then act as a one-stop shop for the collection of information for researchers and help to inform patients along the way using an interactive platform. In the specific case of a research project aiming at the construction of organoids from donor cells or cell lines obtained from donor cells (e.g. iPSC), the researcher will be asked to describe the constitution of the organoids produced and the related research. For each project, an online consent form will be offered to the patient.

In the particular case, where biological samples and associated data are transferred to a foreign team, the patient must receive transparent information on the reason for this transfer and on the identity of the research team and the consent must include a clear explanation of the transfer and the fate of the biological samples and associated data.

The last part of the options may concern consent for the use or even the transfer of organoids to industry and other non-academic structures.

4. Consent can be defined as entrusted to a third party, when exchanges between donors and biobanks be processed by an independent intermediary body, responsible for representing the rights and interests of the donors. Donors retain their right to withdraw from the study at any time (where possible), but delegate consent for the planned research projects to the intermediary organisation.

Several aspects need to be considered in the choice of such an intermediate governance body, such as constant attention to data confidentiality, constant public engagement in the whole process, fairness measures and ethical institutions involved to give ethical advice on the design of the project involving organoids.

- Privacy by design, incorporating privacy safeguards throughout the organoid exchange infrastructure. The most appropriate confidentiality standards are framed by the General Regulation ((EU) 2016/679 of the European Parliament and of the Council of 27 April 2016)

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on data protection, apply by default, with systematic anonymization of biological samples and associated data.

- Commitment of participants: Substantial involvement of (groups of) donors and/or the general public in the design and ongoing adaptation of biobank governance.
- Benefit sharing in the case of the commercialization of the samples: The equitable sharing of monetary and non-monetary benefits generated by the exchange of organoids among all parties involved, including donors, patients and society.
- Ethical oversight: The involvement of ethical oversight bodies in the different stages of organoid exchange.

The above list can be completed and adapted to the cultural and evolving context of organoid research and commercialisation, and several remarks and improvements can be added to the proposed model.

Further developments will be needed to handle questions regarding use of cells or tissue derived from initial cell donations (such as iPSC or organoïds) and will depend on choices made about conditions of withdrawal of consent.

6.9 Need of a taskforce for further analysis on consent

Taking into consideration the complexity of defining the best strategy for achieving informed consent (for both participants and researchers), types of consent, as well as the numerous questions regarding withdrawal of consent, the HYBRIDA consortium decided to create a taskforce dedicated to this particular subject and to continue reflection and analysis on this subject before proposing clear guidelines regarding the typology and particularities of informed consent in the organoid field. Results will be available in the future versions of the Guidelines (V2 and V3).

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7 OPEN ETHICAL QUESTIONS

The Operational Guidelines will address the following open questions:

- *Nomenclature and moral status of embryo models*
- *Functions of nervous system organoids and assembloids and their relationship to sentience, pain, consciousness*
- *Do we need a wider definition for organoids on chips, tumoroids….?*
- *Can an organoid producing germ cells be allowed?*
- *Organ-on-chip versus organoid-on-chip (see appendix 1 from Xavier Gidrol TO BE ADDED)*
- *Is a factoroid still an organoid? An organoid mimics one or more functions of an existing organ and a factoroid can significantly deviate from this definition.*

7.1 Embryos and ethical questioning: HYBRIDA's second taskforce

Recent years saw the development of embryo models generated from aggregates of pluripotent stem cells that exhibit aspects of embryonic development. Such embryo models are not models of organs like organoids but models of organisms. They are useful to study mammalian development. Considering the many commonalities with organoids, we consider that they enter in the field of the HYBRIDA project. We take here the definitions developed in the most recent ISSCR recommendations concerning stem cell-based embryo models:

> *"Advances in cellular engineering make possible the assembly, differentiation, aggregation, or re-association of cell populations in a manner that models or recapitulates key stages of embryonic development. Such experimental systems can provide essential insights into embryo and tissue development but raise concerns when such structures achieve complexity to the point where they might realistically manifest the ability to undergo further integrated development if cultured for additional time in vitro. There are two types of stem cell-based embryo models.*
>
> *Non-integrated stem cell-based embryo models: These stem cell-based embryo models will experimentally recapitulate some, but not all aspects of the peri-implantation embryo, for*

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example differentiation of the embryonic sac or embryonic disc in the absence of extraembryonic cells. These stem cell-based embryo models do not have any reasonable expectations of specifying additional cell types that would result in formation of an integrated embryo model. Gastruloids are an example of a non-integrated stem cell-based embryo model.

Integrated stem cell-based embryo models: These stem cell-based embryo models contain the relevant embryonic and extra-embryonic structures and could potentially achieve the complexity where they might realistically manifest the ability to undergo further integrated development if cultured for additional time in vitro. Integrated stem cell-based embryo models could be generated from a single source of cells, for example expanded potential human pluripotent stem cells capable of coordinately differentiating into embryonic and extraembryonic structures. Alternatively, integrated stem cell-based embryo models could also be generated through the formation of cellular aggregates where extraembryonic/embryonic cells from one source are combined with embryonic/extraembryonic cells from different sources to achieve integrated human development. This might include using non-human primate cells as one of the sources. Previous restrictions on preimplantation human embryo culture (the "14-day/primitive streak rule") were not written to apply to integrated stem cell-based embryo models. Thus, these guidelines specify the imperative for specialized review when such research is designed to model the integrated development of the entire embryo including its extraembryonic membranes. A guiding principle of review should be that the integrated stem cell-based embryo models should be used to address a scientific question deemed highly meritorious by a rigorous review process. Blastoids are an example of an integrated stem cell model[26]*"*

The recent development of so-called "synthetic mouse embryos" by the teams of Jacob Hanna and Magdalena Zernicka-Goetz raised major ethics concerns among the scientists, especially as a biotech company plans to make "human synthetic embryos" in the near future[27]. As there are no precise regulations on this emerging "synthetic" technology, the field of bioethicists revolves to the natural human embryo research, questioning and regulation. Debating on the moral status of the human embryo might prove useful to see how their surrogates could be foreseen and regulated later on.

In this sense, the HYBRIDA Consortium decided to dedicate several discussions and a joint working group on the development of different scientific embryo models. In order to better understand the use and development of various embryo models, please check the below typology.

[26] International Society for Stem Cell Research, *Guidelines for Stem Cell Research and Clinical Translation*, Laboratory-based Human Embryonic Stem Cell Research, Embryo Research, and Related Research Activities Chapter, 2021. Accessible at: isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.

[27] CBN News. *Israeli Biotech Firm Plans to Create Human Embryos to Harvest Organs, Field Experts Say There are Ethical Concerns*, 16/09/2022. Accessible at: https://www1.cbn.com/cbnnews/health/2022/september/israeli-biotech-firm-plans-to-create-human-embryos-to-harvest-organs-field-experts-say-there-are-ethical-concerns

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7.1.1 When studying the properties of embryos, several types of entities are likely to be used:

a. The various **embryonic models for scientific use** (EMSUs.) They can be created because the stem cells are capable of forming structures that recapitulate aspects of embryo organization and development. Some authors such as John Aach or Antonio Regalado refer to the emergence of "synthetic embryology".

b. **The chimeras.** These are organisms that contain at least two groups of genetically different cells, coming from individuals or different species (intraspecies or interspecies chimeras). These are obtained by introducing pluripotent stem cells, embryonic stem cells (ESC) or iPS cells into an embryo (blastocyst). Each cell population retains its own genetic character and the result is a mosaic. The interspecies chimeras notably include human-animal chimeras (human embryo into which animal cells are introduced) and animal-human chimeras (animal embryo comprising human cells).

c. **The hybrids and cybrids**. A hybrid is formed when a spermatozoa from one individual is used to fertilize the ovum from another individual of a different species. As a consequence, each cell of the hybrid organism has the chromosomes of both species. A cybrid is a cytoplasmic hybrid created when the nucleus of a cell of an organism is introduced into an enucleated ovum of an individual from another species or the same species. The cybrid is a virtual-clone of the organism whose nucleus has been transferred. Hybrids and cybrids are often, inaccurately, referred to as chimeras. We must emphasize again that many countries ban the creation of entities combining human and animal genetic heritage.

d. **Cloning** is a procedure used to identically reproduce the initial biological entity, for example monoclonal antibodies, which are all identical to each other. Nuclear transfer can be a technical stage of cloning if the purpose is reproductive and the transfer is between two syngeneic animal cells (with the same genome). This is not the case for scientific research in which the embryo must be destroyed at the end of the experiment and in which the embryonic entity constructed is not similar to the embryo supplying the nucleus transferred.

e. **The parthenotes.** These are embryos obtained through parthenogenesis, i.e. through the division of an unfertilized female gamete.

f. The **embryos constituted by the micromanipulation** of constituent cell elements (e.g. mitochondrial donation) or by eliminating some of their constituents (e.g. restoration of diploidy). Mitochondrial replacement therapy is a case of intraspecies cybrid.

g. T**he embryos created for research by IVF**.

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7.1.2 Two main ethical issues can be identified

A) Inappropriate naming

As the writer and philosopher Albert Camus said, "*to misname an object is to add to the misfortune of this world [mal nommer un objet, c'est ajouter au malheur de ce monde]*". In the case of new technologies, the words "synthetic", "embryo-like", "human entities", etc., should be prohibited. As mentioned in several publications quoted below, such as the Guidelines of the ISSCR, or the INSERM Ethics Committee articles on the ethics of embryo models from 2019, the use of "synthetic embryos" or "stem cell-derived embryos does not help in conveying a clear message to the public reflecting the state of scientific innovations. An accurate description of the models described in Hanna's and Zernicka-Goetz works would be "mouse embryo models E8.5".

To make ethical overview intelligible, transparent and accountable, researchers must report on their research in clear and well-defined terms[28]. As yet, models are rudimentary and imperfect. They only partially reflect the *conceptus* and they lack the capacity to develop into a living organism[29]. Because of these limitations, these models are typically not included, neither biologically nor legally, under the class of embryos in the large majority of jurisdictions. The term 'synthetic' or 'artificial' embryo is sometimes used to refer to these structures. However, in order to accurately reflect the state of the research, the ISSCR suggests to use the term 'embryo model' instead[30]. The reason is that these models form from stem cells that spontaneously but imperfectly unleash their intrinsic potential to re-enact developmental processes. They are thus neither synthetic nor artificial but rather reflect attempts for potent cells to 'act naturally' by expressing their potential.

Moreover, terms like 'synthetic' indicates the use of non-natural elements (obtained by synthesis) while, at the same time, erroneously indicating that we are dealing with an embryo proper. Such an inadequate terminology implies the value judgment that these are embryos, although outlandish ones. The terms 'synthetic' and 'artificial' also belie the historically evolving understanding of the embryo by suggesting that the same structure is 'natural' or 'unnatural' solely because of its origin (Ball 2011). Furthermore,

[28] Kirstin R W Matthews, Daniel S Wagner, Aryeh Warmflash, Stem cell-based models of embryos: The need for improved naming conventions, Stem Cell Reports, 2021. Accessible at: https://pubmed.ncbi.nlm.nih.gov/33770498/.

[29] Eszter Posfai, John Paul Schell, Adrian Janiszewski, Isidora Rovic, Alexander Murray, Brian Bradshaw, Tatsuya Yamakawa, Tine Pardon, Mouna El Bakkali, Irene Talon, Natalie De Geest, Pankaj Kumar, San Kit To, Sophie Petropoulos, Andrea Jurisicova, Vincent Pasque, Fredrik Lanner, Janet Rossant, *Evaluating totipotency using criteria of increasing stringency*, Nature Cell Biology, 2021. Accessible at: https://www.nature.com/articles/s41556-020-00609-2.

[30] Amander, T Clark, Ali Brivanlou, Jianping Fu, Kazuto Kato, Debra Mathews, Kathy K Niakan, Nicolas Rivron, Mitinori Saitou, Azim Surani, Fuchou Tang, Janet Rossant, *Human embryo research, stem cell-derived embryo models and in vitro gametogenesis: Considerations leading to the revised ISSCR guidelines,* Stem Cell Reports, 2021. Accessible at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8190666/.

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"synthetic" is an adjective that is often negatively connoted. Merriam-Webster definition for synthetic[31] is the following:

(1) **:** of, relating to, or produced by chemical or biochemical synthesis especially **:** produced artificially synthetic drugs synthetic silk
(2) **:** of or relating to a synfuel
b **:** devised, arranged, or fabricated for special situations to imitate or replace usual realities
c **:** factitious, bogus

John Aach also proposed Synthetic Human Entities with Embryo-like Features (SHEEFs). To speak of "human entity" brings to mind a human being, which these models are not. They are human in the sense that the genome of their cells is human, but they do not have all the characteristics that make the human embryo a human being.

The worse of all should be “Mini-Mes". All authors rightly consider that this expression is meaningless to characterize these entities. Moreover, even natural embryos are not mini-mes, which implies a personal identity that does not yet exist.

Finally to be more clear and to make easy to understand the difference between the naturally occurring phenomenon and the scientific artifact used to model it, the Inserm Ethics Committee in its 2019 opinion[32] proposed “embryonic” and not “embryo”. Indeed “embryonic” indicate both “relating to an embryo” and being in an early stage of development**:** *incipient*, *rudimentary* (adapted from Meriem-Webster).

7.1.2.2- The moral status of embryonic models

The use of embryonic models allows to gather scientific knowledge and eventually societal benefits, while avoiding the constraints normally associated with the use of embryos. Scientific advances are narrowing the gap between models and embryos and, consequently, the moral and legal gap between models and embryos. For example, Australia now considers that embryonic models are similar to embryos. Eventually, embryonic models will pass a tipping point after which there is no reason to value and regulate them differently from embryos. Put differently, at a certain point of experimental sophistication, the embryonic models could pass a 'Turing Test’, which entails that an evaluator who lacks information about the origins of the embryonic model would not be able to tell it apart from a human embryo. To our mind, from this point on, any meaningful distinction between the embryonic model and the embryo, biologically as well as morally, has disappeared. We thus propose that a more truthful path for terminology is to name them embryonic models, thus recognizing their current limits, but that once they are assumed equivalent, they become fully entitled as embryos regardless of the way they were formed.

[31] Merriam Webster Dictionary. Accessible at: https://www.merriam-webster.com/dictionary/synthetic
[32] Bernard Baertschi, Marc Brodin, Christine Dosquet, Pierre Jouannet, Anne-Sophie Lapointe, Jennifer Merchant, Grégoire Moutel, *Research on Embryos and Embryonic Models for Scientific Use* (EMSUs), , Accessible at: https://www.hal.inserm.fr/inserm-02373609/document.

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The extent to which embryonic models approaches this tipping point is of course dependent on how the embryo is defined. In other words, the accurate description of scientific advances, the adequate formulation of clinical research aims and the quality of moral reasoning and policymaking pertaining to embryo models require a definition of the embryo that is congenial to these ends.

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8 CONCLUSIVE REMARKS AND RECOMMENDATIONS

8.1 General remarks

An organoid does not have the same properties and functions as the organ. It is therefore incorrect to refer to organoids as mini-organs, and communicating an incorrect information is a misconduct.

8.1.1 For the Research field

Do not use the term "mini-organ" to designate organoids: use cerebroid, nephroid, hepatoid. Invent a name for each type of organ (cardioid?, etc.)

Do not use human on chips (prefer avatar on chip) or organ on chips (prefer, cerebroid on chip, etc., or physioid on chip if interconnections between organoids)

8.1.2 For the Bioproduction field

- Do not use the term organoid instead of “factoroid” or “manufacturoid” in the bioproduction context.

- As for the production factories, the production process by factoroids must be validated by the regulatory agencies according to what is produced (medicine, dietary supplements, graft, etc.)

- Use the mode of thinking already underway for the factory of the future

- Based on the model of the factories of the future, there will be work to do on the management of *factoroid* banks. Mission to visit existing bioproduction centers[33].

[33] Such as the Yposkesi example of therapeutic vector and cell batch production. Accessible at: https://www.yposkesi.com.

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8.1.3 For the Pre-clinical field

- Build the statistical toolbox linked to the use of innovative approaches (validation of care protocols rather than of molecules on more or less precisely stratified cohorts)

- Define the advantages and disadvantages (benefit/risk balance) of the use of organoids (e.g., blood-brain barrier or intestinal barrier) in relation to the models currently accepted by the regulatory agencies.

- Based on the model of the testing centres, preclinical CRO and Hubrecht institute, there will be work to be done on the management of organoid banks (conservation, storage of organoids and associated data). Mission to visit existing reference centres.

8.1.4 For the Clinical field

Define the GMP quality level for organoids clinical use for all three objectives. Be inspired by what exists for cell therapy. Keep in mind that this is the guidelines section

- Do not use the concept of 'symbiote', but rather that of »innovative medical bio-devices" (possibly linked to digital medical devices-DMD-). This relates to the Code of conduct for research integrity section (Interaction with public)

- For ITD, innovative medical devices (IMD) and translational research (personalization of treatment) parts, description relates to the regulatory part that we will have to define. An organoid cannot be a graft because there is always a modification.

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9 GLOSSARY

Ethics Terminology Unwrapped

Autonomy:

Evaluator to evaluator: in order to evaluate, there must be consent from the researcher being evaluated, and therefore a procedure that is sufficiently clear for the evaluated person to understand and accept it.

Accountability:

Researcher to Evaluator: Anticipate as much as possible the positive and negative impacts of my work in a given context and at a given time

Evaluator to researchers: anticipating the impact of the evaluation done

Evaluator towards the institution: anticipation of the impacts of the evaluation on the functioning of the institution (suffering at work for example)

From the institution to the evaluator: provide the means to carry out the evaluation according to the defined principles, avoid paradoxical injunctions (DORA versus bibliometric index).

From the institution to the researcher: working conditions to enable researchers to develop honest, fair and responsible research, in a collaborative rather than competitive framework.

Benevolence (benevolence):

Evaluator to evaluator: consistency in evaluation follow-up.

Reliability:

Researcher to researcher: what I do can be reproduced and in the absence of a hidden variable, can be replicated (technical robustness)

Honesty:

Researcher to researcher: the data produced are not fabricated, falsified, embellished or plagiarized

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Evaluator to researcher (**equity/fairness**): independence from any relationship or conflict of interest. Treatment of all files as objectively as possible

Justice:

evaluator to evaluator: the principles of justice are explicit and identical for all committees. Serving on a committee means accepting these principles

Opening:

institution to institution: commitment to open science (open access, open data -FAIR- open methodologies and protocols) promotion of interdisciplinarity, multidisciplinarity and transdisciplinarity, promotion of collective work

Non-maleficence:

Evaluator to evaluator: encourage accompanying evaluation rather than punitive evaluation.

Norm

A norm is a proposition that expresses what must or must not be done.

Ex. you shall not kill!

Principle

A principle is a standard that expresses an important moral consideration and serves as a general guide.

Ex. The principle of beneficence in medicine

Rationality of a research work

Ability to decipher the research strategy, particularly through the proper use of citations and the description of the current state and the questioning

Respect:

Researcher to evaluator: acceptance of evaluation protocol, acceptance of decisions

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Evaluator to researcher: acceptance of a counter argument

Institution to evaluator: acceptance and use of evaluation results

Transparency:

Researcher to researcher: I give access to my raw data, my methodology and source of material used, as well as the description of my environment and the rationality of my scientific strategy (illustrated by the description of the state of the art and the citations that document it) and the conditions that allow me to carry out the work in complete safety (**safety**, **transparency**)

Evaluator to researcher: access to evaluation procedures and the rationale for each evaluation.

Evaluator to institution: validation by the institution of the evaluation procedures.

Institution to evaluator: feedback to the evaluator on the use of the evaluation work

Institution to researcher: the rules of governance are clearly defined so that researchers can evaluate their constraints on freedom of research and expression, and know the procedures for scientific arbitration (choice of priority themes), within a constrained budget

General Terms in the Organoid Filed

Anonymised (data): the data has been rendered anonymous in such a way that the data subject can no longer be identified (and therefore is no longer personal data and thus outside the scope of data protection law).

Pseudonymised (data) means to divide the data from its direct identifiers so that linkage to a person is only possible with additional information that is held separately. The additional information must be kept separately and securely from processed data to ensure non-attribution.

Replicability in research

Ability to reconstruct a set of data from the description of the materials and methods and the research strategy and then from this new set of data to reproduce the results and conclusions if there are no hidden or unaccounted for variables (e.g. particularities of the working environment, specificity of the animal house, etc.)

Reproducibility in research

Ability to reproduce figures and discussion of results and conclusions based on access to raw data and description of materials and methods used

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11 ANNEXES

11.1 Annex 1 WP5 INSERM team

Hervé Chneiweiss (MD-PhD) is a neurologist and neuroscientist, research director at the CNRS. He has been involved in neurogenetic research on diseases such as cerebellar ataxias and then the molecular mechanisms involved in glial plasticity and the development of brain tumors. Technical approaches include proteomics, metabolism, epigenetics, cell cultures, animal models, single cell. He has published over 170 original scientific papers (h=46). He is currently director of the Neuroscience Paris Seine - IBPS research center (CNRS/Inserm/ Sorbonne University). HC is also involved in bioethics, first (2000-2002) adviser for life sciences and bioethics to the Minister of Research and Technology, member of the Scientific Council of the Parliamentary Office for Scientific and Techniques assessment (2003-2016), member of the National Consultative Ethics Committee (CCNE; 2013-2017), and currently as Chairman of the Inserm Ethics Committee and of the UNESCO International Bioethics Committee. Former editor in chief of Medicine/Sciences (2006-16). He has published several books for the general public (latest: "Notre cerveau", L'Iconoclaste, 2019).

MD by degree, with an MSc in molecular biology, Dr. Anne Dubart-Kupperschmitt has a long experience and expertise in the biology of human stem cells, gene transfer and molecular and cellular gene therapies. Her research interests are currently focused on the differentiation of human pluripotent stem cells into hepatic cells, mainly hepatocytes and cholangiocytes, as well as the generation of liver organoids from patient-specific iPSCs in order to model liver diseases, setup gene/cell therapy approaches or for drug screening and toxicology studies. She published more than 100 peer-reviewed articles. She is a member of the steering committee of Research Group on organoids of the French alliance for life sciences (Aviesan) in health technologies and molecular basis of life, where she is more specifically in charge of the bioethics work package. She is also member of the Inserm Ethics Committee.

A Philosopher by degree, Dr. Bernard Baertschi was Senior Lecturer at the Institute for Biomedical Ethics and at the Department of Philosophy in the University of Geneva (Switzerland) till 2014, when he retired. His doctoral dissertation was dedicated to a French philosopher from the post-enlightenment, Maine de Biran, but he was soon interested in moral philosophy and bioethics. He was a member of several ethics committee in Switzerland: the Federal Ethics Committee on Non-Human Biotechnology (ECNH), the Ethics Committee for Animal Experimentation of the Swiss Academy of Science (ScNat), and in France he is presently member of the Inserm Ethics Committee, where he leads the Working Group on organoids. He published several books on the ethics of biotechnologies (genetic engineering and medically assisted procreation), of synthetic biology and of neurosciences.

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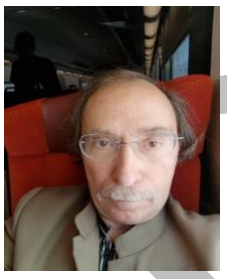
Dr. Jean-Luc Galzi graduated in biochemistry before receiving his PhD in biorganic chemistry. He then trained 8 more years in molecular neurobiology at the Pasteur Institute, Paris, before starting his own research group on dynamics and pharmacology of G Protein-coupled Receptors in Strasbourg. He is currently research director at the CNRS, Director of the Research Institute of the School of Biotechnology and principal investigator in chemical biology of chemokines and their receptors. His research interests are in pharmacology, and to do so, in all techniques and tools facilitating drug discovery and development. He published more then 100 peer-reviewed articles mostly in chemistry and pharmacology, filed 10 patents and founded a startup company in drug discovery. JL Galzi is currently directing a national research infrastructure in bioactive compound discovery (probes and drug candidates) comprising academic chemical libraries, screening platforms, chemoinformatics and preclinical ADME studies. He also coordinates a work group on organoids with four main topics on design and construction, characterization, applications and training on organoids.

Corinne Sébastiani is a molecular Biologist by degree focused in Genomic (sequencing and cartography), with an MSc in intellectual property and patent law and with extensive experience in clinical research focused on new technologies (such as cellular therapy, gene therapy, vaccine). Her main research interests include the animation and the steering of the French community on new health technologies. She is a member of steering committee of Research Group on organoids of National Centre for Scientific Research (CNRS) including work packages of clinical research and regulation, bioethics and training. She is also member of the Inserm Ethics Committee.



Jacques Haiech is Honorary Professor of Biotechnology at the University of Strasbourg. He holds a master's degree and an agrégation in Mathematics, a master's degree and a thesis in Biology. He has worked on the understanding of information management by the cell both in its fundamental research aspect and to develop drugs (oncology and inflammatory pathologies). Through his responsibilities in research administration (Director of the National Genomics Program, Director of the Biology-Health Department of the French Ministry of Research and Higher Education, Scientific Delegate to the AERES), he has worked on research evaluation methodologies and more recently, on the links between scientific integrity and modes of evaluation of scientists.

PhD in Sociology from the École des Hautes Études en Sciences Sociales, Ioana Andreescu is an associated researcher at the Raymond Aron Centre for Sociological and Political Studies. Previously, she has been in charge of developing and implementing an education strategy for a better harmonization of innovative and socially responsible degree programs within EIT Health. She has contributed to several international projects, such as 'Digital Futures' or the 'European Space' from the European Commission. In 2015, she won the Henri Desroche Prize for social transformation projects.

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11.2 Annex 2 Ten conceptual uncertainties pertaining to the ontological status of organoids as hybrids (WP1)

One potential way to clarify the status of organoids given their extensive 'hybridity' is to explore explicitly the ways in which common conceptual distinctions break down when applied to this complex case. In this section, we provide a list of ten conceptual distinctions that are briefly defined in very general terms and applied to organoids. By reviewing some of the classical conceptual distinctions that can be applied to organoids, we provide a first conceptual map to be mobilized to form ontological judgments about organoids and in future discussions on ethical and regulatory issues raised by these entities.

The conceptual distinctions listed below rely on common sense, on canonical, philosophical concepts, and on more recent theoretical developments in philosophy of science:

1. From a legal viewpoint, human organoids are things, but they might also be related to persons in specific manners that should be investigated.

2. Organoids are objects of research and development, yet they might become subjects.

3. For many scientists, organoids are more than a mere cell culture, but they are not full organs, and even less organisms.

4. Are organoids living entities, or should we identify them as mechanisms?

5. Referring to another classical philosophical distinction, one could ask: are they natural entities or artefacts?

6. Organoids belong to science, as ways to gain knowledge, and they are also technologies, that is, objects designed to have an impact on the world we live in.

7. They belong at the same time to the category of research tools and to the category of potential clinical devices.

8. As tools for research and clinic, organoids are mere means, but they can also be seen as ends from the perspective of technological development or regenerative medicine.

9. We tend to think of organoids as actual biotechnological entities that have a certain nature, but most research using organoids is focused on their development and thus conceives them as part of a larger process oriented toward the future.

10. Certain kinds of organoids, such as chimeras, tend to blur the distinction, entrenched in common sense, between human and animal.

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11.3 Annex 3 What is behind the "ethics by design" requirement? (WP1)

1. Introduction

Ethics by design (ED) has been developed recently as **an approach prompting developers of new technologies to take into consideration ethical issues at the stage of the design process**. As can be seen through a short survey of the academic literature and the grey literature dedicated to the topic, **the main field of application of ethics by design is artificial intelligence** (AI). Yet, as mentioned sometimes, the ethics by design approach refers to a broader perspective on the ethics of new technologies that could be applied to many emerging technologies, including biotechnologies.

The H2020 SwafS call for proposal for organoids stipulated that: "The work undertaken is expected to produce operational guidelines for the field. The guidelines should ensure 'ethics by design' and be drafted to support the work of the research community, research ethics committees and integrity bodies" (p.47). What is the approach underlying the drafting of guidelines so that these guidelines "ensure ethics by design"? What is expected under this label? How to develop a methodology that meets the requirement?

The ED approach is guided by the need to anticipate effectively ethical issues that will arise with emerging technologies (=technologies in the making that are not yet entrenched in society). This is especially the case with AI, as strong impacts are expected on society, economy, social life, medicine, warfare, and other domains. When the impact of a technology is supposed to be strong (impact society as a whole, or have important consequences) and almost immediate (there will be no time to mitigate the risk once the technology is disseminating), the assessment of ethical issues and implementation of ethical principles have to occur at the earliest stage of technological development, that is, the design process. A technology that is designed as conforming to certain ethical standards is more likely to limit the negative consequences that may arise when it becomes widely used.

According to the family of "by-design" approaches, it is possible to implement certain options into the technology so that it conforms to the values that matter. For instance, instead of protecting privacy by placing limits on the use of data, privacy-by-design prompts the developer to produce a tool that can be functional while requiring a minimal amount of data. Indeed, it offers more guarantee to design a tool that collects a limited amount of sensitive data than to build a tool that collects a large amount of data and then to impose restrictions on their conservation and use.

The fact that ED has been developed with AI and robotics as main targets deserves further consideration. AI systems are not only artefacts that shape our environment, or artefacts that we use: they contribute to decision-making in very concrete ways. As *intelligent* systems, they are asked to sort, discriminate, or choose for us, in what could be *ethical* judgments (see for instance the debate on autonomous vehicles). The "laws of robotics" proposed by Asimov is a clear expression of the kind of constraints that we want to implement on technological artefacts that will make decisions.

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The problem is thus the following: is this approach fit for our object, organoid technology? Organoids do not make decisions. They are not artificial moral agents. However, they may be considered more generally as artefacts, or technological devices, and ED would apply to them in this general sense. But organoids are not any kind of artefacts, they are *biotechnologies*. Biotechnologies are a family of technological devices that build upon biological material and possess certain properties of living beings. Biotechnologies have a capacity to evolve and convey a sense of uncertainty – in a sense, researchers do not know what these entities are capable of. Also, the questioning around the development and use of organoids refers mostly to biomedical research. Contrary to many emerging technologies that are precisely the target of the ED approach, biomedical research is already regulated, with many procedures in place. For instance, research using human material or engaging human participants is supervised by laws and guidelines — up to the point that biomedical research is considered as a reference for developing regulations in other domains. What would we gain by *considering organoids as emerging technologies*? Is there something in the ethics of emerging technologies that could benefit bioethics/biomedical research ethics?

In this document, we will try to answer these questions by an in-depth analysis of ethics by design and its history, before turning to its application to biotechnologies.

2. Definition and history of ethics by design

There are several elements of context that should be reminded in order to capture the general ideas behind ED—and before asking how this approach can be put to use in our context. The expression "ethics-by-design" has been put forward for a couple of years in the EU as a keyword, up to the point that a recent EGE (European Group on Ethics in Science and New Technologies) statement claimed, in a somehow retrospective reading of history, that the "design turn and the idea of the value-laden nature of scientific and technological innovation has also been foregrounded by EU research funding in the last decades." (EGE 2021) This is especially the case through two European SwafS projects: SIENNA & SHERPA. SIENNA (Stakeholder-Informed Ethics for New technologies with high socio-ecoNomic and human rights impAct, 2018-2021) provided ethical frameworks for human genomics, human enhancement, artificial intelligence, and robotics. It contains also a reflection on the methodology on the production of guidelines for emerging technologies that is of particular importance for HYBRIDA (Brey et al. 2021). SHERPA (Shaping the ethical dimensions of smart information systems—a European perspective, 2018-2021) addressed smart information systems with a specific emphasis on ethics by design. Both projects prompt software designers and developers to follow the ED approach, proposing concrete steps to take action.

To say of something that it has to be ethical *by design* is equivalent to saying that it has to be designed as ethical. The ED approach has particularly been developed in the context of EU SwafS projects SIENNA and SHERPA. One of the objectives of these projects was the production of guidelines ensuring ED for AI developers. According to these projects, ED starts from the definition of general principles, or ethical values, that we want to respect (e.g., fairness). These values are translated into more specific requisites at the system level (e.g., in order to comply with fairness, we want the system not to produce discrimination, such as gender or racial bias). **Guidelines are proposed to ensure that the requisites are**

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taken into consideration during the development of the product (e.g., test/screen for bias at steps X and Y) and that the approach can be adapted to many development methodologies, until the most technical level.[34]

Ideally, ED aims at embedding ethical values in the system itself. It aims at "guaranteeing ethical behavior 'by design', i.e., embedded in the system's implementation" (Dignum et al. 2018). The translation of ethical values in concrete requisites and actions in the course of development is what ensures that the product (software, algorithm…) is conforming to a certain desideratum and avoids leading to unethical consequences. On the face of it, ED does not prevent from other forms of ethical oversight and follow-up.[35] Furthermore, **ED is neither an off-the-shelf toolbox nor a specific methodology that has to be followed strictly, but a general approach**. To adapt the ED approach to different software development methodology or different fields of research requires some research (Coeckelbergh 2019; Brey et al. 2021), and this is precisely what we want to do here.

One obvious reason for the development of the ED approach is **the need to anticipate ethical issues that will arise with emerging technologies**. Emerging technologies are technologies that are not yet entrenched in society. We cannot deal with ethical issues raised by emerging technologies (e.g., medical nanotechnologies, internet of things, metaverse) the same way that we do with issues raised by entrenched technologies (e.g., automotive technology, antibiotics, nuclear power) (Brey 2017). In this context, the development of the technology can bring unexpected damageable consequences very rapidly. Nobody wants the technology to produce damages, so good sense commands that we anticipate carefully the potential consequences of developing a technology that will have an impact on society. This is especially the case with AI, with strong expected impacts on society, economy, social life, medicine, and warfare. As the impact is supposed to be strong (it will impact society as a whole, or have important consequences) and almost immediate (there is no time to mitigate the risk once the technology is launched, as soon as the technology develops, it begins to impact the lives of people), there is obviously a need to anticipate the risks.

As a consequence, ethical issues should be taken into consideration right at the conception phase. This concern is already expressed in a family of "X-by-design" (Fischer 2019) concepts, ethics by design being only the latest in a series. For instance, "privacy-by-design" aims at protecting users from abuse through the unjustified collection of personal data. Instead of protecting privacy by placing limits on the use of data, privacy-by-design prompts the developer to produce a tool that can be functional while requiring a minimal amount of data. It offers more guarantee to design a tool that collects a limited amount of

[34] This problem is specific to software development (the ED approach should be adapted to, e.g., AGILE), but there is an analogy with our problem: how specific should be the guidelines regarding different methods for developing organoids? Referring to SIENNA/SHERPA five layers (values, requisites, guidelines, methodology, tools), we have to ask ourselves how many layers we have in biomedical research and how the guidelines produced by HYBRIDA can identify (target) each of these layers. For instance, SIENNA does not go into detail for each methodology but gives an example of how the ED approach can be implemented in AGILE.

[35] Nobody claims that ED will solve all ethical issues raised by emerging technologies. Some documents present for instance both "ethics by design" and "ethics of use" (European Commission 2021).

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sensitive data than to build a tool that collects a large amount of data and then to impose restrictions on their conservation and use.

During the last decades, there has been **a general boom in the development of guidelines, charts, codes of integrity, and so on**, in all fields of research (Iphofen 2020). This kind of "soft law approach" can be seen as a second best compared to regulation by law, as there are often no legal constraints if one fails to conform to the advice and standards provided by the code/guideline. Yet, the law is condemned to stay somehow undetermined, with a certain level of abstraction, covering different fields of application, while standards can go into the detail of a technology. Also, guidelines offer a more practical approach than the general reiteration of universal principles or ethical values that everyone agrees with. Again, there is added value in the translation of values into concrete requirements.[36] There are several ways to articulate soft and hard law. They can be seen as opposite: "In all cases, the alternatives being considered can be divided into two types: regulation by means of legislation and standards, or design, ensuring that the systems themselves take ethical decisions at all times" (Dignum et al. 2018), or as complementary, as guidelines propose concrete procedures that the law cannot offer.

The ED approach is currently enjoying a certain success among developers and AI ethics, as can be seen through the recent references in the literature (Felzmann et al. 2020; Iphofen and Kritikos 2021; Urquhart and Craigon 2021; Nussbaumer, Pope, and Neville 2021). Although there are debates on the best implementation of ED (for instance, importance of data instead of software development (Gerdes 2021), there seems to be a consensus on the interest of developing such an approach.

3. The philosophy behind ethics by design

3.1. Ethical artefacts?

The main philosophical hypothesis behind the ED approach is the idea that ***values are embedded in artefacts***. The idea is emphasized in the EGE statement: "Everything designed, every artefact, piece of technology and human-made system contains the preferences, values and worldview of its designers and makers" (EGE 2021). This is a longstanding view in the philosophy of technology, akin to the claim that "artefacts have a politics" (Winner 1980). A well-known example taken by Winner is the bridges over Long Island highway, which were built intentionally low so that buses conveying a population of lower social status could not access certain places. By the constraints that they impose on society, artefacts represent a certain social order or favor certain groups or individuals in society. They constrain the course of our actions, or incline us in certain directions, thus limiting and orienting choices.

Ethics by design builds on this idea to propose that **artefacts are produced so that the constraints they impose are somehow *ethical***. There is an interesting connection with the debate on dual-use (on technology and warfare), as, in a sense, ethics-by-design is symmetric to dual-use. While dual use is the development of a technology (e.g., nuclear power) that can be developed overtly for a civilian purpose

[36] The same problem occurs with the principist approach of biomedical ethics and has been a subject of debate for decades: with the very same "principles of bioethics," one can defend a position or its opposite, depending on the ponderation and interpretation of the principles.

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and transformed quickly in a military device, an artefact designed as ethical offers the guarantee that it cannot be misused. Hence, producing artefacts that embed ethical values is a kind of democratic ideal where our objects, which circulate and disseminate in our society and around the world, are bringing these values to the world and cannot be diverted. If artefacts behave ethically – or constrain human behavior so that it is doomed to be ethical – then in a way we do not have to rely on human judgments that are always susceptible to err.[37]

This being said, **there is a specificity of the AI systems that justifies the current trend in ED in this very particular field**. AI systems are not only artefacts that shape our environment, or artefacts that we use, they are **artefacts making decisions**. As *intelligent* systems, they are asked to sort, discriminate, choose for us. They do not impose only passive constraints, as the low bridge. They make decisions that are at the level of ethical judgments. Here, the debate is more on the side of robotics and autonomous machines (e.g., autonomous weapons) than on the side of general objects. The Asimov laws nicely express the kind of constraints that we want to impose on artefacts that can make a decision.

Now we can progressively ask how does all this apply to organoids, as organoids are neither simply *artificial* objects such as bridges, nor systems that can make decisions by themselves.[38] This methodological inquiry aims precisely at clarifying these points. Before doing just that, let us turn to more general points that can be extracted from the ED approach.

3.2. Anticipating potential ethical issues

Anticipation is a main keyword for all ED approaches. The adjective (borrowed from administration and business language) "proactive" is recurrent, as opposed to reactive. "Ethics by Design is intended to *prevent* ethical issues *from arising in the first place* by addressing them during the development stage, rather than trying to fix them later in the process" (European Commission 2021).

The need to anticipate is justified by the idea that emerging technologies will have an impact on society anyway. In the AI case, there is no window to experiment properly without impacting real people. If we want the AI to work, we have to feed it with real data, and as soon as the algorithm is used, it will have an impact. All artefacts might not exhibit this feature so clearly – a car can be built and tested while crashed with a mannequin in it. For AI systems, a proper consideration of ethical issues ought to occur at the very beginning of the process. One obvious example is data collection: if data are biased, then all the system will be. Other formulations stipulate that ED "implies bringing the debate on the ethical and societal implications at the primary stage of the research process" (D'Aquin 2018) or that "ethical reflection is required across the whole product lifecycle, including the early conception phase" (Keber 2021).

The general idea of anticipating as early as possible – and not waiting until products hit the market to regulate – is surely laudable, but how is this specific to the ED approach? In a way, it seems that

[37] Which raises further questions on what it means to behave ethically if this behavior is constrained by technology, but this would be out of the scope of the current discussion.

[38] As far as we know and in the near future – maybe one can envision a neural organoid so complex that it forms a network on which an artificial intelligence could run.

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anticipating the consequences of technologies has been the bread and butter of a bunch of scholars for decades, from philosophers of technology to bioethicists. Regulation itself does always intervene *afterward*, there are always mechanisms to anticipate the consequences (e.g., market authorization for drugs).

In defense of ED, we could say that **this capacity to anticipate was precisely in lack of a specific methodology and that there have been many failures of these oversight mechanisms** (e.g., in health, environment). In other words, the anticipatory net has many breaches, and the State, or authorities, are sometimes powerless when we realize that something that they authorized is doing more harm than good (e.g., pesticides). In this sense, ED would be opposed – at least methodologically – to several current approaches in the ethics of emerging technologies. Ethics committee approaches are often limited in the sense that committees authorize research based on an analysis of the conduct of research (Is data managed properly? Does research respect the rights of participants?) without considering the long-term impacts of the research on society. Furthermore, the ethics committee gives approval at an early stage with no incentive to reflect on ethical issues that might arise once the project is launched (D'Aquin 2018). ELSI-type approaches have also been often criticized as parts of projects that are already launched, in a way that ethical concerns cannot take the lead over the scientific program in case of conflict (see the many objections to ELSI approach in, e.g., nanotechnology, synthetic biology).[39] There is more than anticipation, there is a concern related to the production process of science (i.e., the role of ELSI, and ethics more broadly, in governance).

We said earlier that one characteristic of emerging technologies is that they will have an impact on society anyway. There is no methodology to anticipate perfectly all the potential impacts of a technology. Starting from the premise that we cannot foresee everything, the introduction of a new technology in society can be considered as a kind of social experimentation. "The question, therefore, is not simply one about determining whether and under what conditions a given technology is to be deemed morally acceptable, but also about whether it is morally acceptable to test a given technology openly within our societies, and under what conditions this can be said to be the case." (Nurock, Chatila, and Parizeau 2021). Under these circumstances, **the ED approach offers a way to mitigate risks when we cannot avoid uncertainty: experimenting in and with society**.[40] The EGE states that in the absence of anticipation and early engagement, the ethical choices remain in private hands: "We cannot leave the design of our future world to coincidences and to those who design for self-serving purposes outside democratic control. Moral reflection should therefore be situated when and where it can make a difference" (EGE 2021). Ethical regulation is not only about constraints, we need a positive construction of ethics in the system, leading

[39] For instance, it can be almost impossible to reorient the course of action of a scientific program once the program has been launched (Rabinow and Bennett 2012).

[40] The situation is quite different from one domain to another. This discourse is relevant for AI, but we could analyze the situation differently for drug testing. Testing a drug (for safety and efficacy) is always making a leap, and the protocols for clinical research are intended to ensure that the leap is as circumscribed and reasonable as possible at each step. If there is an issue, then we want to make sure that the issue is circumscribed to the participants, people engaged in the test and covered by a medical follow-up.

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to human flourishing (Coeckelbergh 2019). This means not only drawing red lines but finding a way to empower society through technology.

3.3. Responsible innovation with all stakeholders

Another major element in the philosophy of ED is the inheritance from the "responsible research and innovation" field. The RRI field is growing for two decades and the move to ED can be interpreted as an operationalization of RRI in certain domains of research. In that case, an interpretation of the "by-design" requirement for organoids guidelines would be simply that **we want organoid research to conform to RRI**.

What does RRI entail? First, the involvement of stakeholders at an early stage of the process. Research is not only *for* society but *with* society. Stakeholders are of course potential users of the technology and private entities with an interest in the development of the technology (companies, civil organizations…). Another methodological point is interdisciplinarity: responsible research cannot reach all stakeholders and examine all potential ethical issues without support from social science and the humanities. The AI ED literature insists that ED is not only a toolbox for coders/researchers in AI to use by themselves, it is also a promise of engagement with other disciplines (Coeckelbergh 2019; Gerdes 2021; Nurock, Chatila, and Parizeau 2021). An ethical design should identify the critical steps where an ethical assessment will be required and who will take part in this assessment.[41] In this regard, it is worth noticing that the ED approach does not propose to "inject" ethics at an early stage and then get rid of it, it fosters continuous discussion among researchers and stakeholders, at least theoretically (EGE 2021). According to Coeckelbergh, ED offers a practical solution to bridge the gap between the general principles of ethics and concrete actions. Governments, advisory bodies, or even corporations often publish nice documents that put general ethical principles forward, with few guarantees that stakeholders will follow and that those discourses will have an impact on the course of action. ED is aimed at ensuring this kind of impact.

Note that some authors see a tension between the technicality of the work (implementation in technology – first level of expertise – of ethics – second level of expertise) and the call for external stakeholders and broad participation (Gerdes 2021). The emphasis on stakeholders' participation and global discussion can in a way downplay technical aspects.

Now, we have to consider how we can bring the discussion back on the track of biomedical research, with a focus on organoids. How could we apply, or import, an approach that has been developed for AI into the field of biomedical research, and what are the challenges?[42]

[41] For instance, suggesting, as it has been done elsewhere (REF), that a cellular biologist with no competence in cognitive science or in philosophy of mind should *not* decide by herself whether a given brain organoid is conscious or not and how to assess this possibility, would correspond to this interdisciplinary-hence-more-likely-ethical-by-design framework.

[42] The current framework and practices of biomedical ethics are proposed as a gold standard for engineering ethics and ICT ethics, to which ED belongs. For instance, Nurock et al. (2021) propose that we bring "care" in digital ethics. If ED is "a coders' version of the Hippocratic Oath" (Nurock et al.), then we could ask why we would need another translation from AI ethics to biomedical ethics.

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4. Application to organoid research ethics: step 1

One solution is to look at documents that explicitly argue for the generalization of ED to other technological domains and see how the requirements are coherent with biotechnology in general and organoids in particular. We will draw especially on SIENNA deliverable 6.3 (Brey et al. 2021) This document provides methodological guidance for building ethical guidelines in general, with a chapter dedicated to ED guidelines. It defines ethics by design as the "systematic inclusion of ethical values, principles, requirements and procedures in design and development processes." (p.53)

The process is detailed into 5 steps or 5 layers in guidelines development (assuming that this sequencing is partially chronological/partially logical, the SIENNA 6.3 report is not totally clear on this point).

1) Reach consensus on the key **moral values and principles** that apply to the technology field and that we want to respect. Concretely, this means establishing a "list of values" that should guide the development process. For instance, the SIENNA project imports a list of values[43] from the *Ethics guidelines for trustworthy AI* of the EU high-level expert group on AI. This raises the issue of identification of the main values: how do we agree on essential values? make sure that there are no misunderstandings? that values are not empty keywords? And, in our case: where should we look for values relevant to biomedical and organoid research? are the 4 principles of bioethics (autonomy/beneficence/non-maleficence/justice) relevant and sufficient?

2) A deductive process goes from the values to **ethical requisites**. Ethical requisites are norms, general do's and don'ts that are derived from the identified values. Asimov's laws are requisites. Again, the methodology for translating general values into ethical requisites is not clearly developed (the document appeals to brainstorming and intuitions). We should already have a good idea of the potential issues raised by the technology and the technical options before formulating relevant requisites.

3) The next step is to choose and describe an established **design methodology**. Design methodology refers to standardized production processes (in the sense of the Agile method). We can ask if this is relevant for biomedical research. At least we need an overview of the "production cycle" of the biotechnology, with the aim of identifying where issues are likely to arise and where ethical interventions are required.

4) **Translate the ethical requisites to actionable methodological guidelines**. The ethics guidelines identify the specific steps in the development process where ethical assessment/intervention should take place. Guidelines are proposed to ensure that the requisites are taken into consideration during the development of the product.

[43] The values are: human agency; privacy and data governance; fairness; well-being; accountability and oversight; transparency. Each value should be explained in a couple of sentences or paragraphs, as keywords might not speak for themselves.

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5) Develop **tools and methods** to address specific issues, consider special topics (for instance, if we develop guidelines for organoids, there should be an annex for "brain organoids" as a special topic).

Illustration: if fairness is an essential value, the requisite is that we want the AI system not to produce discrimination, such as gender or racial bias, and the guidelines will identify specific ways for developers to test and screen for bias at steps X and Y in their development process.

Remarks:

- The identification of values and their translation into ethical requisites are important in the final report (the final guidelines should indeed include a list of values) but **one cannot rely on a list of values as a foundation and methodological starting point for the deduction of the guidelines**. The same holds for requisites, as there is no method for the deduction. Concretely, we should start the other way around: see where issues are likely to occur in the development process and go back to relevant values.
- **We should have a clear idea of the "design process" of the biotechnologies of interest**, from the idea to the final product: a model that details the steps and the actors of "organoid production" (the equivalent of the overall "design process" that we have for a software or a robot from decision to actions, e.g., prototype design, testing…).

Beyond the SIENNA 6.3 document, we can draw on the growing ED literature to extract some general features that can be applied to technologies other than AI. Some of the recurrent keywords (or methodological requisites for ED) are the following:

- ANTICIPATION of all the consequences of the emerging technology under scrutiny.
- The attention of the EVOLUTION of the technology through a life cycle (ethics is not just a green light at the beginning of the research project, it should cover all aspects of the technology, as distinct issues might arise at distinct stages of technology development).
- INCLUSION of all stakeholders potentially concerned when dealing with ethical issues.
- INTERDISCIPLINARITY (one cannot reach all stakeholders and examine all potential ethical issues without support from the social sciences and the humanities).
- RESPONSIBILITY of technology developers (at the end, they are responsible for the integration of the ethical requisites into the data/software/technology) and, symmetrically, ethics by design as a form of DEMOCRATIC CONTROL over technology development.

All these keywords would be shared by the field of RRI (responsible research and innovation). One interpretation of the reference to ED in the SwafS call for proposal would thus be that the guidelines should be developed with social responsibility/RRI in mind. In that sense, we could develop our own methodology for organoid guidelines with a very loose connection to what is concretely done under the label "ethics by design." If, in the end, our guidelines ensure that the ethical issues raised by organoid

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research are tackled early, with all stakeholders in a sense of responsibility, then we would have completed the job.

However, there is something more specific about ED (compared to RRI in general) as an approach to *emerging technologies* and the idea that we could implement the right values into them. ED proposes a specific procedure to incorporate values in the technology. Yet, as said above, there are already procedures in bioethics and biotechnology is not any emerging technology. So, we need a more complex answer than the import of an off-the-shelf methodology or the reference to a general framework that makes us free of constraints: we need to see how, precisely, values are embodied in organoids.

5. Application to organoid research ethics: step 2

Now, we can go back to the philosophical hypothesis stipulating that *values are embedded in artefacts*. How can we take this option seriously and assess how this consideration applies to biotechnology and organoids? To phrase it differently: what can the idea of considering organoids as artefacts change the way we assess the ethical issues related to these entities?

The EGE document mentioned above (EGE 2021) insists on the importance of choosing and designing our artefacts so that they embody the 'right values.' The problem might not be here in the identification of the 'right values,' but to clarify the idea that **artefacts embody values** and learn **how to identify concretely the values embodied in artefacts**. What does it mean, to say of a technology that it embodies certain values? I will explore quickly several options and examine how this applies to organoid ethics and guidelines writing.

A preliminary remark is that this claim is intended to go against a familiar statement according to which technologies are 'neutral' and morality depends on how human beings use technologies. A weapon would be good in good hands and bad in bad hands. A gun could be used indifferently as a vintage decoration in a country house or as a tool for an atrocious murder: in both cases, the gun is not to praise or blame, the user is the only one responsible for its action. This view is clearly not popular in all fields of contemporary philosophy of technology, holding that technologies are generally *not* neutral. In what sense?

The generic idea is that artefacts have some characteristics that express some values. They are made *for* something, and this 'something' is often a value, a norm, something that we hold for desirable, an outcome that we want. Engaging in the production of an artefact of some sort, at the expense of other ones, says something about our priorities, what matters for us. For instance, investing massively in military equipment is a sign of a government/society that values (military) strength (other options are investing in, e.g., economic development or education with respectively well-being or knowledge as corresponding values). Even at a more detailed level of analysis, there are different technological options that embrace different values (military weapons are more or less ethical, for instance, chemical weapons/gazes that will mostly target civilians without equipment while letting the military intact is obviously a perverse option). Ethics by design precisely aims at choosing the 'right' option whenever possible during technology development.

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Beyond the intentional purpose that is behind the production process of artefacts, there are some properties that we might oversight but which corresponds also to certain values. In an example given by philosopher of technology Andrew Feenberg, engineers of the nineteenth century that do research to adapt an assembly line for making children working on it are facing what they call 'technical' problems (and not ethical issues), yet by pursuing this research they endorse the statement that children's work is desirable, which is obviously, from our common standards, a bad requisite.

Below we review several declinations of the idea that artefacts embody values.

A. (**Intentionally) embedded constraints on social life** (Winner 1st argument: "specific features in the design or arrangement of a device or system could provide a convenient means of establishing patterns of power and authority in a given setting," Winner 1980). Artefacts in our environment produce constraints that limit (or allow) some uses. Famous example of bridges over Rhodes Island highway in New York designed to prevent buses (carrying lower social status travelers) to access leisure places (these bridges were designed intentionally with this property by an architect prejudiced with social bias – the value embodied here would be inequality, and the requisite discrimination). Constraints will stay with the artefact, even when the designer passed away.

We can also look at constraints the other way around: the artefact can be an enabler (against **unintentionally embedded constraints**). For instance, accessibility to handicapped persons was not taken into consideration in the design of buildings/stores/public places until recently. Being able to move one's own body in space was seen as an implicit requisite to take part in social life. If we want to respect values of justice or inclusiveness, we have to adapt (or get rid of) all these old artefacts that embody the wrong norms.

Application to biotechnology: in the design of artefacts, certain choices are made and these choices have consequences on potential users. Some elements of this chain (from the choice of a design for the technology until what users can do and cannot do with the technology down the stream) can be seen as the embodiment of values in artefacts. The analysis should look at the values/choices behind the development of organoids, the intended use, the supporting visions, and so on. I suppose that this is an analysis of this sort that we are going to conduct in WP2 amended HTA.

B. Some intrinsic properties of the technology are linked to a form of power. (Winner 2nd argument: "intractable properties of certain kinds of technology are strongly, perhaps unavoidably, linked to particular institutionalized patterns of power and authority" Winner 1980). A classic example is nuclear power: the development and maintenance of nuclear power plants require scientific and administrative elites and a form of centralized control (which is often linked to monopolies). It can be seen as less democratic than other forms of deconcentrated energy production (such as solar/wind energy) that allow distributed production, many small producers, and so on.

Application to biotechnology: the production and use of organoids may rely on some structural constraints (e.g., women exploitation for oocytes production, animal exploitation for extracellular matrix production, a form of power/intellectual property linked to the work of private companies…). These elements would

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have to be taken into account in the global picture of the values that one endorses when one defends organoid research.

C. Inclination toward action because the technology exists (Latour argument). This is a counterargument against the 'neutral technology' view. It can be applied to gun control: against the idea that guns are not the problem (the 'problem' would be in bad behaviors, less self-control, low degree of morality…), one can state the simple fact that when guns are available to everyone, there are more shootings and more damages. In this case, the technology does not embody a value strictly speaking, but it inclines to action in the direction that is suggested by the technology itself. Latour takes also the example of the speed bump, which inclines the driver to go slower. this inclination is stronger than a simple sign on the side of the road, yet this is not a full barrier (in contrast with Winner 1).

Application to biotechnology: do we really envision all that can be done with the technology? Should we consider all that can be done as a 'serious option'? What is the value of saying that "we can do all the *in vitro* research we want but implementation is a red line" if the step between *in vitro* and implementation becomes smaller?

D. The technology of interest plays a functional role in a network of actors, other technologies, and social structures, that share some values (Marx argument). The value may not be manifest in the technology itself, but the context of its development entails some values. Karl Marx would say that technology development is a way of disqualifying labor and craftsmanship, leading to a loss of competencies and a concentration of production forces in the owner of the capital.

Application to biotechnology: private companies aim for profit (at an executive committee meeting "why shall we develop this drug?" means "how much will it cost in terms of investment and what are the expected benefits?") / public research is supposed to be directed to knowledge and public good (at a university lab meeting "why shall we work on this model?" means "what are we going to learn from that?"). Should these values be taken into consideration in the analysis and how?

E. The artefact mediates our relation to the world and thus defines a range of possibilities, including moral status (Verbeek intrinsic morality argument, Verbeek 2008). Contemporary leading philosopher of technology Verbeek develops the argument that the development and massive use of echography change the moral status of fetuses. Fetuses are more and more seen as babies, and parents are waiting for 'pictures' before birth. This obviously changes our relation to the unborn and might be a factor for a change in its moral status.

Application to biotechnology: I suppose this framework is relevant for the use of organoids in precision/predictive medicine. How organoids could renew some ethical issues? For instance, the issue of incidental findings, of anonymity/privacy… Will these issues be reframed by the availability of improved models of development, and how? And how to assess whether this outcome is desirable or not (the ED approach does not suggest anything here)? It is distinct from Winner 1 argument that would stipulate that the values of anticipation and foresight are embedded in the use of organoids in 4P medicine.

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6. Conclusion

There is some inspiration to draw from ethics by design in order to improve the way biomedical ethics deal with emerging technologies, but the implementation deserves further research and discussion. Requiring that our biotechnologies conform to ethics by design means that the focus is not only on the early assessment of safety and validation procedure until the product hit the market or the clinical field, but it is also a call for anticipating long-term social consequences. It calls for an in-depth analysis of the technology from the inside, and not only an external evaluation from the ethical point of view. In this sense, the requirement that nothing ethical cannot be done without involving all stakeholders is twofold. It means that researchers cannot avoid engaging with society when developing their products, but it means also that ethical procedures cannot be imposed ex-post or from the outside once the product is developed. Ethics starts from a clear idea of the design process of biotechnology and goes until its clinical applications and the farthest implications for society.

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11.4 Annex 4

Standard and value

Norms and values are different moral categories (Max Scheler):

A standard expresses:	**A value is expressed:**
an assignment as a task	an ideal duty to be
the property is imperative (mandatory)	the good is attractive (= object of a desire)
e.g.: Human beings must be treated fairly	e.g.: Women should give birth without pain

They determine statements of different types:

Standard	**Value**
deontic or normative statement	axiological statement
e.g.: It is obligatory not to lie	e.g.: It is good not to lie
e.g.: You must not lie!	e.g.: Truthfulness is a good

Standards and values have different characteristics:

Standard	**Value**
mandatory, prohibited, must	good, bad, desirable
thin concept (= without descriptive content)	thick concept (with descriptive content: cruel, honest,...)
not related to emotions	linked to emotions (admirable, frightening,...)
categorical (must / must not)	gradual (more or less admirable)

The basis of morality: norms or values?

Two opposite positions (Kant versus Aristotle):

Standards are primary and foundational to moral values	Values are primary and some are the basis for standards
e.g.: Life has a moral value because it is	e.g.: It is forbidden to kill because life has great

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forbidden to kill	value
In morality, obligation is first	In morality, the desirable is first
Samuel de Puffendorf: "Natural goods becomes morally significant when it is enjoined by law and brought about voluntarily because of law."	

Realism and anti-realism of values

"Is that which is pious approved by the gods as being pious, or is it pious because the gods approve it?" (Plato, *Euthyphro*)

Two opposing positions:

Realism (Aristotle)	Anti-realism (David Hume)
The value of something is the value *it has* according to its properties	The value of something is what *we attribute to it* according to its properties
Aristotle: "We desire a thing because it appears to us to be good, rather than because it appears to us to be good because we desire it."	Hume: "It is a common observation, that the mind has a great propensity to spread itself over external objects, and to conjoin with them the internal impressions which they occasion."

The case of dignity

Dignity is presented as a value. It is therefore gradual: a behavior can be more or less dignified. However, it is said that all human beings possess the same dignity, that it does not vary and must be respected, whatever their behavior. Two solutions to this difficulty:

1. Dignity is based on belonging to humanity, which is the same for all human beings, and therefore the dignity of each person is invariable.
2. Dignity is not a value, but a norm. Affirming the equal dignity of every human being means that we have a duty to behave with the same respect towards each of them.

Learn more about this:

Ruwen Ogien and Christine Tappolet, *Les concepts de l'éthique*, Paris, Hermann, 2008.
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11.5 Annex 5

11 March 2022

Minimal Information about Organoid and its Use for Researchers (MIAOU)

First Working session – Paris, Biopark

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11.6 Annex 6

29 March 2022

Minimal Information about Organoid and its Use for Researchers (MIAOU)

Second Working session – (Online)

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11.7 Annex 7 EChOES I Participants List

11 May 2022

Evaluation Checklist for Organoid Ethical Studies (EChOES)

First Working session – Paris, Biopark

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