HYBRIDA

Executive summary of HYBRIDA's operational guidelines

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1. What are organoids?

Organoids are products of biotechnology that emerged in the early 2000s, building on decades of research on the potential of human cells to proliferate and renew even outside ofthe body. Intuitively, "organoid" seems to describe an entity that has similarities to an organ in the cellular composition and/or with a similar architecture that reproduces at least some of the features and functions of an organ. However, the term is more generally used by scientists to refer to a family of entities made from various types of natural or engineered stem cells of healthy or pathological origin. Organoids differ from conventional cell cultures in that cells can self-organize into three-dimensional complex structures that share some anatomical and functional properties of developing organs. Organoid research has been accelerated by (i) overall advances in stem cell research and (ii) innovations in culture media reagents and devices that make three-dimensional expansion possible, consistent and reproducible between laboratories, whilst capturing physiological tissue functions.

Here are some examples of entities (among many) currently referred to as "organoids" or related to organoids:

- Intestinal organoid: stem cells issued from patient intestinal biopsies can be cultured in vitro such that small three-dimensional structures adopt the shape of an intestinal crypt. Such organoids can be expanded indefinitely and used to study normalgut physiology or better understand intestinal diseases in patients.
- Neural organoid: skin cells – or other cells of the body – are reprogrammed to induce pluripotent stem cells and then differentiated into neural tissue that can resemble different parts of the immature nervous system. How the tissue self-organizes, or the different forms of neural cells, can provide insights into brain development or neurodevelopmental pathologies.
- Tumoroid: cancer cells taken as a biopsy from tumors in patients can be grown in vitro such that they are a near replica of the original tumor – the (personalized) tumoroid can be used to test drugs and make predictions on whether a drug will be effective in treating the patient or not.
- Embryonic model: pluripotent stem cells can differentiate in vitro such that they replicate some of aspects of early embryo development rather than a specific organ. This kind of laboratory model might help understand why miscarriages occur, improve in vitro fecundation procedures, etc.
- Organoid-on-chip: stem cells or organoids can be introduced into engineered microfluidic devices made of plastic or silicon (the 'chip') that provide them with nutrients, oxygen, or drugs under conditions of fluidic flow or flexible substrates resembling real tissue.
- Assembloid: organoids from different cell types or tissues are grown together (or assembled). For example, a brain organoid might be connected to a muscle organoid to mimic innervation of muscle tissue, or gut and stomach organoids coupled to mimic the gastrointestinal tract. These models do not focus only on a specific organ but give insights into global, physiological or pathological processes in the body.
- Chimera: namely a mixture of cells originating from two different species. In the case of organoids and related fields, after being grown *in vitro*, human organoids can be transplanted

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into animals to enable further development and physiological integration including vascularization. This has mostly been reported for neural and kidney organoids. Transplantation aims to mimic normal physiological conditions in tissues resulting in an improved maturation of the human organoids. A main ethical issue is to know if such transplant confers human properties to the engrafted tissue. In example :. engrafted into injured visual cortex in rats, human neural organoids survived for up to 3 months, formed afferent and efferent connections with the host visual network, and responded to visual stimulation.

2. What are organoids used for?

Potential applications of organoids range from fundamental biology (understanding mechanisms of development) and disease modeling (understanding how diseases develop) to use in drug discovery and therapeutic protocols for (personalized) clinical application in medicine.

More specifically, organoids are, or will be, used in:

- *Basic research*. Organoids as models of development offer windows into the physiology and pathology of an organ. They are useful for basic research in developmental biology and in understanding the mechanisms underlying diseases.
- *Preclinical research towards therapies*. Preclinical research tests potential therapies for effectivity prior to clinical trials in patients. Organoids can be used to test whether disease phenotypes are reversed, check toxicity and whether the treatment affects metabolism, etc. Models based on human stem cells could eventually replace some animal models in assessing effectivity and toxicity.
- *Clinical use*. Organoids are increasingly used as tools for personalized treatment selection in the clinic, but could also be a source of biomaterial for regenerative medicine, for example for transplantation as Advanced Therapy Medicinal Products (ATMPs).
- *Bioproduction*. Organoids could be engineered and used for the production of biomaterials, for example virus production for vaccines and gene therapy that already have clinical utility.

With regard to the interests of patients, the most important distinction is between research (fundamental or biomedical) and immediate clinical applications (such as personalized medicine, where a single use model is created for each patient) or bioproduction to allow access to expensive drugs by decreasing the production cost. The vast majority of organoids developed in laboratories today are for research. Clinical applications are still under development although in trial in some advanced research settings.

Basic research	Developmental biology
	Disease modeling
Preclinical research	Drug development and controls
Clinical research	Personalized treatment screening
	Material for regenerative medicine
Bioproduction	Produce molecules, proteins, viruses for treatments, vaccines…

Applied to the specific field of organoids and related researches, two main areas are considered as priorities for a specific ethical review as they may be subject to measures related

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to the precautionary principle: i) organoids associated with the dissemination of genetic material in the offspring, and ii) organoids challenging moral values such as embryonic models and complex neural organoids in which higher order brain functions such as consciousness or suffering may emerge.

Four ethical categories are proposed:

- **Cat. 1a**: there is no difference or additional ethical problems in comparison to usual cell cultures: a "simple" approach to organoids (kidney, liver, etc.).
- **Cat. 1b**: specific ethical consideration is recommended to the researcher and certain declarations must be made to the authorities: sexual reproduction organoids, “simple” neural assembloids (interconnected organoids not reaching high order brain functions) and gastruloids.
- **Cat. 2**: cases where specific approval by an Ethics Committee is required: blastoids, complex assembloids such as cerebral cortex neural organoid connected to sensory and possibly motor systems.
- **Cat. 3**: a prohibited research because there is a lack of compelling scientific rationale and/or ethical standpoint concerning: gestating human stem cell-based embryo models, or the transfer of human-animal chimeric embryos to a human or non-human primate uterus

Cat. 1a	General ethical review	“Simple” organoids (kidney, liver, etc.)
Cat. 1b	Specific ethical consideration recommended	“Complex” organoids (neural, sexual reproduction organoids, etc.)
Cat. 2	Specific approval by an ethics committee required	Blastoids, complex neural assembloids, etc.
Cat. 3	Prohibited	Gestating human stem cell-based embryo models, transfer of human-animal chimeric embryos to a human or non-human primate uterus, etc.

3. Why do organoids deserve a specific attention from the public, bioethicists, and regulators?

Beyond the variety of entities that fall under the umbrella term “organoids” and the many applications of organoids, there is uncertainty related to the precise definition of the term: what does “being similar” to something actually mean? Does an organoid become an organ or does it stop short? Current organoids are not “mini-organs” and are not off-the-shelf spare parts for failed organs, as is sometimes postulated in the popular media. In fact, an organoid does not have the same properties and functions as an organ. It is therefore incorrect to refer to organoids as mini-organs, and communicating incorrect information constitutes misconduct. Misnaming would be both prejudicial for the advancement of science and for the trust of the public.

Researchers generally refer to them as ‘models’, because they are essentially biotechnological avatars built to study specific tissue features of interest. They resemble the phenomenon or object of interest to some extent, but cannot be conflated with it. If the model is not an organ, what is its nature exactly and how do we relate to it? Organoids are typically hybrid entities – both biological, alive, made from living material, and artificially and technologically human-made.

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As products of an emerging technology of an uncertain, hybrid nature, organoids might fall within regulatory gaps, if for example, practical, moral or legal issues that are not satisfactorily covered, addressed, answered, or overcome by existing legal instruments or legally binding definitions. Organoids and related technologies might, however, be subject to over-regulation, for instance if current regulations are such that there is uncertainty as to which laws apply, if applicable laws give rise to conflicting legal requirements, or if there is a lack of appropriate regulatory harmonization across EU Member States.

A series of workshops within HYBRIDA identified several issues raised by the public that will need addressing at some point: whilst there was general support for biomedical research and innovative technologies to find new treatments and improve public health, informed consent and responsible governance were highlighted as concerns throughout the deliberations. Addressing these is essential to safeguard ethical and acceptable use. Proper guidelines for organoid research are needed to ensure that any economic interests do not prevail over patient safety and prevent exploitation. Commercialization of organoids is essential for their implementation in biomedical and preclinical research, but it is sensitive, with participants expressing concern on use, ownership and remuneration. These points need clarification in donor consent forms (see below for discussion of the impact of uncertainty on donation and consent), keeping in mind that contemporary biomedical research on organoids should not add to existing healthcare inequalities. Potential misuse and breach of the privacy of personal data in connection with data storage and donation is also another concern.

4. How to promote responsible research with organoids and related technologies?

To ensure integrity in science and ensure the interests of all stakeholders are respected, researchers need to comply with general quality standards for scientific integrity and codes of conduct for research integrity in their institute and country of origin. Many procedures are already in place in biomedical research to ensure the ethical conduct of research, especially when it comes to research with human material, including human stem cells. Most researchers are familiar with these prerequisites which also apply to organoid research. Does organoid technology call for additional recommendations or not?

Some forms of organoid research introduce new uncertainties: this may relate to sensitive cell types like germ cells and gametes, being formed, or, as noted above, brain-like structures. Guidelines are one way of coping with uncertainty, especially regulatory uncertainty. The proposed guidelines aim at building trust among the various stakeholders in organoid research by ensuring that scientific knowledge builds upon reliable data and simple tools are available to assess the different aspects of research proposals. Guidelines encourage researchers to report data and metadata in a standardized format that will clarify the methods and purposes of the organoid research that will be carried out. These guidelineswill also help funding bodies or other evaluating committees, as well as ethics committees, toensure that the research is reported in a commensurable way. Guidelines cannot replace lawand will leave some ethical issues open (see section Are some organoids more problematic than others?) as they are generally open to a certain degree of interpretation and provide flexibility in considering unforeseen and rapid developments.

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4.1. A set of requirements to ensure the quality of reporting for research conducted with organoids

To enable a real assessment of the quality of research reporting, each batch of organoids should be associated with standard information (metadata). This includes description of the tissue/cell sources, procurement protocols, validation and conservation of raw material, protocols and databases used, as well as culture and differentiation protocols and quality control criteria for each level of organization such as biobanks. In this way, researchers receiving organoids can rely on the data describing and characterizing the organoid (structural data: omics; morphological data: imaging and functional data). Further, the metadatashould include all regulatory aspects that have been complied with in the relevant jurisdiction, noting that the recipient researcher may be subject to different legislation, so asto avoid ethics dumping: material transfer agreement with provisions for the use of the organoids, prior verification of patient consents, authorization from regulatory agencies for organoids created from patient cells, declaration of collection and of material transfer if applicable.

We call this standard set of requirements the **Minimal Information about an Organoid and its Use for Researchers** (**MIAOU**). It addresses the following: the origin of biological material (including informed consent from cell donors), efficacy/reproducibility, quality of results (size, morphogenesis, cell composition), reliability, genetic integrity, minimization of communication errors (accurate and documented description of materials and methods), compliance with safety, security and research integrity rules, prevention of research misconduct and miscommunication with the lay public. A template questionnaire is provided and will be implemented as a user-friendly webpage.

A second checklist mirrors MIAOU: it is directed to scientific bodies in charge of assessing research proposals on organoids and related technologies. Its goal is to facilitate the work of scientific committees charged with evaluating proposals concerned with building, characterizing and using organoids. This **Evaluator checklist for organoid ethical studies** (**EChOES**) describes how to evaluate the quality of organoid descriptions in a grant application for reproducibility, replicability and rationality of the proposed organoid research.To assess the quality of an application, some elements are mandatory for scientific evaluation, while the others are contextual (depending on, e.g., the call requirements, the application domain). It is up to the evaluators to judge whether the answers are acceptable for a given project.

4.2. A practical guide for ethics committees

The Research Integrity Committee Organoid checklist (**RICOCheck**) intends to provide a tool for Research Ethics Committees (RECs) and Research Integrity Offices (RIOs), that will ensure transparency and anticipate ethical issues. Several principles need to be considered by RECs and RIOs, such as data confidentiality, the societal impact of the research project and its anticipated results, the approval of patient associations and the fair and responsible behavior of ethics committees involved in the evaluation of projects that use organoids.

The research should be based on privacy-by-design, incorporating privacy safeguards in all steps of organoid research. Donors and/or the general public should be substantially

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involved in the RECs and RIOs, societal benefits and any potential harm to donors, patients, and society should be anticipated.

5. How to act responsibly when applying organoids and related technologies in the clinic?

The clinical applications of organoids are still emerging at the research stage. As such,potential applications are still being explored as a prelude to examining clinical efficacy. In this regard, particular effort should be made to collect properly controlled evidence, to avoid publication bias that could create hype, and after any successful proof-of-concept studies,move to registered clinical trials. Every clinical research outcome, even those that are negative, should be documented, in line with the FAIR principles. Particular attention shouldbe paid to how best to collect clinical evidence: how does information a patient-derivedorganoid relate to clinical phenotypes manifest in the patient? What are the relevant clinical outcomes? In the case of n-of-1 trials (where research is conducted in a single patient,because of a rare genetic mutation, for instance), how should these outcomes be documented?

General efforts should also be made to ensure standardization. As in basic and preclinical research, standardization includes the reproducibility and replicability of experiments, different organoids from the same donor, organoids with the same disease from different donors, the same experiments carried out in different labs and how and if the technology works. Without well-documented procedures on how to grow and use organoids, and how to report their use, etc., it will not be possible to generalize findings or to build robust drug discovery pipelines. Failure to standardize procedures associated with organoid production and characterization has ethical consequences. The value of patients' donations will be undermined if the results cannot be generalized in an honest, transparent and responsible way, and this will hamper trust between scientists, clinicians and the general public. Furthermore, standardization will be essential to future clinical use: clinicians will require scalable, safe and good manufacturing practice (GMP) products, available at a reasonable cost, in order to enable general access to innovative therapies.

As clinical applications of organoids are only just emerging, researchers should be wary of creating high expectations for patients and other stakeholders, sharing only a general perspective of what might be possible in years to come once certain scientific hurdles have been overcome and treatments fully validated by evidence. It is of utmost importance for researchers to refrain from exaggerating prospects of clinical use of organoids, that is,creating 'hype' or ideology of promise. Precision in communication is essential: clinical prospects should be properly delineated and placed within a reasonable timeframe. Hype is not only relevant in communicating with the general public but is also of importance in reviews written for the scientific community. Obstacle to progress are not always explicit or are even obscured. For instance, practical difficulties in growing organoids (success rate, time, labour…) are hurdles to all applications. Not reporting these difficulties might persuade the reader, even a researcher (scientist or clinician) or a funder, to expect outcomes of the technology to be closer to clinical application than justified. A first step towards more responsible communication is to be explicit about all known limitations and hurdles, especially feasibility, and to keep in mind that clinical standards might be higher than those sufficient for proof-of-concept in research.

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6. Are some organoids more problematic than others?

We have used so far two distinct strategies to classify organoids. One classification is based on its intended use (organoid destination: basic research / preclinical research / clinical application / bioproduction) and the other is based on organoid type (i.e., the kind of organ or physiological process to be modelled). In this regard, some organoids and some potential applications raise more serious concerns than others and they may call for different levels of reflection and regulation. A piece of tissue extracted from a tumor and developed into a tumoroid will unlikely raise the same ethical issues as induced pluripotent stem cells turned into entities that model early human embryos. In the last 3 to 5 years, a collective discussion has emerged regarding the status of the following organoid-related technologies:

- Embryonic models: advances in three-dimensional stem cell culture as in organoid technology have provided new opportunities to study the development of embryo-like structures in vitro. Scientists can produce models of human embryos made from embryonic- or induced pluripotent stem cells to study the early stages of development. Depending on how this is done, these entities can share some features of natural embryos. Although research on human embryo is highly regulated, the status of these embryonic models is unclear in most jurisdictions. These models have been inappropriately called 'synthetic embryos' by some authors, but they are neither synthetic, since they derive from natural stem cells, taking benefit from their spontaneous auto-organisation properties in given conditions, nor embryos, because such entities do not develop as an embryo. Furthermore, for human models of embryos it is widely considered unethical to even try to implant them in a uterus. However it is important to consider future developments of embryonic models. Even if current models are not equivalent or even close to viable embryos, the technology may advance such that they become increasingly closer to their natural counterpart; these entities will undoubtedly deserve new moral consideration.
- Organoids of the nervous system, and assembloids composed of various neural organoids: the nervous system supports cognitive function, and although the molecular and cellular bases of cognition are unknown, it is possible that cerebral organoids or similar entities could develop a form of sentience or consciousness, although no consensus yet exists regarding the definition of these two terms. Given the current state of the art, there is instead broad consensus among biologists and neuroscientists that the possibility of consciousness in organoids is negligible at present. However, in the longer term, this may change as organoids and assembloids become increasingly complex, or they develop as chimeras (as cerebroids transplanted into the brains of animals). The tools necessary to assess this possibility still need to be developed by cognitive neuroscience; the normative status of these artificial and sentient entities would need to be discussed, alongside the criteria applied to detect sentience and consciousness.
- Naming: An organoid does not have the same properties and functions as an organ. It is therefore incorrect to refer to organoids as mini-organs, and communicating incorrect information constitutes misconduct. Misnaming is both prejudicial for the advancement of science and for the trust of the public. The HYBRIDA project recognizes the effort of the scientific community to raise a consensus for an adequate nomenclature, for example for nervous system organoids and assembloids, proposes a simple set of guidelines for naming that is rooted in developmental neuroanatomy. We anticipate that this effort will facilitate communication and scientific advancement, promote collaborations, and initiate the development of quality control measures and benchmarking in the field.

For the reasons mentioned above, these specific organoids call for wide-ranging debate on their status

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and regulation. Depending on scientific advances, *in vitro* models of embryos and the nervous system might fall into a regulatory gap in years to come. As models start to better simulate their natural counterparts, general design principles and values will not be sufficient to ensure ethical behaviour. Collective discussions on the status of these artificial entities will be essential. Such discussions are ongoing in bioethics regarding embryo models and brain organoids, but models of the reproductive organs (gonads) and germ cells also need to be taken into account.

7. Do organoids change anything about informed consent?

Organoids are relatively new entities that can be derived routinely in most laboratories from donor tissue. The HYBRIDA consortium reviewed different models of informed consent. Proper informed consent regarding the deposition and use of human biomaterials faces two specific challenges when it comes to organoid research. First, given the unknown future direction of research, it is impossible to anticipate all the potential information and uses that might derive from a given biological sample. Second, integration of the material collected in biotechnological constructs that are shared among laboratories makes it difficult to envision how donors would be able to withdraw their consent, even though it is one of their fundamental rights as stipulated in the Declaration of Helsinki.

In order to address these two specific challenges, one solution might be to use dynamic consent, which provides for continuous information to pass between the donor and users on new projects, allowing the donor to agree for the reuse of their biological samples. This solution involves obtaining initial consent from the donor for the collection and storage of their biological samples in a biobank, and continuous information which requires intense logistics regarding implementation. Because the issue of re-contacting donors poses practical and ethical problems, an alternative might be to adopt the consent for governance model where consent and agreements for the reuse of biological samples would be entrusted to an independent third party representing the donor.

In addition, the donor should be further informed in anticipation of the potential use of their donation so that they can allow or decline specific uses. HYBRIDA is thus proposing a **Donor's Tissue Research Under Secure Transparent Ethical Donation** (**TRUSTED**) that anticipates the conditions of use of biological samples according to the donor's preferences. Donors should complete a questionnaire at the time of donation as part of the consent procedure (see procedure page 41) which also specifies the restrictions they would like to impose on any future use of their tissues, trusting the initial researchers and the secondary users and if necessary with the support of a third party to ensure that these wishes are respected. The TRUSTED would facilitate implementation of the use of biological material, while respecting both the donor's participation and the researcher's investment. We believe that future European regulations regarding informed consent lie beyond the scope of HYBRIDA but we nonetheless call for European action based on our analysis in order to compile appropriate and updated regulations.

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FINAL RECOMMENDATIONS

The HYBRIDA Operational guidelines conclude on 7 groups of recommendations that emphasize the need for a holistic and anticipatory approach to the ethical challenges of organoid research, integrating ethical considerations throughout the research process, and engaging with a broad range of stakeholders to ensure that organoid technologies develop in a way that is socially responsible, inclusive, and aligned with human values.

1. **Anticipate and Address Ethical Concerns Proactively**: Stakeholders in the field of organoids are called to employ an ED/RAD framework to proactively anticipate ethical concerns, including the social implications of organoid research. This involves engaging in ethical reflection and assessment from the conceptual stage through to clinical applications, considering long-term societal impacts.
   - **1.1.** Utilize the MIAOU/EChOES questionnaires for reporting organoid research to ensure comprehensiveness and standardization. Moreover, these questionnaires will be used to establish a representation of knowledge related to organoids and will allow to detect evolutions both in knowledge and in the use of organoids.
   - **1.2.** Put special emphasis on the confidentiality and privacy concerns related to genetic information derived from organoids, aligning with GDPR and other relevant data protection frameworks.
   - **1.3.** Address potential misuse of organoids in research and therapy, such as creating organoids with sentient potential or for purposes not aligned with ethical guidelines and societal values.

2. **Incorporate Responsible Research and Innovation (RRI) Practices**: Adhere to RRI principles by involving stakeholders early in the research process, promoting interdisciplinarity, including social sciences and humanities, and ensuring that research is conducted for and with society.
   - **2.1.** Use the RICOCheck questionnaire for ethical self-assessment, in line with the European ethical self-assessment document.
   - **2.2.** Update RICOCheck to follow the evolution of the European ethical self-assessment and the evolution of the social impact of organoids.

3. **Ensure Continuous Ethical Engagement**: Maintain ongoing ethical dialogue among researchers, stakeholders, and society, from the initial stages of research to all conceivable applications. This continuous engagement allows for the adaptation of research practices in response to evolving ethical standards and societal expectations.
   - **3.1.** Use HYBRIDA Operational Guidelines on the ethical procurement of human tissues and biological material when creating organoids.
   - **3.2.** Anticipate future use and reuse in accordance to the donor's TRUSTED list, with potential agreement delegation to an independent third party representing the interest of the donors.

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4. **Implement Ethical Reflection**: Combine RAD methodology with ED to allow for swift adaptations as ethical considerations and scientific knowledge evolve. This integration facilitates the ethical development of organoids by enabling rapid prototyping, stakeholder feedback, and iterative refinement.
   - **4.1.** Initiate discussions to clarify the status of embryo models
   - **4.2.** Initiate discussions on sentience and consciousness of complex neural organoids
   - **4.3.** Initiate discussions on consent withdrawal
   - **4.4.** Initiate discussions on chimeras involving organoids
   - **4.5.** Monitor all emerging issues, through a task force involving all stakeholders
   - **4.6.** Prevent as much as possible inequitable access to benefits by recognizing and mitigating risks related to the commercialization of organoids, ensuring equitable access to advancements in organoid-based therapies and diagnostics

5. **Foster Public deliberation and transparent regulation over Organoid Development**: Advocate for transparent oversight and regulation over the development and application of organoid technologies. This involves transparent decision-making processes that include a broad range of stakeholders, ensuring that organoid research aligns with deontological practices and ethics.
   - 5.1. Establish a Public Advisory Committee for Organoid Research inside an existing agency that includes scientists, ethicists, patient advocates, policymakers, and laypersons to provide oversight and input into the direction of organoid research. Implement transparent research agendas and reporting of this committee.
   - 5.2. Promote open access to research agendas, funding sources, and findings in the field of organoid science. This includes the requirement for researchers to publicly disclose objectives, methodologies, results, and implications of their work, enabling public scrutiny and input.
   - 5.3. Promote Initiatives to enhance public understanding of organoid research, including its potential benefits and ethical considerations, fostering an informed dialogue between researchers and the public.

6. **Facilitate Ethical Literacy and Education in the field of organoids**: Develop educational resources and training programs to enhance ethical literacy among organoid researchers, stakeholders, and the broader public. This includes fostering an understanding of the ethical dimensions of organoid research and the importance of ethical design principles.
   - 6.1. Avoid misnaming such as using terms like "mini-organ" or "synthetic embryo" that might mislead about organoids' capabilities.
   - 6.2. Prevent exaggerated claims, hype as well as fears, regarding clinical applications to maintain public trust and realistic expectations.
   - 6.3. Develop an Open-Access Ethical Literacy Platform: Launch a digital platform offering a comprehensive suite of resources on the ethics of organoid research. This platform would host interactive modules, case studies, expert lectures, and guidelines designed to enhance ethical understanding and decision-making skills among researchers and the broader community.
   - 6.4. Integrate Ethics into STEM Curricula (Science, Technology, Engineering and mathematics): Work with educational institutions to integrate ethics modules specifically tailored to organoid research within existing STEM curricula. This initiative should aim at instilling a foundational ethical mindset in scientific education, preparing future researchers to consider ethical implications inherently in their work.

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7. Commit to respecting the informed consent process:

7.1. Upstream of any project of organoid derivation, provide both verbal information during consultations with the donor and a comprehensible information letter detailing i) the research topic, ii) objectives, iii) the procedure for sample or tissue collection, handling of biological samples, iv) the fate of biological samples and associated data, in particular if reuse is planed, v) the procedure to protect patient anonymity, vi) the right to withdraw consent without prejudice, and vii) the right to be informed about reuse of their biological samples as well as on the follow-up and the results of the study.

7.2. Implement and include with informed consent the "TRUSTED" questionnaire, enabling donors to explicitly authorize or prohibit specific potential uses of their biological material and data.

7.3. Formalize signed informed consent in a pseudonymized passport-style document - letter of information, informed consent form and TRUSTED list - accompanying biological samples distributed by biobanks.

7.4. Involve, if applicable, an independent third party responsible for reviewing sample use and reuse, ensuring compliance with donor preferences.

7.5. Entrust the Public Advisory Committee for Organoid Research, mentioned in recommendation 5.1, to assess various consent forms and define the most appropriate consent options, as well as the modalities and consequences of a possible withdrawal of consent for all parties.

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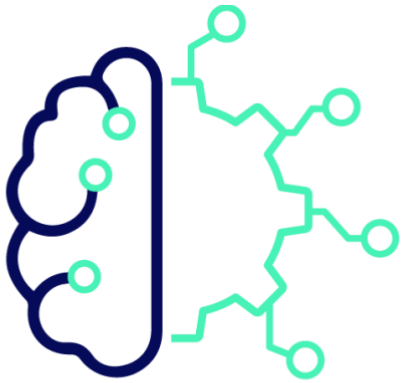

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CONSORTIUM MEMBERS

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