HYBRIDA

Pocket-sized informed consent for research on organoids and related fields

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1. Why is informed consent an issue in the context of research on organoids and related fields?

Informed consent is a basic fundamental prerequisite for any type of research involving human subjects, including work on the use of tissues/cells and associated data collected in the context of medical care and further used for research. Organoids are products of biotechnology that emerged in the early 2000s, building on decades of research on the potential for human cells to proliferate and renew themselves, even outside the body. Organoids are a family of entities made from various types of natural or engineered stem cells of healthy or pathological origin that have similarities to an organ in terms of their cellular composition and/or a similar architecture that reproduces at least some of the features and functions of an organ. 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.

Informed consent is a process that includes both oral and written information, and signature of a form attesting to completion of the information process and that a donor has freely consented to the use of their cells or tissues. It is not sufficient to just provide information: this information needs to be clear enough to be understood by each donor, and the procedure must also be simple and understandable. This implies that the researchers must enable donors to make an autonomous and voluntary decision, without any type of incentive and without this having any effects on their medical follow-up, if applicable. For organoid research, this means providing information on which organoid will be derived, with which degree of engineering and for which application.

Informed consent implies informing donors of the initial aims of the research but also of its progress/evolution involving their donation. It also implies transparent information on possible storage for secondary use, on redirection of the initial research project to achieve another purpose, on possible transfer to a foreign country, on the future of their biological material and associated data and on the identity of the research team, as well as the donor's right to exercise their independent right to agree or refuse to participate, at any time. This raises issues regarding the unknown future use of cells or tissues. Some organoids may give rise to more questions than others, and the conditions for potential withdrawal must be fully explained. We have identified complex nervous tissue organoids and embryonic models as examples of derivations that might raise ethical issues for donors.

2. HYBRIDA's proposals regarding specific informed consent for organoids and related fields

2.1 Various types of informed consent

We first tried to determine the best procedure regarding informed consent relative to organoids and related fields. We identified five types of informed consent, each with its own advantages and drawbacks concerning reuse:

Traditional or specific consent provides transparency and good protection of donor rights but it does not protect the work of organoid researchers and makes reuse very difficult, if not impossible. By contrast, broad consent does not protect donor rights but ensures flexibility regarding the conduct of research. We considered that general consent is not ethical because it is too vague. Dynamic consent, which takes advantage of recent information technologies, appears to offer a good compromise but it requires complicated logistics and high degree of donor involvement. Finally, the consent for governance model provides for mediation between the donor and researcher and in our view should be further explored, in view of its respect for privacy

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and donor rights, as well as of the efforts of researchers in a temporal perspective, ensuring the continuity of their work.

Several aspects need to be considered when choosing any form of consent, such as constant attention to data confidentiality, constant public engagement in the entire process, measures to ensure and obtaining ethical advice from the ethical institutions regarding the design of projects involving organoids.

2.2 The difficult question is that of the unforeseen reuse of cells or tissues.
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 of the full D5.1 document) 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.

Whichever type of consent is chosen for a given study, and in light of the results of the public consultations organised within the framework of HYBRIDA, we consider that information must be as complete as possible and provided beforehand. Consequently, we propose the implementation of informed consent in the form of a three-part document that includes:

- Written information (in addition to any oral information that must be provided),
- A donor wish list (**TRUSTED**) in the form of a questionnaire in which donors will explicitly authorise or not the potential uses of their biological material and associated data,
- A consent form signed by the donor.

We also propose the establishment of a type of passport for cells, organoid derivatives and associated biological data that could be distributed by suppliers (biobanks, commercial suppliers or other researchers) together with the cells/organoids. This would include the TRUSTED, the written information given to the donor and the blank consent form. This proposal would enable the third parties responsible for representing the interests of donors to respect their wishes, and allow Research Ethics Committees (RECs) and Research Integrity Offices (RIOs) to verify that the donors' wishes have been respected.

The second major difficulty concerns the withdrawal of consent, given the amount of work required to manufacture and maintain organoids.

3. Remaining open questions regarding informed consent for research on organoids and related fields

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a. Collection from biobanks: when purchasing cells from a commercial provider or even from institutional biobanks, scientists do not often have sufficient information about the origins of the cells and the process and content of the initial informed consent. We therefore recommend that each biobank should constitute a review board composed of scientists, clinicians, ethicists and representatives of patient organisations in order to fulfil the critical mission of managing informed consent with respect to both donor rights and the work of researchers.

b. **Withdrawal of consent:** in view of the numerous practical difficulties inherent in a withdrawal of consent, one recommendation could be to follow the guidelines of the International Society for Stem Cell Research (ISSCR) which point out the current use of informed consent documents which only allow for donor withdrawal before the cells enter processing. However, from an ethical point of view, the question arises as to how donor rights and the TRUSTED are respected in such a context. It is therefore necessary for the community of researchers involved in organoid production and/or use to initiate reflection on finding an acceptable consensus which respects scientific work and the advancement of knowledge on the one hand and donor rights and the compliance with the TRUSTED on the other.

HYBRIDA suggests creating an **EU taskforce** focused on questions regarding the specificities relative to withdrawal of consent in the fast-changing field of research on organoids.

Extract from the HYBRIDA final recommendations

Commit to respecting the informed consent process:

1.1. 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.

1.2. 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.

1.3. 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.

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

1.5. 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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