# Ethics Considerations Regarding Donors' and Patients' Consent

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## 6.1 Introduction

Informed consent is a crucial factor in determining whether particular uses of brain organoids for research and clinical translation are ethically acceptable. However, while appropriate consent is a necessary condition for determining ethical acceptability, it is not alone sufficient to do so. Scientifically exciting and interesting potential research uses of brain organoids include experiments designed to enhance understanding of human brain development, elucidating the pathogenesis of diseases and conditions, identify potential drug candidates to pursue for possible clinical development (e.g., infectious diseases, dementias) and examining the foundations of consciousness. Promising pathways for the potential clinical translation of brain organoids include personalized medicine (e.g., selecting drugs likely to be safe and effective in particular patients with cancers, psychiatric diseases, and dementias) and transplantation (e.g., degenerative neurologic diseases, stroke, and trauma). In the context of basic research, consent of donors whose tissues are used to derive brain organoids is of primary concern, whereas in clinical translation the consent of both allogeneic donors and patients may be relevant.

In this chapter, I examine key ethical issues related to informed consent for brain organoid research and clinical translation. In order to do so, I first describe both a standard conceptual approach to informed consent that aims at meeting the ethical goal of respecting the autonomy of persons and some of the other ethically relevant functions of informed consent. This conceptual work provides a foundation for mapping some of the ethical issues related to informed consent in regard to the decision-making capacity and voluntariness of those being asked to consent, disclosure requirements associated with the use of brain organoids in general and

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for particular proposed uses in particular, threats to understanding that must be overcome, and considerations for authorization. Finally, I conclude by offering some suggestions for grappling with such informed consent challenges related to brain organoids.

## 6.2 Conceptual Considerations

From an ethics perspective, informed consent is a means of respecting the autonomy of persons. While there are a variety of conceptual models and practices regarding informed consent, to be ethically sound it arguably should generally include a set of necessary elements. Following the work of Tom Beauchamp and James Childress, these elements can be categorized as: Threshold, Information, and Consent. The Threshold, or precondition category, includes Competency and Voluntariness; the Information category includes Disclosure and Understanding, as well as offering a Recommendation (in clinical, but not research contexts); and the Consent category includes Decision and Authorization.[1] Although it is beyond the scope of this chapter to comprehensively explore the justifications and scope of each element, nor exceptions to the requirement to obtain informed consent, they provide a helpful framework for capturing ethically essential aspects of the informed consent process. In addition, in practice, these categories can generally be understood as steps in the process of obtaining informed consent. At the risk of oversimplification, each of these steps will be briefly described, recognizing that there is substantial scholarship regarding all of them.

Competence, or decision-making capacity, is a precondition for an informed consent process. Whereas competence is a legal status in many jurisdictions, decision-making capacity captures the ethically salient criteria for informed consent. In general, adequate decision-making capacity includes the ability to understand current circumstances, appreciate the implications of particular choices, make a rational choice, and express that choice. Voluntariness requires not being under the control of others, which precludes the use of coercion and undue influence.

The disclosure element involves providing necessary information about a proposed clinical intervention or research use. Although there are specific jurisdictional legal requirements in particular clinical circumstances and research settings, disclosure generally includes providing information about the nature of an intervention or use, its risks and burdens as well as its potential benefits and alternatives. The understanding element demands that this information be comprehended by the person being asked to consent. As mentioned earlier, in clinical settings, consistent with clinicians' fiduciary obligations towards patients, it can be appropriate to provide a recommendation about a proposed approach.

[1] Beauchamp and Childress (2019).

Once these other elements have been satisfied, a decision can be taken about whether or not to proceed. Finally, the decision is authorized, which may be oral or written depending upon the context. When written authorization is obtained, the consent document typically includes key information that was disclosed during the consent process.

Even though the standard or primary ethical justification of consent is based on the ethical principle of respect for autonomy, recent scholarship regarding consent in the research setting makes evident that consent can serve additional "participant-centered ethical functions: (1) providing transparency; (2) allowing control and authorization; (3) promoting concordance with participants' values; and (4) protecting participants' welfare interests. In addition, … [there are] three systemic or procedural functions that are more policy focused: (5) promoting trust; (6) satisfying regulatory requirements; and (7) promoting the integrity of research and researchers."[2] Recognizing these other ethical functions can help identify ethically relevant considerations for informed consent and underscore the necessity of obtaining consent for uses of brain organoids as well as facilitate helping to meet these goals in practice.

## 6.3 Threats to Decision-Making Capacity and Voluntariness

Brain diseases and conditions obviously can, but do not necessarily, undermine decision-making capacity. Consequently, ensuring decision-making capacity warrants special consideration in brain organoid research and clinical translation. While formal assessments of capacity are unlikely to be necessary when obtaining tissue from persons unaffected with brain diseases and conditions, there should be a rebuttable presumption for doing so with affected patients. While trained and experienced clinicians are generally able to make determinations of decision-making capacity, sometimes the special expertise of psychiatrists or neurologists may be necessary.

In situations where an affected person lacks decision-making capacity, where permissible by law, proxy consent for such a use must be obtained. Similarly, if the proposed use involves children, parental permission, ideally with the assent of the child for nontherapeutic research uses, substitute for individual informed consent.

In addition, given the devastating nature of many brain diseases and conditions as well as the lack of viable curative options, patients and their family members may face challenges related to voluntariness. Accordingly, those seeking to obtain consent must be sensitive to this concern and take measures to address this. This could include emphasizing that proposed research is optional, that research options are unproven, and that standard care will still be provided regardless of a decision regarding a proposed use.

[2] Dickert et al. (2017).

## 6.4 General Disclosure Requirements

As mentioned earlier (under Sect. 6.2), disclosure involves providing information about the nature of the proposed use(s), its associated risks and burdens as well as its potential benefits and alternatives. For brain organoid research and clinical translation, an essential starting point involves providing information about the nature of organoids.

### 6.4.1 The Nature of Organoids

Although research with a wide range of organoids is burgeoning, the vast majority of those asked to contribute tissues to make organoids and participate in their clinical translation are currently unlikely to have an accurate understanding of them. Consequently, the disclosure process must include an explanation of the nature of organoids. However, emerging empirical research regarding patients' perspectives on organoids suggests it will be challenging to do so in a manner that will be truly understandable. Of note, interview studies in both the Netherlands and the USA have found that patients tend to imagine both positive and negative attributes associated with organoids, ranging from their being markedly beneficial in ways that exceed current capabilities to frightening scientific fictions.[3] Furthermore, interviewees generally view brain organoids as ontologically and morally distinct from other types of organoids.[4] These findings reinforce the need for careful explanation.

In describing organoids, information must be provided about how organoids are made, including the types of cells used to produce them (e.g., resident "adult" stem cells in tissues, induced pluripotent stem cells, and human embryonic stem cells). When induced pluripotent or human embryonic stem cells are used to make organoids, consistent with differing legal requirements and professional guidelines,[5] information specific to them must be provided.[6] While using induced pluripotent stem cells to create brain organoids does not raise concerns related to the destruction of human embryos inherent to deriving human embryonic stem cells, they nevertheless can be morally salient to patients.[7]

### 6.4.2 Other General Disclosure Requirements

Consistent with general expectations of disclosure for related life sciences research and clinical translation, information must be provided about immortalization, genetic

[3] Haselager et al. (2021); Bollinger et al. (2021).

[4] Bollinger et al. (2021).

[5] ISSCR (2021).

[6] Lowenthal et al. (2012).

[7] Dasgupta et al. (2014).

modification, sharing of materials, and measures to protect privacy and their limitations.

In addition, any commercial uses of brain organoids and financial conflicts of interest should be disclosed. While disclosure and consent may not resolve all of the ethical tensions when there are financial interests at stake, they are minimum requirements in any management plan regarding them. Of note, the need for this disclosure in the context of commercial uses of organoids is reinforced by the fact that such uses can raise concerns among those asked to participate in brain organoid research and clinical translation.[8] Moreover, early data suggest that commercial use is of relevance to patients who have been involved with organoid research and see the informed consent process as one safeguard for it.[9]

## 6.5 Specific Disclosure Requirements Based on Proposed Use

In addition to general disclosure requirements, providing information about the proposed use is a core part of the informed consent process. Of course, the information to be disclosed is contingent upon the type of use (i.e., basic science, biobanking, personalized medicine, and transplantation) and then tailored to it.

### 6.5.1 Basic Science

Although some in vitro basic science research involving brain organoids is unlikely to raise significant ethical concerns, the ethical implications of other basic science research efforts are currently unsettled as is the appropriate type of oversight of them.[10] Hyun and colleagues'[11] recent observations are sobering:

> Ethical concerns also arise when research teams generate brain organoids using iPS cell lines derived from anonymized or de-identified tissues samples procured from tissue banks. At this time, it is not a standard practice that the informed consent for tissue collection used by most tissue banks actually discloses to tissue donors the possibility that their biological specimens could be used for iPS cell derivation and use in general, and much less to generate brain organoids. It is currently unknown whether tissue bank donors approve of the use of their biospecimens for brain organoid creation and their subsequent use for nearly limitless future applications, as this is a very recent application and data on donor preferences and objections are lacking. The main ethical concern here is that, while donors' tissue samples can be anonymized or de-identified by a tissue storage facility, it cannot be assumed that tissue donors have given their consent for their participation specifically in brain organoid research.

[8] Boers et al. (2016).

[9] Boers et al. (2018).

[10] Chen et al. (2019) and Chapman (2019).

[11] Hyun et al. (2020), p. 3.

As such, ensuring that proposed basic science uses are at least consistent with the provenance and consent of the biomaterials being used is a minimal requirement. However, absent data on previous tissue donors' attitudes and potential concerns about brain organoid research with their tissues, given emerging data regarding patients' perspectives on brain organoids (see Sect. 6.4), using materials that have been obtained with prospective consent that satisfied the general disclosure requirements delineated above is ethically preferable to relying on broad consent that could not have anticipated the full range of uses that some people find to be morally troublesome. Relatedly, the types of brain organoid research that can raise moral concerns should be disclosed during the consent process. These include research involving chimeras, complex organoids, and assembloids and work directed towards understanding consciousness.

While research involving chimeras is commonplace, it can raise moral concerns, especially when organoids "humanize" a resulting chimera.[12] As summarized elsewhere, there are some important settled and unsettled considerations in determining the ethical appropriateness of specific neurologic experiments involving chimeras.[13] Regardless, a necessary, but clearly not sufficient, criterion for conducting such research is consent for this proposed use. While much of the scholarship related to these issues has been in the setting of stem cell and brain tissue research, research with human brain organoids should at least *prima facie* be held to the same standards at least in regard to consent.

Nonetheless, the conceptual literature regarding brain organoids includes substantial debates about the moral status of brain organoids as they become more mature and complex due in large part to concerns about consciousness and sentience.[14] There are related normative issues regarding assembloids. Specifically, given uncertainties regarding the moral status of complex organoids and assembloids,[15] explicit consent for these types of experiments is indicated.

While the valence of most ethics discussions raises concerns about the development of consciousness or sentience in brain organoids, paradoxically brain organoids may be the most preferable scientific means of understanding the nature of human consciousness. Of course, such research would raise complex ethical considerations that would need to be addressed, yet given these uncertainties and moral concerns about creating consciousness, explicit consent for this work would also be needed.

### 6.5.2 Biobanking

In addition to standard biobanking of biological materials used to make brain organoids, living biobanking of brain organoids holds great promise for basic research

[12] Munsie et al. (2017).

[13] Greely et al. (2007).

[14] Munsie et al. (2017).

[15] Hyun et al. (2020).

and clinical translation.[16] As in biobanking in general, specific issues to be disclosed during the consent process will be predicated in large part on the structure and function of the biobank and permissible uses of banked of organoids or the human biological materials used to generate them. Accordingly, of great relevance will be the scope of consent and permissible uses, the governance model for determining use and distribution of banked organoids, including the permissibility of commercial uses. In addition, since brain organoids will have a genetic relationship to tissue donors, this must be disclosed along with precautions taken to protect privacy of any associated clinical or demographic information. Furthermore, any provisions for providing results that may be of clinical significance to donors as well as benefit sharing should be transparently described.

Building upon earlier approaches employed in other research settings,[17] Boers and Bredenoord[18] have argued for obtaining "consent for governance" for organoid biobanking. This deviates from most conventional approaches to consent that tend to encapsulate potential uses at the time of consent by obtaining consent to particular approaches to future decision-making through an articulated governance mechanism. As such, consent for governance includes an initial consent procedure incorporating the information delineated above with emphasis placed on describing privacy measures (given the actual inability to anonymize biomaterials), participant engagement, benefit sharing, and ethical oversight.

### 6.5.3 Personalized Medicine

Organoids can be used to help select medications that are likely to be effective in particular patients. A paradigmatic example derives from the use of gastrointestinal organoids to select medications in patients with cystic fibrosis.[19] There is hope that such an approach might also be useful for selecting medications for a variety of conditions effecting the brain (e.g., schizophrenia) as well as brain cancers (e.g., glioblastoma), where efficacy of particular treatments across populations of patients is variable, yet treatment toxicity is high. However, challenges to such use will likely require the generation of patient-specific brain organoids with known correlates of efficacy or toxicity. Because obtaining brain tissue requires an invasive procedure with some risk, where scientifically appropriate, the likely approach to making brain organoids for many diseases and conditions will probably employ skin biopsies and the derivation of induced pluripotent stem cells from them. In this setting, disclosure should include information about the current uncertainties associated with the possibility of producing a suitable organoid, the time needed for organoid maturation and testing, the lack of data on predictability in selecting

[16] Li et al. (2020).

[17] Lavori et al. (2002).

[18] Boers and Bredenoord (2018).

[19] Dekkers et al. (2013) and Berkers et al. (2019).

medications, and the alternative of simply trying another medication without using brain organoids.

### 6.5.4 Transplantation

Brain organoid transplantation might eventually provide viable treatment options for certain neurologic diseases and conditions. For example, autologous organoid transplants might prove useful for certain types of cerebrovascular accidents and Parkinson disease. Experience garnered in similar settings, such as the use of fetal substantia nigra transplants and pluripotent stem cell derivatives for the treatment of Parkinson disease, helps to identify information that should be disclosed for such research. These include the inherent risks related to interventions into the human brain, including collateral damage due to transplantation and uncontrolled cell growth, which can have profound effects in the brain that may not be reversible.

## 6.6 Ensuring Understanding

As described earlier (see Sect. 6.2), it is essential that those being asked to provide informed consent understand the information that has been disclosed. This can be especially challenging in situations where the science is novel and in clinical settings where standard treatment options are not ideal.

Emerging empirical data on patients' perception of organoids in general and brain organoids in particular (see Sect. 6.4) hint at some of the challenges that will be encountered in this setting. Specifically, the proclivity for patients to use science fiction when conceptualizing and describing organoids needs to be countered by current realities. To make matters worse, the hype associated with the use of brain organoids must also be overcome so that informed consent can be obtained.

Given this state of affairs it may be prudent to develop and use balanced standard materials describing brain organoids during the consent process. Such materials could help trigger discussion about organoids as well as the specific proposed use, which promises to be helpful since extended discussions during the consent process are associated with enhanced understanding.[20] In situations where the risks are particularly high, consideration should be given to formally assessing understanding prior to seeking consent.

## 6.7 Authorization

The documents used when obtaining written authorization should include key aspects of what has been disclosed during the consent process. The International Society for Stem Cell Research has offered sample consent documents that have

[20] Nishimura et al. (2013).

some relevance to brain organoid research. Similarly, at Johns Hopkins Medicine, the Institutional Review Board has drafted templates to be used in specific research settings, which can then be tailored based upon the proposed research and certain regulatory requirements. For example, the informed consent template research involving pluripotent stem cells suggests the following text in regard to basic science research organoids: "We may use the cells taken from your [specify source of cells, e.g. skin] to create what is sometimes called an 'organoid.' An organoid is an organized cluster of cells, grown in the lab, which are designed to mimic organ structure and function. Organoids can be used to help understand diseases and treatments for them."[21]

## 6.8 Concluding Comments

While the ethical requirement to obtain explicit informed consent for brain organoid research and clinical translation seems clear, doing so in practice may be challenging due to rapid scientific progress, changing policies and practices, baseline understanding of brain organoids, and local contexts. Properly addressing these challenges will be facilitated by empirical data and sharing experiences regarding effective (and ineffective) approaches. For example, gathering additional data regarding patients' knowledge, attitudes, and beliefs about brain organoid research in different settings is needed. In addition, the materials used to disclose information about brain organoid research and clinical translation could be developed using formative research methods to help ensure understanding.[22] Similarly, novel approaches to consent (e.g., consent for governance) should arguably be tested rather than simply implemented since even well-considered interventions aimed at improving consent can fail in practice.[23] While such efforts will require time and resources, they should help to meet the ethical justification for informed consent as well as some of its ethically important goals.

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