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COMMENTARY

Xenotransplantation clinical trials: Should patients with diminished capacity be permitted to enroll?

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1 | INTRODUCTION

Before xenotransplantation clinical trials begin, it is essential to establish clear and equitable participant selection criteria. Selection criteria have been suggested in the literature, as well as in a proposed kidney xenotransplantation phase 1 clinical trial.[1–4] In each, inclusion criteria is predicated on patients possessing clinical decision-making capacity. Ensuring informed consent for xenotransplantation clinical trials with patients who have decision-making capacity is recognized as complex for the following reasons: the possibility of therapeutic misconception, potential for xenozoonosis, and the potentially burdensome requirement for lifelong biosurveillance.[5,6] Informed consent for enrollment in a xenotransplantation trial with adult persons who have diminished capacity would involve additional complexities. By diminished capacity, we mean to describe someone who—for various medical reasons—does not have the ability to provide informed consent. To our knowledge, no xenotransplantation investigator, nor the proposed kidney xenotransplantation phase I clinical trial in the United States, currently proposes including persons with diminished capacity. Nonetheless, the topic has been broached, and we believe it requires additional independent scrutiny.

1.1 | Current recommendations for including persons with diminished capacity

Xenotransplantation clinical trials with persons who lack decision-making capacity have not been considered at length and would likely be controversial. The Nuffield Council on Bioethics recommended that "the first xenotransplantation trials should not involve adults incapable of consenting to participation on their own behalf" (7.25).[7] It made an exception, however: "The Medical Research Council has recommended that the participation of incapacitated adults in therapeutic research may be justified if, in addition to evidence that the procedure will benefit the individual, it relates to their incapacitating condition and the relevant knowledge could not be gained by research in adults able to consent" (7.26).[7] Similarly, the United States Department of Health and Human Services (DHHS) stated: "enrollment of mentally impaired individuals into xenotransplantation protocols should be limited to those in whom mental capacity is likely to be restored by the procedure."[8] Additionally, in the DHHS guidelines, a surrogate must confirm that the clinical trial aligns with the person's preferences or would promote their best interests and that they are "likely to adhere to lifelong follow-up requirements."[8]

In 2012, the American Medical Association (AMA) Council on Ethical and Judicial Affairs posited that it "would be ethical to include children and incompetent adults in xenotransplantation research protocols only when the patients are terminally ill and alternative treatments are not available" (Opinion 2.169.4).[9] The AMA *Code of Medical Ethics* states:

Physicians who choose to participate in clinical research that involves transplantation of organs or tissues from nonhuman sources should:

(e) Ensure that if participation by individuals who lack decision-making capacity is contemplated, appropriate measures are taken to safeguard their interests.[10]

1.2 | Critique of current recommendations

The current recommendations for enrolling participants with diminished capacity into a xenotransplantation clinical trial are vague and insufficiently ethically justified to be practicable. The AMA states that "appropriate measures" should be taken to safeguard the interests of those enrolled, yet what constitutes such measures, aside from trying to ensure the surrogate has any assistance they need to assess quality of life pre- and post-intervention, is largely undefined for xenotransplantation. In the DHHS guidelines, three requirements are envisioned to enroll persons with diminished capacity: (i) the procedure must be "likely" to restore the mental impairment; (ii) the surrogate decision-maker must have evidence that xenotransplantation is what the person wanted or, if such evidence is lacking, determine that xenotransplantation is in the person's best interest; (iii) confirm that the patient is a responsible person who is "likely to adhere to lifelong follow-up requirements." DHHS guidelines are unlikely to be satisfied—at least in the earlier phases of clinical trials. Condition (i) may prove difficult to initially meet. Given the lack of xenotransplantation outcomes in humans, "likely" benefit is tenuous. Additionally, some clinical and biological causes for diminished capacity may be irreversible. Condition (ii) is difficult to establish, as very few people are likely to discuss xenotransplantation and all the implications of receiving a xenograft (e.g., biosurveillance) in advance. There is also no clear definition as to what evidence would be acceptable to meet such criteria. Condition (iii) will always be difficult to determine with any certainty because it will be dependent on several variables, for example, their degree of physical dependency and need following their restored capacity. Even individuals with capacity and a social support system can be non-compliant with medical requirements. It is also worth drawing attention to the importance of ensuring that any lifelong biosurveillance requirements carefully balance what is clinically necessary against how burdensome they are for a patient and how logistically feasible enforcement is. After all, the more burdensome the requirements are, the less likely that a patient may be to comply—in either the short or long-term—especially in cases where informed consent was given by a surrogate.

A phase I clinical trial is unlikely to meet the threshold for the DHHS requirements that the xenograft is "likely" to restore the patient's impaired capacity. A phase I trial's purpose is to assess safety and evaluate certain limitations and advantages. While xenotransplantation could theoretically restore capacity in very limited instances, there are existing therapeutic options that are less risky and more clinically appropriate for end-stage renal disease and end-stage heart failure (e.g., hemodialysis, allotransplantation). Due to the experimental nature of the therapy, the requisite likelihood of success would be too low to be deemed acceptable in the context of a phase I trial. The case for a favorable risk-benefit evaluation is lowest at the phase I stage and becomes more favorable at each subsequent clinical trial phase. However, if we suppose that dialysis is not a viable clinical option and the likelihood of receiving an allograft is low, it may be appropriate to consider such patients for inclusion in later phase clinical trials given that a degree of safety and efficacy would have been demonstrated; in such cases, if a xenograft may offer a sufficiently reasonable likelihood of restoring capacity, then the balance shifts. However, as most guidelines recommend post-xenotransplantation monitoring for xenozoonotic disease, further complications exist with the DHHS recommendations regarding how a person can be reasonably expected to comply with monitoring when they never agreed to comply with such, potentially burdensome, conditions.

1.3 | Comment

It would be a high benchmark to meet, as well as require significant justification, to determine that an unproven and risky clinical trial is likely to restore capacity or has the highest probable net benefit among available treatment options (including continued dialysis; allograft waitlisting; palliative care) and is therefore in the patient's best interest. If xenotransplantation proves to be a safe and effective clinical option, it may also be unethical to withhold participation in a later phase clinical trial (e.g., phase III) to individuals with diminished capacity and who need a transplant. Striking a balance between advancing clinical research and protecting the rights and well-being of vulnerable individuals requires careful ethical reflection and the development of robust safeguards. At this point, the current recommendations to allow persons with diminished capacity to participate in early xenotransplantation clinical trials are under-developed and should not be considered ethically permissible. Nevertheless, in later phase clinical trials where the clinical risk may be sufficiently reduced it might be ethically acceptable for certain patients with a diminished capacity to be considered for inclusion. The case would be strongest for those patients that are not eligible for allotransplantation, but where there is a realistic likelihood that a xenotransplantation could reverse the cause of their diminished capacity or possibly improve their quality of life.

DISCLOSURES

None.

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REFERENCES

1. Cooper DKC, Wijkstrom M, Hariharan S, et al. Selection of patients for initial clinical trials of solid organ xenotransplantation. *Transplantation*. 2017;101(7):1551-1558. doi:10.1097/TP.0000000000001582
2. AMA Council on Ethical and Judicial Affairs. AMA code of medical ethics' opinions on organ transplantation. *AMA Journal of Ethics*. 2012;14(3):204-214.
3. Jagdale A, Kumar V, Anderson DJ, et al. Suggested patient selection criteria for initial clinical trials of pig kidney xenotransplantation in the United States. *Transplantation*. 2021;105(9):1904-1908. doi:10.1097/TP.0000000000003632
4. Locke JE. US National Library of Medicine. *ClinicalTrials.gov*. 2022. Accessed August 5, 2023. https://clinicaltrials.gov/ct2/show/NCT05340426
5. Padilla LA, Hurst D, Maxwell K, et al. Informed consent for potential recipients of pig kidney xenotransplantation in the United States. *Transplantation*. 2022;106(9):1754-1762. doi:10.1097/TP.0000000000004144
6. Silverman H, Odonkor PN. Reevaluating the ethical issues in porcine-to-human heart xenotransplantation. *Hastings Cent Rep*. 2022;52(5):32-42. doi:10.1002/hast.1419
7. Nuffield Council on Bioethics. Animal-to-Human transplants: the ethics of xenotransplantation; 1996.
8. US Department of Health and Human Services Secretary's Advisory Committee on Xenotransplantation. Informed Consent in Clinical Research Involving Xenotransplantation; 2004. Available at. Accessed August 5, 2023. https://www.tts.org/images/stories/ixa/regulatory_documents/8_SACX_Informed_consent_US_DHHS_June_2004.pdf
9. AMA Council on Ethical and Judicial Affairs. AMA code of medical ethics' opinions on organ transplantation. *Virtual Mentor*. 2012;14(3):204-214. doi:10.1001/virtualmentor.2012.14.3.coet1-1203
10. American Medical Association. Code of Medical Ethics. Opinion 6.3.1. Xenotransplantation. Accessed May 31, 2023. https://code-medical-ethics.ama-assn.org/ethics-opinions/xenotransplantation

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