Recommendations for First-in-Human Pig Kidney Xenotransplant Clinical Trials

■ Karen J. Maschke, PhD
The Hastings Center for Bioethics

■ Michael K. Gusmano, PhD
Lehigh University

■ Elisa J. Gordon, PhD, MPH
Vanderbilt University Medical Center

We conducted a four-year study, "Informing Ethical Translation of Xenotransplantation Clinical Trials," that examined ethical and policy challenges to the development, oversight, and conduct of first-in-human pig kidney xenotransplant clinical trials (henceforth referred to as pig kidney clinical trials). Genetically modified pig kidneys have been transplanted into living human recipients under the U.S. Food and Drug Administration's (FDA's) Expanded Access/Compassionate Use pathway, and FDA-approved pig kidney clinical trials using genetically modified pig kidneys are expected to begin in 2025.

These recommendations were developed for sponsors and transplant programs conducting pig kidney clinical trials, Institutional Review Boards (IRBs) that review pig kidney clinical trial protocols, and transplant regulators. The recommendations were informed by data collected from in-depth interviews with 28 kidney transplant candidates; an online survey of 142 kidney transplant candidates; in-depth interviews with 28 transplant experts; and in-depth interviews with 23 IRB chairs and other research ethics experts. The recommendations were also informed by existing guidance for xenotransplantation from national and international regulatory and advisory bodies, the literature on xenotransplantation, and input from a 17-member multidisciplinary Advisory Committee composed of transplant clinicians, transplant recipients, a living donor, xenotransplant researchers, transplant regulators, transplant health services researchers, and experts in human research ethics.

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1. Eligibility for Participation in a Pig Kidney Clinical Trial

A critical issue for pig kidney clinical trials is establishing inclusion and exclusion criteria that facilitate obtaining sound scientific data about the safety and efficacy of a xenotransplant. At minimum, participants should be medically stable and have cognitive capacity to follow post-transplant treatment requirements. We address below three issues regarding clinical trial eligibility about which there is ongoing discussion in the xenotransplant literature.

Patients unlikely to receive a human kidney. Given the uncertainty about the risks associated with a pig kidney clinical trial, we recommend limiting eligibility to patients who would be medically and surgically cleared for a human kidney transplant, but who are unlikely to receive a human kidney in the foreseeable future. Being placed on the national transplant waiting list for a human kidney represents an optimal proxy by which to consider a patient as eligible for a pig kidney transplant. However, there are numerous disparities in patients' access to the waiting list, which could limit some potentially eligible patients from referral to transplant programs for consideration in a pig kidney clinical trial. Therefore, waitlisted patients who are likely to die before a kidney becomes available (e.g., older patients) could be suitable for participation in a pig kidney clinical trial. Additionally, clinical trial participation would also be appropriate for dialysis patients who would be medically and surgically cleared to undergo an allotransplant but who may or may not yet be waitlisted and who may be running out of vascular access sites for dialysis or who may be experiencing poor dialysis treatment outcomes. Thus, we do not believe participation in a pig kidney clinical trial should be limited to patients who are already placed on the human kidney waiting list.

Sensitization. Sensitization against human kidneys should not exclude a patient from participating in a pig kidney clinical trial. Patients who are highly sensitized to human kidneys may be at risk of graft rejection due to an overactive immune system. However, highly sensitized patients may not necessarily be highly sensitized against pig antigens. Potential clinical trial participants should therefore be screened to assess expected immunological compatibility with the pig kidney being used in the clinical trial.

Social/psychological criteria. Participants in a pig kidney clinical trial should meet clearly specified social/psychological criteria relevant to xenotransplantation that suggest they will follow post-trial monitoring for porcine infectious disease transmission and immunosuppression treatment regimens. We recommend that these criteria be explicit and applied consistently across all clinical trial sites. Variation in social/psychological criteria across trial sites could result in some patients being inappropriately denied access to clinical trial participation.

2. Porcine Infectious Disease Monitoring for Pig Kidney Clinical Trials

To address the information needs of kidney patients recruited for a xenotransplant clinical trial so they can make an informed decision about whether to participate, it is essential to provide detailed information about porcine infectious disease monitoring post-transplant, if such monitoring is part of clinical trial participation.

Nature of participant monitoring. The informed consent process and informed consent form should specify if monitoring for porcine infectious disease transmission will differ from the type of monitoring that allotransplant recipients undergo. Specific information should be provided about how monitoring will be conducted (e.g., whether monitoring involves blood draws, collection of tissue samples, or other monitoring procedures), the time intervals for monitoring, and where the monitoring will take place. Potential participants should be informed whether transmission of some porcine infections would require mandated reporting to public health authorities and might result in measures such as isolation and quarantine. Trial participants should be provided with an information sheet that describes the kind of symptoms to be aware of and which healthcare professionals participants should contact if they suspect they have an infection.

The time length for participant monitoring. There is disagreement in the research ethics and xenotransplant research communities about whether trial participants should be required to agree to long-term and possibly lifelong monitoring (sometimes referred to as a "Ulysses contract"). A core principle of research ethics is that research participants have a right to withdraw from research at any time. Yet withdrawing from a pig kidney clinical trial that involves porcine infectious disease monitoring could pose a public health risk if the transplant recipient was infected with a transmissible porcine pathogen and the infection was not discovered due to the absence of monitoring. Potential clinical trial participants should be informed that providing informed consent to enroll in the clinical trial means that participants are also agreeing to be monitored for the time length specified in the informed consent form. Clinical trial participants should also be informed that the purpose of porcine infectious disease monitoring is to safeguard their health as well as the health of their close contacts and the public. However, if participants decide to withdraw from the clinical trial and decline to continue following monitoring requirements, they should be permitted to do so. If after withdrawing, they exhibit symptoms that might be associated with a porcine disease infection, standard public health measures can be implemented to address the situation.

Monitoring trial participants' close contacts. There has been little discussion in the literature about whether the close contacts (e.g., intimate partners, household members) of participants in a pig kidney clinical trial should be required to undergo porcine infectious disease monitoring. Similarly, there has been little commentary about whether patients will be ineligible to participate in a pig kidney clinical trial if their close contacts refuse to be monitored. We do not support mandatory monitoring of close contacts as a condition for patient enrollment in a pig kidney clinical trial. Clinical trial sponsors/researchers cannot compel individuals who are not enrolled in a pig kidney clinical trial to agree to trial procedures.

Potential participants should be informed that there may be circumstances when close contacts might need to be monitored, and a definition of close contacts should be provided by the clinical trial sponsor. Including close contacts in the informed consent process would provide an opportunity to inform patients and close contacts about monitoring requirements. Specific information should be provided to close contacts about how monitoring will be conducted (e.g., whether monitoring involves blood draws, collection of tissue samples, or other monitoring procedures), the time intervals for monitoring, and where the monitoring will take place. Close contacts should be informed whether transmission of some porcine infections would require mandated reporting to public health authorities and might result in measures such as isolation and quarantine. Close contacts should be provided with an information sheet that describes what kind of symptoms to be aware of and who they should contact and how if they experience those symptoms.

3. Financial Compensation/Reimbursement/Incentive to Clinical Trial Participants

Clinical trial sponsors commonly provide financial compensation and reimburse research study participants for some of the research study-related costs they incur when enrolled in a research study, e.g., parking fees and meals during research visits at clinical trial sites and/or lodging expenses for overnight stays at a hotel near a clinical trial site that is geographically far from their home. These compensation efforts are designed to make study participants 'whole.' Alternatively, for some clinical trials, sponsors may also provide a financial payment as an incentive to enroll in the clinical trial. A financial enrollment incentive is different from compensating/reimbursing participants for research-related expenses they incur while enrolled in a clinical trial.

Financial compensation/reimbursement. Compensating/reimbursing clinical trial participants is a way to help mitigate financial burdens that participants might incur for parking, meals, and lodging when at the clinical trial site during the research study. Compensation/reimbursement is also a way to help reduce barriers to participation and facilitate fairness in access to a pig kidney clinical trial. IRBs should carefully review the items for which compensation/reimbursement will be provided to ensure that the items are reasonable for compensation/reimbursement. IRBs should also be attentive to the compensation/reimbursement amounts described in the clinical trial protocol and informed consent form to determine if the amounts are appropriate for each clinical trial site and not an undue inducement to participate in a clinical trial.

Financial incentive to enroll in a pig kidney clinical trial. There is disagreement in the research ethics and transplant research communities about offering prospective research participants a financial incentive to motivate their enrollment in a clinical trial. Some commentators raise concerns that a financial incentive can be an undue inducement to participate in a clinical trial, depending on the amount. The FDA and the U.S. Office for Human Research Protections permit sponsors/researchers to offer eligible clinical trial participants a financial incentive to enroll in a clinical trial. If clinical trial sponsors/researchers propose to offer a financial incentive to enroll in a pig kidney clinical trial, IRBs should be attentive to the monetary amount of the incentive that

is described in the protocol and informed consent form to determine if the monetary amount is appropriate and does not comprise an undue inducement to participate. If sponsors/researchers offer a financial incentive to participate in a pig kidney clinical trial, the monetary amount should be the same across study sites collaborating within the same clinical trial.

4. Outcome Metrics for Evaluating the Success of Pig Kidney Clinical Trials

Standard outcome metrics. Many outcome metrics that are used to evaluate the success of allotransplant kidney clinical trials are also appropriate for pig kidney clinical trials. These should include: graft functionality; complications and hospital readmissions related to the transplant; patient survival; quality of life; and cause of death.

Outcome metrics specific to pig kidney clinical trials. Specific metrics regarding complications should include infection rates of porcine-related infections among xenotransplant recipients and their close contacts.

Community engagement. Outcome metrics should be informed by a community-engaged process. We recommend that outcome metrics used to assess pig kidney clinical trials should be informed by people and communities who would be most affected by pig kidney clinical trials. These communities include potential transplant recipients, transplant recipients, and the family members and intimate partners of potential or actual transplant recipients.

5. Exit Strategy for Pig Kidney Clinical Trial Participants

The clinical trial sponsors should establish an 'exit strategy' for xenotransplant recipients whose graft no longer works. The research investigator should disclose options that might be available to the xenotransplant recipient if their graft stops working, such as allotransplant, another xenotransplant, dialysis, or conservative management. A description of the exit strategy should be provided in the informed consent form and discussed during the informed consent process.

6. Expanded Access/Compassionate Use for Pig Kidney Xenotransplants

The FDA's Expanded/Access Compassionate Use pathway for a pig kidney transplant should remain an option for patients who are eligible for this pathway when they cannot participate in a pig kidney clinical trial. The option should be available because some patients will have a prognosis that is too poor to enroll in a clinical trial or they will not live long enough to enroll.

The use of the Expanded Access/Compassionate Use pathway should be limited. Under the Expanded Access/Compassionate Use pathway, patients whose disease or condition is serious or poses an immediate threat of death may be eligible

to get access to a drug, biologic, or medical device outside of clinical trials when no other medical treatments are available. Pig kidney clinical trials should be conducted to accomplish the goal of obtaining valid and reliable data about the safety and efficacy of xenotransplantation.

Involve a patient advocate. To facilitate safeguarding patients' interests, a patient advocate should be involved in the informed consent process for receiving a pig kidney transplant under the Expanded Access/Compassionate Use pathway. The patient advocate should be someone who has knowledge of the patient's situation and robust knowledge about the science of xenotransplantation. Transplant program and kidney patient advocacy organizations should partner to develop guidance that specifies the role of a patient advocate in the informed consent process and describes the criteria and process for selecting advocates.

7. Xenotransplants with Decedents

Decedent models are ethically permissible, but the length of decedent model xenotransplant experiments may need to be limited. The value of the knowledge that may be gained by continuing decedent experiments should be weighed against potential concerns about respect for the dead that may be shared in some communities. Research teams should conduct a community-engaged process to learn about these community perspectives and use this information to inform the length of time for which deceased bodies are included/engaged in these experiments.