Pig Kidney Xenotransplant Clinical Trials Teaching Guide and Case Studies for Transplant Teams

■ Michael K. Gusmano, PhD
Lehigh University

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

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

To facilitate best practices for the ethical conduct of pig kidney xenotransplant clinical trials (henceforth referred to as pig kidney clinical trials), we developed case studies for transplant teams who are conducting or planning to conduct pig kidney clinical trials. The case studies are intended to help transplant teams reflect on the ethical issues these trials raise and facilitate discussion so that transplant teams and clinical researchers will become better prepared to conduct pig kidney clinical trials.

To develop the case studies, we conducted interviews with 28 transplant clinicians and other transplant experts to identify ethical issues that are likely to arise when conducting pig kidney clinical trials. We also obtained 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. Thereafter, we conducted another 12 interviews with transplant clinicians to obtain feedback on the case studies for refinement and clarity. Based on this stakeholder feedback, we identified four ethical questions around which to develop case studies:

- Who should be eligible for participation in pig kidney clinical trials?
- Do monitoring requirements of pig kidney clinical trials conflict with participants' right to withdraw from research?
- How can transplant teams mitigate patients' and providers' therapeutic misconception when recruiting participants for pig kidney clinical trials?
- Is it appropriate to use financial incentives to encourage participation in pig kidney clinical trials?

The accompanying Teaching Guide for the case studies is an adaptation of a "Teaching and Learning Guide" developed for two online clinical ethics casebooks (Chin et al. 2014). There is no need to have any prior training or experience in ethics to use the cases, or this process, as a teaching and learning tool.

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TEACHING GUIDE:
How to Lead a Structured Discussion Session

- Each case study should take 10-30 minutes to discuss, depending on the number of people engaged in the discussion.

Prior to the discussion session

Step 1: Choose the case or cases that address the issue or issues that are of greatest concern to your transplant team. You can modify the details of the case or you may use a case as a model for developing your own unique discussion case.

Step 2: Identify the ethical questions that you want to explore during your discussion session. You may want to use or adapt the reflection questions at the end of each case. If you have the opportunity to do so, ask the transplant team members for questions of concern to them.

Step 3: Read the case closely, identifying the ethical issues that the case presents, so that you are prepared to discuss these issues.

Step 4: Identify the arguments that you want transplant team members to consider as they work through how best to resolve the ethical uncertainty presented by the case.

During the discussion session

Step 1: Present the case, or your modified version of it. Asking a participant in the discussion session to read the case aloud, or for several participants to read the parts of the different characters in the case, are good ways to encourage participants to engage with the case and the issues.

Step 2: Present the questions and arguments for transplant team members to consider, giving them opportunities to suggest their own questions and arguments. One useful approach, particularly for teams that have not had formal training in ethics, is called the ABC Toolbox for Ethical Analysis. The toolbox offers a step-by-step approach to develop an ethical argument. Below is a modified version of this toolbox approach. You may ask transplant team members to walk through these steps in an effort to address the ethical questions presented by the case.

Identify relevant facts and values

The first step when developing an ethical argument is to identify the facts and values of the case. All cases involve facts and values, but facts cannot resolve conflicts among values. The facts are often relevant to making an ethically sound decision but the facts, including law and policy, alone cannot tell us what we should do. Once you have identified relevant facts, describe the values that are in conflict in the case.

Balancing principles and intuitions

There are four principles that reflect the broadly held values in medicine. These have been highly influential in clinical teaching and practice. These principles are:

- Respect for persons (autonomy or self-determination)
- Do no harm (non-maleficence)
- Do good (beneficence)
- Act fairly (justice)

Ask whether these principles capture the full range of values that you have identified in the case. Also, ask whether there are additional principles that reflect values implicit in clinical researchers' duties pertaining to research ethics. We all have gut reactions about what we believe we ought to do in a given situation. We often feel strongly that something is right or wrong, even if we have difficulty explaining why. These moral intuitions are a good starting place for ethical analysis, but it is important to go beyond gut reactions and develop a more systematic ethical argument based on principles that should guide our actions. In many ethically challenging situations, ethical principles conflict with each other, and principles and personal intuitions may also conflict. Resolving ethical conflicts involves applying principles to practice and identifying trade-offs. It may be impossible to fully reconcile competing principles. Try to reach agreement on a course of action that is consistent with ethically sound practice.

Step 3: Discuss the questions and arguments with reference to the case and conclude by identifying lessons or other insights that transplant team members can take with them into the real world of clinical research.

CASE STUDIES

CASE 1:
Eligibility Case

Two nurses, Nancy Ulman and Janice Richman, are members of a clinical team at the university's medical center that is about to launch a pig kidney clinical trial. After work, they stop in the parking lot to have a conversation about the new pig kidney clinical trial and share their concerns about its design.

Nancy Ulman is a transplant nurse at the university hospital. As she is walking toward her car in the parking garage, she spots her colleague, Janice Richman, a nurse on the clinical transplant team. "Hello Janice! Do you have a minute to chat before you head home?"

"Of course," said Janice. "What's on your mind?"

"I'm curious to know what you think about the eligibility rules we are using for the pig kidney clinical trial. I am concerned that we may be excluding people who may want to participate in the trial. I realize it is out of our hands, but this has been keeping me up at night."

"Really? I think the plan makes a lot of sense," remarked Janice. "We need to use the same eligibility criteria for xeno recipients as human organ recipients to be good stewards of scarce organs, and I think that is what we'll be doing. We will be recruiting patients from our kidney transplant waiting list and excluding patients with a history of cancer or other conditions, patients who are highly sensitized, and those with a history of psychosocial problems. I think those restrictions make a lot of sense."

"I understand," said Nancy, "but I wish we were allowed to include patients who are not eligible for a human organ. I think it makes sense to include waitlisted patients for whom a human kidney is unlikely to be offered any time soon, but I worry that if we limit enrollment to people who are already on the waiting list, we may exclude some of the patients in greatest need. If a patient has greater psychosocial needs, shouldn't we make a greater effort to address them rather than exclude them from the trial? And why would we exclude people who are highly sensitized? People have antibodies to lots of things, but unless the person you're talking about has developed antibodies to the pig, it doesn't matter if they have antibodies to HLA or not!"

Janice shook her head. "I don't think it makes sense to include patients who are not already on the waiting list. How would we even identify them? And I think exclusion criteria are helpful. I feel differently about sensitization. Including patients with high levels of sensitization in the pig kidney clinical trial could really complicate the trial results. It would be unclear, even if the crossmatch to the pig is negative, whether those antibodies could react to the swine leukocyte antigens. If that happens, the participants may reject the pig kidney even though it could have worked well in a patient without those antibodies. This would set back the xeno research agenda!"

Nancy responds, “But shouldn’t we be investigating these questions?”

Janice shrugs. “Perhaps that is something we will investigate in a future study, but I am glad we are not taking this risk in the first-in-human clinical trial. There is too much riding on the results of this work.”

“Well,” said Nancy, “I am sure those are the reasons why the trial sponsor and the FDA did not want us to include those patients, but it still bothers me that the patients we are excluding are often the ones in greatest need for an organ, and I think they could benefit from participation in this pig kidney clinical trial if we offer sufficient social supports.”

“I share your desire to help patients in the greatest need,” said Janice, “but it is important not to lose sight of the fact that this is a phase I safety trial. We should not talk about patient benefit because we have no idea how well the pig kidneys will function. The participants should be enthusiastic about contributing to science and helping future patients, but they may not benefit directly.”

“I don’t know,” Nancy sighed. “It just seems like we’re not helping the people who need this. If the phase I clinical trial goes well, I hope we’ll be able to expand participation into the next phase of the research.”

Questions for Reflection

1. What are the trade-offs in terms of the scientific value of the study by including only patients who are waitlisted for a human organ? Or those who are not highly sensitized?

2. Since patients on the human organ waitlist have to meet specific psychosocial criteria, should these criteria also be used as eligibility criteria to enroll in a pig kidney clinical trial?

3. What criteria make a patient healthy enough to be enrolled in a pig kidney clinical trial, i.e., what co-morbidities should exclude them from participation?

CASE 2:
Monitoring Case

A patient who received a pig kidney in a first-in-human xenotransplant clinical trial refuses to come in for routine monitoring three years after receiving the organ. The clinical research team discusses what, if anything, it might do to require the patient to continue participation in the study.

Mary Rosemond, a highly experienced transplant research nurse on the university medical center's xenotransplant research team, is leading a meeting with her clinical research staff to discuss updates on monitoring participants in their ongoing pig kidney clinical trial. She learns at the meeting that Mr. Smith, one of their first recipients of a pig kidney, has missed his last 6-month monitoring appointment. She asks, "Has he been contacted to find out what happened? If there is a problem with transportation, we can cover the cost of that."

Jordan Gold, another member of the xenotransplant nursing team, says, "I spoke with Mr. Smith on the phone and he told me that he no longer wants to come in for blood tests and interviews. It has been just over three years since he received his pig kidney, and he said that he feels great and thinks we've learned all we need to know about the transplant. He said that he agreed to participate in the pig kidney clinical trial because he was sick of his schedule being controlled by his kidneys and now he wants to enjoy his freedom."

After the meeting, Ms. Rosemond alerts the project's Principal Investigator, Dr. Frank, about the situation and asks what they can do to enforce patient adherence to post-transplant monitoring.

Dr. Frank's first response is frustration. "I can't understand this! Mr. Smith knew that participating in the pig kidney clinical trial would involve lifelong monitoring and he signed a contract promising to do so. The number of participants in this trial is small and any loss of participants in the follow-up stage is a big problem for us. Our ability to learn about the long-term prognosis of the pig kidney transplant is compromised if we are unable to collect data about this patient's health."

Ms. Rosemond agrees and raises the concern that the team will be unable to identify early signs of rejection or other health complications associated with the transplant. She asks, "Could the medical center take legal action to force compliance with the contract?"

Dr. Frank offers a wry smile and says, "I think our lawyers and our IRB would be on Mr. Smith's side. We ask all the participants to sign the contract to instill an ethical obligation to continue with monitoring, but as you may recall, it does not specify any consequences for failing to comply. Remember, Mr. Smith received his pig kidney as part of a research study—and all research participants have the right to withdraw from research, so we have no way to compel Mr. Smith's continued participation. I'm really not sure what options we have."

Questions for Reflection

1. Are there participant communication or engagement strategies the transplant teams could use during the informed consent process and post-transplant to reinforce the importance of obtaining scientific data about the graft and the recipient's health post-transplant? Would using a researcher-participant partnership approach facilitate obtaining scientific knowledge that will help future patients?

2. Should research teams use Ulysses contracts, or other mechanisms designed to encourage participants to adhere to the monitoring requirements of the pig kidney clinical trial?

CASE 3:
Hope versus Therapeutic Misconception Case

A patient who is being recruited to participate in a pig kidney clinical trial is reviewing the informed consent form with the physician Principal Investigator and research nurse. After the patient gives informed consent to participate and leaves for another appointment, they reflect on whether the patient has taken the process seriously. The research nurse is concerned that the patient is too hopeful about the benefits of participation and is dismissing the risks.

Dr. Hawkins is an abdominal transplant surgeon at the university medical center. After several years of conducting pre-clinical research, she and her team are recruiting patients to participate in a first-in-human pig kidney xenotransplant clinical trial. Dr. Hawkins and Amy White, the research nurse on the university medical center's xenotransplant research team, are meeting with Mr. John Densmore, a 60-year-old patient who is being recruited to participate in the study. Mr. Densmore is the first eligible patient to be recruited in the first-in-human pig kidney clinical trial.

Mr. Densmore had received a human kidney transplant, but the graft failed after ten years, and he has been on in-center hemodialysis for the past seven years. He finds dialysis exhausting, his quality of life has diminished, and he has been increasingly hospitalized over recent years, leaving him worried that he will die if he does not receive a new kidney within the next few months. When his nephrologist told him about the pig kidney clinical trial taking place at the university medical center, he immediately asked how he could get into the clinical trial and arranged to meet with the research team the following week.

During their meeting with Mr. Densmore, Dr. Hawkins and Ms. White explained the purpose of their phase I trial and reviewed the informed consent form with him. Dr. Hawkins explained that the purpose of the research study was "to primarily find out if a pig kidney from a genetically modified pig is safe to use in a living human transplant recipient, and secondarily to find out if a pig kidney transplant could work in a living human transplant recipient." Mr. Densmore nodded, indicating his understanding. A few minutes later, when Dr. Hawkins discussed the potential benefits to others from the research study, she stated how this study "will hopefully help us figure out how we can help patients survive longer in the future."

After hearing this, Mr. Densmore brightened up and said, "That's what I wanted to hear! I'm happy to contribute to science and this can help me live longer without dialysis!"

In response, Dr. Hawkins said, "Well, we certainly hope so, but remember the goal of this trial is to test the safety of the pig kidney and see if it works. We will need additional trials to better understand how well a pig kidney works and how long it may last."

"That's right," Ms. White interjected. "It is important for you to understand that there is still a lot we don't yet know about pig kidneys that are transplanted in humans."

“Of course. I get it.” Mr. Densmore continued, “But you are going to transplant the pig kidney into me and you believe that it will work, right?”

“Well, the animal studies done to date suggest that there is a chance that this could work, but we don’t know for sure. Let’s finish reviewing the entire informed consent form so you understand all of the potential benefits and risks associated with participating in this clinical trial,” cautioned Dr. Hawkins.

“You bet, I am all ears,” Mr. Densmore chimed.

Dr. Hawkins reviewed the rest of the informed consent form, including the extensive section on risks, which explained that the pig kidney might not work; that Mr. Densmore’s body might reject it; and that there was a risk of zoonotic disease infection. She and Ms. White periodically paused while reviewing the rest of the informed consent form to make sure that Mr. Densmore understood the information and offered to address any of his questions. To diligently confirm Mr. Densmore’s comprehension, Dr. Hawkins asked Mr. Densmore to explain what he thought the risks were. Everything Mr. Densmore said checked out.

By the time they had finished their discussion, Mr. Densmore exclaimed, “You explained everything perfectly. I’ve been through the informed consent process before when I received my human kidney. I don’t have any questions and I am excited to have this opportunity. I never thought I would ever get this second chance.”

Dr. Hawkins thanked him for confirming his understanding and asked for his signature. After Mr. Densmore left, Dr. Hawkins turned to Ms. White and said, “Well, I thought that went well. He is exactly the sort of patient I was hoping we could recruit for this study.” Ms. White hesitated a moment and said, “I agree, but do you really think he understands what he’s getting into? He seems awfully convinced that the pig kidney is going to save his life even though we don’t really know if this will work!”

Dr. Hawkins paused and said, “I hear you, but we went over all of the risks, and we were really clear about the purpose of the study. Mr. Densmore is an experienced patient and I think he knows what he is signing up for.”

After Dr. Hawkins left the room, Ms. White lingered behind for a few minutes to gather her files. She thought to herself, Is this guy really making an informed decision, or did his hope for a cure lead him to only hear what he wanted to hear? I wonder if we did enough to communicate with him.

Questions for Reflection

1. For a first-in-human clinical trial using a kidney from a genetically modified pig, how can the informed consent process improve patients’/participants’ comprehension of the known and unknown risks associated with the trial?

2. What should the transplant team do if they believe a patient did not fully comprehend/understand the risks of the xenotransplant? Should they conduct an additional session with the patient, or a more rigorous teach-back session to ameliorate any concerns they have about the patient’s willingness to participate in the trial?

CASE 4:
Incentives Case

Dr. Ida Frank, an abdominal transplant surgeon, had a conversation with her colleague, Dr. Tom Oliver, about their transplant center being a trial site for a pig kidney clinical trial. Their team was putting the finishing touches on their FDA application for a first-in-human clinical trial involving pig kidneys, and she wanted to discuss whether they might be able to offer trial participants compensation to cover the time and burden of their study participation.

"Good morning Tom," said Dr. Frank. "Thanks for meeting with me."

"Sure, how can I help?" asked Dr. Oliver.

"I've been thinking about the pig kidney clinical trial we plan to conduct next year," said Dr. Frank. "I'd like to hear your thoughts about an idea for offering incentives for patients to participate in the trial."

"OK. What do you have in mind?" asked Dr. Oliver.

"Because this is a safety trial," said Dr. Frank, "and we don't know whether patients will benefit from participation, I think we should offer them some compensation. And it might help with recruitment.

Perhaps we could offer a financial incentive, considering their long-term time commitment and follow-up, and the burden of undergoing research tests. This incentive could also help recognize their contributions to science.

Or, maybe we could get permission from OPTN/UNOS to offer additional points on the allotransplant waiting list for patients who participated in a pig kidney trial but whose pig kidney failed. After all, patients who participate in these trials will be taking a risk, contributing to science and society, and deserve to be rewarded for doing so."

"That's an interesting thought," said Dr. Oliver, "but allocating additional points on the allotransplant waitlist seems like a non-starter. First, these patients would maintain their place on the waitlist even if they participated in our trial and received a pig kidney. According to the OPTN/UNOS, organ transplants only refer to human organs, and animal organs are considered by the FDA as biologics, not as organs regulated by the OPTN. Beyond that, patients should not be allowed to jump the line because they decided to participate in research. There will be so many people who won't have access to that opportunity. It is not fair to people who do not have access to these trials. No other transplant research studies offer that option. It's just not done. Moreover, revising the point system would require a major OPTN/UNOS policy change, and I can envision this drumming up a lot of controversy."

Dr. Frank nodded. "You are right about that; offering points would be very problematic, but what about the option of offering a financial incentive?"

"Well, offering financial compensation is a possibility," replied Dr. Oliver. "It's common for many clinical research studies to compensate participants for their time, burden, and effort. But in the context of transplantation, financial compensation might raise ethical concerns because this could be seen as an undue inducement to participate in the trial. We need to guard against undue inducement because patients who are most likely to participate are those who feel desperate for a kidney. We don't want to make this problem even worse by offering a financial incentive that is too large."

Dr. Frank sighed. "You are probably right, but I wish we could compensate these brave patients for all their time and effort in this trial."

Questions for Reflection

1. Would offering participants financial compensation, to recognize the burden and time commitment involved in study participation, comprise an undue inducement to participate?

2. What would be an acceptable amount of financial compensation that would not result in an undue inducement to participate?

3. Should participants be offered some type of compensation as recognition of their contribution to science?

Reference

Chin, J. (editor-in-chief), N. Berlinger (consulting editor), M. Dunn, C. Ho and M.K. Gusmano (associate editors). "Teaching and Learning Guide," in *Making Difficult Decisions with Patients and Families: A Singapore Bioethics Casebook.* Singapore: National University of Singapore, the Hastings Center and the Ethox Centre, University of Oxford (bioethicscasebook.sg), 2014. http://www.bioethicscasebook.sg/making-difficult-decisions-with-patients-and-families/

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