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Patients' Information Needs for Informed Consent to Participate in First-in-Human Pig Kidney Xenotransplant Clinical Trials: A Mixed Methods Study

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ABSTRACT

Background: Transplant programs preparing to initiate first-in-human pig kidney xenotransplant clinical trials must be especially careful when obtaining participants' informed consent. Little is known about the kind of information patients want for making an informed decision about trial participation.

Methods: We conducted semi-structured telephone interviews with waitlisted kidney transplant patients about information needs regarding participating in a first-in-human pig kidney xenotransplant trial, which guided development of a prototype consent form. Subsequent usability testing interviews sought patient feedback on the consent form. We analyzed qualitative data by thematic analysis and quantitative data by descriptive statistics.

Results: Twenty-eight patients participated in semi-structured interviews; 16 patients participated in usability testing interviews. Most interview participants were male (68%, 56%), White (54%, 56%), or Black (36%, 31%), respectively. Interview participants identified five types of information needs: (1) the potential for infection contraction and transmission; (2) risks, benefits, and impact of xenotransplant trials; (3) xenotransplant clinical trial and recipient experience; (4) clinical trial logistics; and (5) the pig and its kidney. Usability testing participants suggested adding details to the prototype. Participants' preparedness to make a decision about participating in a xenotransplant trial increased after reviewing the prototype (12.5% vs. 31.3%, n.s.).

Conclusion: We identified multiple unique types of information patients desired to make informed decisions about pig kidney xenotransplant trial participation. Transplant programs initiating xenotransplant trials should be prepared to address patients' information needs to optimize informed decision-making for trial participation. The prototype consent form may support a patient-centered approach to informed consent.

Abbreviations: HC, Hastings Center; LU, Lehigh University; NU, Northwestern University; RWJ, Robert Wood Johnson.

1 | Introduction

Transplanting animal organs into humans—known as xenotransplantation—holds great promise for addressing the limited organ supply and saving lives. Many xenotransplant experts anticipate that the US Food and Drug Administration (FDA) will permit the conduct of first-in-human xenotransplant clinical trials involving gene-edited pig kidneys to test the safety of these organs in human recipients [1–5]. Several transplant surgeons intend to request FDA approval to conduct such trials, indicating that trials may soon commence [6–8]. Public opinion surveys show high levels of support for xenotransplantation [9, 10], and that some would participate in trials [9, 11], indicating, in part, trial feasibility.

Prior to launching such trials, tailoring the ethical approach to informed consent in the xenotransplant trial context is urgently needed. The FDA's regulations governing research with humans require that specific information be provided to individuals recruited for clinical trials to make an informed decision about participation. However, the regulation has not established protections for first-in-human clinical trials in general, for which the ethical stakes of informed consent are higher. Xenotransplant trials raise additional ethical considerations that have not yet been addressed.

The informed consent process for participating in a first-in-human pig kidney xenotransplant clinical trial will likely be ethically challenging because limited information is available about the safety, efficacy, and potential benefits of transplanting a pig kidney into humans [12, 13], which may make informing patients about the innovation difficult [14]. Moreover, xenotransplant recipients may encounter unknown risks. For example, it is unknown whether the organ might transmit a porcine infectious disease to recipients and their close contacts [15]. The unknown potential to transmit known and unknown diseases from the pig organ to human recipient [16, 17] elevates the risk profile of first-in-human pig kidney xenotransplant trials.

The five xenotransplants (2 heart, 3 kidney) performed under the FDA's Expanded Access program [14, 18–20] provide some information about how xenotransplants functioned in those recipients (e.g., the fact that grafts survived 2 months). However, the different eligibility criteria, different gene-edited pigs used, and patients' grave conditions mean that their outcomes are unlikely to be commensurate with clinical trial outcomes. Accordingly, the information disclosed to prospective trial participants about such xenotransplants must be qualified.

Magnifying these challenges is that few, if any, treatment alternatives for patients with end-stage kidney disease exist, which can render patients vulnerable and undermine voluntary decision-making [12, 13]. Such vulnerability commonly occurs among patients undergoing innovative surgical procedures for which alternative standard treatments are either ineffective or nonexistent [21]. In regard to first-in-human xenotransplant trials, waitlisted candidates may have exhausted all life-saving options, as in the Expanded Access xenotransplants.

The ethical challenges to informed consent comprise a component of translational research that requires resolution. Current federal regulations (i.e., the National Organ Transplant Act of 1984) lack guidance on informed consent for xenotransplant clinical trials [22]. Organ Procurement and Transplant Network policies only pertain to human organs. Thus, policies on information disclosure may not translate to the xenotransplant context.

Few scholars have made headway in addressing this problem. Padilla and colleagues reviewed The US Department of Health and Human Services nine minimum elements that consent forms must include to protect human subjects, highlighting how these elements should be conveyed in the consent process and in the informed consent form for xenotransplantation [23]. Drawing upon this work, Cooper prepared an informed consent form template tailored to the xenotransplant trial context [24]. However, while Cooper's consent form may reflect what is important for transplant clinicians to disclose, it may not address patients' information needs. Little is known about what information patients need to decide whether to participate in a xenotransplant clinical trial. The National Academies of Sciences called for greater public engagement with emerging innovative areas of biotechnology and biomedical research [25]. This paper presents kidney transplant candidates' information needs for making informed decisions about participating in pig kidney first-in-human xenotransplant clinical trials.

2 | Materials and Methods

2.1 | Study Design

We conducted a sequential, exploratory mixed-methods study involving semi-structured interviews to assess waitlisted kidney patients' information needs, followed by usability testing interviews to assess perceptions of an informed consent prototype for participating in first-in-human pig kidney trials [26].

We conducted a multi-site study at Northwestern University (NU) in Chicago, IL; Lehigh University (LU) in Bethlehem, PA; and The Hastings Center (HC) in Garrison, NY. Rutgers University (RU) in affiliation with the Robert Wood Johnson (RWJ) transplant program in Piscataway, NJ, aided LU in participant recruitment. Institutional Review Boards (IRBs) at NU (STU00214874) and LU (1806245-5) approved the study. NU served as the single IRB. The Standards for Reporting Qualitative Research guided quality reporting of qualitative research [27].

2.2 | Participants and Recruitment

Eligible individuals were: English-speaking, adult (age ≥18 years), and waitlisted kidney patients. Patients who were cognitively impaired and/or waitlisted for multiple organ transplants were excluded. NU and RWJ patients were recruited by email and/or mailed letter followed by a call a week later to gauge interest and schedule interviews. The research staff had no prior relationships with study participants. Patients provided verbal informed consent.

2.3 | Data Collection

We conducted telephone semi-structured interviews from July 2022 to February 2023, and usability testing interviews from March 2024 to May 2024, using standardized interview guides guided by extant literature and feedback from the study's Ethics and Policy Advisory Committee. The Committee comprised 17 stakeholders (e.g., transplant recipients, translational researchers, transplant clinicians, transplant regulators, transplant outcomes experts, a transplant payer, transplant ethicists, and research ethics experts). The multiple Principal Investigators (mPIs) held two 2-hour videoconferences with the Advisory Committee to ensure that the interview guide, usability testing instrument, and informed consent form prototype would expansively and precisely address contemporary clinical, ethical, and policy considerations about xenotransplantation. During the informed consent process and upon initiating each interview, research staff explained the concept of xenotransplantation and xenotransplant trials, and they had no relationship with the transplant center.

2.3.1 | Semi-Structured Interviews

Interviews included open-ended questions about patients' information needs for considering whether to participate in a pig kidney xenotransplant clinical trial, which comprised a subset of the study data (Supporting Information 1). Interviews also assessed demographics, health literacy [28], and clinical characteristics. One mPI (E.J.G.), an experienced qualitative researcher, trained male and female research staff who conducted interviews. Interviews were audio-recorded, transcribed, and lasted 58 minutes, on average. Participants received a $30 e-gift card as compensation.

2.3.2 | Informed Consent Prototype Development

The informed consent prototype was initially developed through an iterative process whereby four staff (M.M., J.G.S., D.M., and K.T.) independently reviewed information from 19 questions in the semi-structured interview transcripts pertaining to patients' information needs for informed consent for trial participation. Using a NU IRB biomedical consent form with template language to fill in as a guide, each staff member developed a draft prototype by transforming the information needs into distinct statements regarding trial purpose, risks, benefits, alternatives, implications for reproduction, and other sections of the consent form, as well as adapting the consent form template language to the xenotransplant study context. One Principal Investigator (E.J.G.) provided initial feedback in simplifying the statement phrasing and organization, guiding the four staff members in revising their drafts and completing transcript reviews. The resulting prototypes were consolidated into one prototype "Master" draft. The mPIs and staff refined this draft for clarification and face validity. Advisory Committee members provided feedback on two sequential versions of the Master prototype. Based on both sets of Advisory Committee feedback, the mPIs revised the Master prototype and submitted it to the NU IRB for approval. After completing usability testing interviews, the staff and mPIs reviewed participants' suggested changes and further refined the prototype for clarity and provided additional information usability testing participants requested. Supporting Information 2 provides the Prototype Informed Consent Form. The prototype retains some template instructions in red font that trial investigators will need to address.

2.3.3 | Usability Testing Interviews

We conducted usability testing interviews using cognitive interviewing techniques [29] to elicit patients' perceptions of the consent form prototype in terms of content comprehensiveness, clarity, and order, and suggestions for improvement. Participants were asked before and after reviewing the prototype: "How prepared do you feel to make a decision about participating in a pig kidney xenotransplant clinical trial?" using a 5-point Likert scale anchored by "not at all likely" and "entirely likely." Interviews lasted, on average, 51 min. Participants were compensated with a $15 e-gift card.

2.4 | Data Analysis

2.4.1 | Qualitative Analysis

Semi-structured interview transcriptions were analyzed using thematic analysis [30] and constant comparison [31]. The mPIs developed an initial deductive code list a priori based on the interview guide, and applied inductive coding methods for codes emergent from the data [32]. The full research team refined the codebook through four analytic retreats to iteratively identify additional inductive codes, which were added and revised until achieving thematic saturation [33]. After finalizing the codebook, five staff independently coded transcripts using NVivo (QSR International) until establishing inter-rater reliability (Kappa > 0.80) [30]. Staff then coded all transcripts in teams of two, resolving discrepancies through discussion. Research staff reviewed all segments for each code to develop code summaries that synthesized patterns and themes [34].

2.4.2 | Quantitative Analysis

We performed descriptive statistics to describe participants' demographic and clinical characteristics using IBM SPSS Statistics (Version 28).

3 | Results

3.1 | Participant Characteristics

Overall, 28 kidney transplant candidates completed semi-structured interviews (NU: $n = 20$, LU: $n = 8$, 33% participation rate), and 16 completed usability testing interviews (NU: $n = 10$, LU: $n = 6$, 28% participation rate). Of the 313 patients sent a recruitment email/letter about the semi-structured interview, we subsequently spoke to or received an email(s) from 94 patients. Of these, nine were ineligible. Of the 85 eligible patients, 57 declined because they were not interested, did not have time, or were not

comfortable with the topic, or could not be re-reached, or did not show up for the scheduled interview. Of the 221 different patients sent a recruitment email/letter about the usability testing interview, we subsequently spoke to or received an email(s) from 66 patients. Of these, eight were ineligible. Of the 58 eligible patients, 42 declined because they were not interested, did not have time, or were not comfortable with the topic, or could not be re-reached, or did not show up for the scheduled interview.

Most interview and usability testing participants were male (68% and 56%), White (54% and 56%), or Black (36% and 31%), with a mean age of 49 and 57 years (Tables 1 and 2). Many semi-structured interview participants who were on dialysis were concerned "a lot" or "entirely" about the impact of dialysis on their ability to survive (n = 7/23, 30% interviews; n = 9/13, 69% usability testing). A few participants were "somewhat uncomfortable" or "not comfortable" with being on dialysis (n = 5/23, 22% interviews; n = 4/13, 31% usability testing).

TABLE 1 | Interview participants' demographic and clinical characteristics, $N = 28$.

Variable	*n* (%)
Age, years, mean [SD] (range)	49 [12.5] (25–69)
Gender	
Male	19 (67.9)
Female	9 (32.1)
Ethnicity	
Not Hispanic or Latino	22 (78.6)
Hispanic or Latino	6 (21.4)
Race	
White	15 (53.6)
Black or African American	10 (35.7)
Other[a]	3 (10.7)
Marital status	
Never married/single	13 (46.4)
Married/domestic partner/civil union	11 (39.0)
Separated or divorced	3 (10.7)
Widowed	1 (3.6)
Education	
High school graduate	4 (14.3)
Some college	11 (39.3)
College graduate	10 (35.7)
Postgraduate degree	3 (10.7)
Employment status	
Employed full time	10 (35.7)
Disabled	6 (21.4)
Retired	4 (14.3)
Employed part-time	4 (14.3)
Not employed	4 (14.3)
Income	
Less than $15 000	4 (14.3)
Between $15 000 and $34 999	6 (21.4)
Between $35 000 and $54 999	4 (14.3)
Between $55 000 and $74 999	2 (7.1)
Between $75 000 and $94 999	3 (10.7)
More than $95 000	9 (32.1)
Primary health insurance[b]	
Private	16 (57.1)
Medicaid or Medicare	13 (46.4)
None	1 (3.6)
Present religion	
Protestant	11 (39.3)
Catholic	8 (28.6)

(Continues)

3.2 | Information Needs About Pig Kidney Trials

Five themes regarding information needs about pig kidney xenotransplant trials emerged: (1) the potential for infection contraction and transmission from a pig kidney; (2) risks, benefits, and impact of xenotransplant trials; (3) xenotransplant clinical trial and recipient experience; (4) clinical trial logistics; and (5) the pig and its kidney. Representative illustrative quotations are presented in Table 3.

3.2.1 | Potential for Infection Contraction and Transmission

Participants desired information about the probability, duration, and curability of contracting "infections," "viruses," "parasites," and "diseases" from the pig kidney. Participants expressed concerns about the potential harms of such infections and desired information about which infectious diseases the pig kidney could transmit, and the probability of transmitting those diseases to others. If they were to contract an infectious disease from the pig, participants wanted to know if the transmissible disease was "curable," and if so, the treatment's side effects, and how long the potential "harm" of the disease and treatment would last. Participants commented:

> "What potential viruses that can happen… Is there any potential viruses that I can give to my family members or to the public." (NU#3004)

> "You know, like there are some infections that are curable and easy to treat. I don't want to have a bigger issue that needs more attention, more bloodwork, more medicine. That's not a good thing." (LU#3004)

TABLE 1 | (Continued)

Variable	*n* (%)
Nothing in particular	5 (17.9)
Jewish	2 (7.1)
Muslim	1 (3.6)
Agnostic	1 (3.6)
Type of diet	
Meat eater	27 (96.4)
Flexitarian	1 (3.6)
Primary health insurance[b]	
Private	16 (57.1)
Medicaid or Medicare	13 (46.4)
None	1 (3.6)
Health literacy, adequate	24 (85.7)
Health status	
Excellent	2 (7.1)
Very Good	4 (14.2)
Good	9 (32.1)
Fair	8 (28.5)
Poor	5 (17.8)
Cause of end-stage kidney disease	
Hypertension	8 (28.6)
Diabetes	7 (25.0)
Polycystic kidney disease	3 (10.7)
Doctors do not know	3 (10.7)
Glomerular	3 (10.7)
Other[c]	4 (14.2)
Time on dialysis (months), median [IQR] (range)	24.0 [32.3] (0–252)
Time on waiting list (months), median [IQR] (range)	21.5 [24.0] (1–168)
Number of prior organ transplants	
0 transplant	23 (82.1)
1 transplant	3 (10.7)
2+ transplants	2 (7.1)
Study site	
Northwestern University	20 (71.4)
Lehigh University	8 (28.6)

Abbreviations: IQR, interquartile range; SD, standard deviation.
[a]"Other" included people who identified as Hispanic or Mexican ($n = 3$).
[b]Percentages add up to greater than 100 due to more than one response from some participants.
[c]"Other" reported causes of ESKD included liver disease, childhood predisposition, cardiac medication, and both hypertension and diabetes ($n = 4$).

TABLE 2 | Usability testing participants' demographic and clinical characteristics.

Variable	Total ($n = 16$) *n* (%)
Age, years, mean [SD] (range)	56.5 [15.3] (26–75)
Gender	
Male	9 (56.2)
Female	7 (43.8)
Ethnicity	
Not Hispanic or Latino	14 (87.5)
Hispanic or Latino	2 (12.5)
Race	
White	9 (56.2)
Black or African American	5 (31.2)
Asian	1 (6.3)
Other[a]	1 (6.3)
Marital status	
Married/Domestic Partner/Civil Union	9 (56.2)
Never Married/Single	4 (25.0)
Separated or Divorced	2 (12.5)
Living with a partner	1 (6.3)
Education	
Less than a high school graduate	1 (6.3)
High school graduate	0 (0)
Some college	7 (43.8)
College graduate	5 (31.2)
Post graduate degree	3 (18.7)
Employment status	
Retired	6 (37.5)
Employed full time	5 (31.2)
Disabled	2 (12.5)
Employed part-time	1 (6.3)
Not employed	2 (12.5)
Income	
Less than $15 000	1 (6.3)
$15 000–$34 999	2 (12.5)
$35 000–$54 999	3 (18.7)
$55 000–$74 999	0 (0)
$75 000–$94 999	1 (6.3)
More than $95 000	7 (43.7)
Prefer not to answer	2 (12.5)
Present religion	
Protestant	6 (37.5)

(Continues)

TABLE 2 | (Continued)

Variable	Total ($n = 16$) n (%)
Catholic	5 (31.1)
Jewish	2 (12.5)
Buddhist	1 (6.3)
Atheist	1 (6.3)
Nothing in particular	1 (6.3)
Type of diet	
Meat eater	16 (100)
Primary health insurance	
Private	4 (25.0)
Medicaid or Medicare	7 (43.8)
Both Private and Medicaid/Medicare	5 (31.2)
Health literacy, adequate	15 (93.8)
Cause of end-stage kidney disease	
Hypertension	5 (31.2)
Diabetes	2 (12.5)
Glomerular diseases	2 (12.5)
Doctors do not know	2 (12.5)
Other[b]	5 (31.3)
Time on dialysis (months), median [IQR] (range)[c]	36 [17.5] (9–300)
Number of prior organ transplants	
0 transplant	10 (62.5)
1 transplant	5 (31.2)
2+ transplants	1 (6.3)
Study site	
Northwestern University	10 (62.5)
Lehigh University	6 (37.5)

Abbreviations: SD, standard deviation; IQR, interquartile range.
[a]"Other" race included the response "unsure" $n = 1$.
[b]"Other" reported causes of ESKD included COVID ($n = 1$), medication ($n = 1$), congenital kidney hypoplasia ($n = 1$), urinary reflux ($n = 1$), and kidney stone disease ($n = 1$).
[c]One Lehigh participant was not asked the question; median [IQR] (range) are based on $n = 15$ (total) and $n = 5$ (Lehigh).

3.2.2 | Risks, Benefits, and Impact of Xenotransplant Trials

Participants desired information about the trial's overall risks and benefits of participation. Specifically, they sought information about the trial's risks of graft rejection and graft longevity. This included any "unforeseen" "short-term and long-term repercussions" or "complications." Participants wished to be informed about the expected "life span" of the pig kidney, including the likelihood of experiencing kidney rejection or failure due to other causes, as well as how the transplant might impact their life expectancy. As one participant stated:

> "Well hell, does it work and how long will this last? I'm not trying to do this again. I don't want to be sick again." (NU#3012)

Moreover, participants desired learning how participating in a trial would affect their "quality of life," when compared to their quality of life on dialysis. These participants desired assurances that their quality of life would improve as a result of trial participation. These issues were conveyed by one participant:

> "Did someone live an extended life? Did they not have additional health issues or problems that were related? How were the drugs? How many drugs do they have to take? What's the post-op treatment like? I mean, I would have to know all those types of details before I would even consider, strongly consider it." (NU#3013)

3.2.3 | Xenotransplant Clinical Trial and Recipient/Participant Experience

Participants reported wanting to be informed of "anything and everything" relating to the trials, including "the full breadth of anything that might go wrong." Specifically, participants desired knowing the number of trials completed, the number of pig kidney transplants performed, and the functional outcomes to date. As one participant questioned:

> "What generation of trial this is? You know, how far along in the trials we are? How many … pig transplants have been done prior, and how far along are they?" (LU#3008)

Participants also desired information about the experiences of previous pig kidney trial participants, including the side effects and complications of the transplant procedure and post-transplant medications. Further, participants desired "success stories" that previously enrolled pig transplant recipients would have potentially experienced. After participating in a pig kidney trial, participants would want to remain apprised of the results of the trial, to know how their "role" in the trial had "made a difference" or a "contribution" to the field of xenotransplantation.

3.2.4 | Clinical Trial Logistics

Participants recognized the importance of post-transplant monitoring obligations for kidney function and "complications." Participants specifically wanted to know logistical information regarding the "where," "schedule," "frequency" of the "testing and appointments," and "how long" they would need to receive monitoring. Some also desired details of the medications they would need to take, as well as other expectations, including exercise, and what diet and drinks they could consume. A few participants inquired into "a backup plan" or "alternatives" if

TABLE 3 | Representative illustrative quotations about information needs for informed consent for first-in-human pig kidney xenotransplant clinical trials by theme.

Potential for infection contraction and transmission
"Well, all the harm. How long will the virus last in my body, all that information. How I can transmit it to somebody else, all that. I would need that information." (LU#3002)
"I think I'd be concerned about general harm in case of infection that I'm not even sure that's possible. There's a potential infection that pig normally get in the body. The human body isn't used to. You know, I'm not sure if my body will be able to defend against that." (LU#3005)
"Need to know that it was definitely a viable option; clear understanding of the risks of getting a pig kidney and clear understanding of possibility of getting a disease or transmitting a disease." (NU#3026)
Risks, benefits, and impact of xenotransplant trials
"What would I need to know is that what are the risk factors regarding the viruses, the kidney shutting down, how long do they think it's going to last, how many types of antirejection medicine am I going to take for how long, what complications, side effects?" (NU#3020)
"I would want to know what the expected longevity of that kidney is for a healthy patient. How long do they expect the kidney to last?" (LU#3001)
"What are my benefits? How is it going to affect my quality of life? How is it going to affect my immediate family's quality of life?" (LU#3006)
"The thing I'm really concerned about is, is the kidney going to work. You know, that's all I'm concerned about, is it going to work. So am I going to have complications, or more liable to infection, or if the medication is going to work with the animal kidney." (NU#3007)
Xenotransplant clinical trial and recipient/participant experience
"How many people before me tried this and what was their rate and life expectancy?" (NU#3027)
"Did someone live extended life? Did they not have additional health issues or problems that were related? How were the drugs? How many drugs do they have to take? What's the post-op treatment like? I mean, I would have to know all those types of details before I would even consider, strongly consider it." (NU#3013)
Clinical trial logistics
"I think mostly I would want to know, like the schedule of when and where I need to be to get various testing done and what that testing looks like. So yeah, the frequency that I would need to go to some place for bloodwork or any other testing that might be done." (LU#3001)
"How long when I have to be monitored? How long is the kidney set to last? I think that's–yeah, that's all I can think of right now….How long I would have to be monitored after getting the pig transplant." (NU#3021)
"Well, he said that I would have to be monitoring and check up and stuff. Is the trial paid for it or is our insurance? Who pays for this?" (LU#3007)
"I guess the amount of testing and appointments I'd have to go to and how my information is shared, if my specific name is published anywhere." (NU#3005)
"If a disease or rejection was to occur, do we have a backup plan or some type of medicine to cover that?" (NU#3021)
The pig and its kidney
"Was the pig in good health? Was the pig free of diseases? Was it screened well? I would just like to know was the pig–had good screening." (NU#3027)
"I'd just want to make sure it's healthy enough to do the transplant. And like I say –the health of the pig actually. Yeah. Was it dying? Did it get killed? … How it was raised." (LU#3003)
"I'd like to know what type of diet this pig had, basically, that would tell how much fat was in it." (NU#3019)
"What kind of environment did it grow up in? … What kind of farm did the pig grow up on?" (NU#3021)
"[W]as it a live pig or was it a modified genetic made in a laboratory and what are the difference between them both?" (NU#3020)

the xenotransplant failed and they needed to return to dialysis. Specifically, participants questioned whether they would go to the top or bottom of the allotransplant waitlist, or if they would remain eligible for an allotransplant if the pig kidney failed.

3.2.5 | The Pig and Its Kidney

3.2.5.1 | Health History and Status of the Pig and Its Kidney. Overall, participants wanted assurance that the pig was "a good healthy pig" and its kidney was "functioning," "healthy," and "top notch." One participant stated:

> "How healthy is it. When a human goes to test to see if they could donate, they run all kinds of tests, yeah? But that's from head to toe of blood work, but for the pig, I'd like to know how healthy the kidney was…how it was filtering prior to its death. I would think that would matter. I'm not a scientist, but I would think it would matter." (NU#3019)

All participants wanted information about the history and health status of the pig and its kidney prior to participating in a trial. Participants wanted to know what "health concerns" or "life-threatening diseases" the pig may have had, especially ones that could have impacted its kidney. A few participants wanted to know if the pig had been "genetically altered," and if so, information related to the genetic modifications. Some desired assurances that the pig and its kidney had been "screened well" to ensure they were free of viruses and diseases, including diabetes and high blood pressure.

3.2.5.2 | How the Pig Lived and Died. Participants desired details of how the pig lived and died. They wanted to know about the "environment" in which the pig was raised, including ensuring "there was no abuse" and that the pig was not "raised angry." Additionally, they were interested in the pig's diet, including if it had been "grass-fed" and "how much fat" it had been fed, the pig's age and weight, and whether it had been "active." A few participants also wanted to know non-clinical, personal information about the pig, such as its name and what it looked like.

Participants wanted to know "the cause of death," whether it was "euthanized" or died of other causes, and "how long it was dead for" prior to its kidney being procured. Participants were motivated to seek such information to be informed of factors that might impact the health of the pig kidney.

3.3 | Informed Consent Form Prototype Feedback

Overall, participants' first impressions of the informed consent prototype were mixed. Some expressed positive thoughts, describing the prototype as "very thorough," "easy to read," and covering "every question that came to the top of [their] head." Participants also appreciated the "honesty" of the content, noting that the prototype did not "sugar coat" information. As one participant stated:

> "It isn't a pie-in-the-sky document… it's also telling you about the worst-case scenario. I think it's a good description of all the different pieces of what can go wrong." (LU#4101)

By contrast, some participants responded negatively, stating that the prototype was "kind of long," needed "better detail," and had sections that "could be better explained in a more positive way." A few participants voiced their hesitancy to participate in a pig kidney xenotransplant trial based on the information in the prototype. Participants commented:

> "[My] general impression was that the way it's written here, I probably would not ever volunteer to do the study. I think that there are a lot of negatives and not enough positives…" (LU#4103)

Participants recommended text clarifications and additions to the prototype. For example, adding more details about the pig and pig kidney, including the pig's age and life expectancy and a "comparison of patients transplanted with human kidneys and pig kidneys" as it relates to risk for infection. Participants wanted details about insurance coverage, what would be financially covered by the study, and coverage of non-FDA-approved medication. Participants suggested adding details to the monitoring section, including the length of time that patients will be monitored and "what close contacts and relatives [will be] monitored for." Additionally, participants suggested the prototype include information about "the experience of the surgeon and the surgical team," to address the question: "Has [the surgeon] done this before or not?"

When asked "How would looking at this consent form make you feel?" most related that they would feel a "bit uneasy," "a little unsettled," and that the consent form "would scare me." Although the consent form made participants uneasy, some clarified that feeling that way seemed appropriate because "you should really think about this before you sign up for it." One participant further explained that the information "…opened my eyes a bit more. I didn't realize how it could affect so many aspects of my life as opposed to a regular transplant."

When asked "Has this informed consent template raised new questions that you had not thought of before looking at it?" some related that all their questions had been answered, while others stated that they wanted more information about the research, data on pig kidney transplants, and the transmission of porcine infectious diseases. One participant explained that "There's a lot of things that prompted me to have more questions. For a basic consent I think it's good, but for me I need to have more like science information. But I think it's good, it's uncomfortable but it makes me hopeful."

Overall, usability testing participants' preparedness to decide to participate in a pig kidney xenotransplant trial increased in the proportion reporting being "very" or "completely" prepared after having reviewed the informed consent form prototype (prior to review: 12.5%; after review: 31.3%; n.s., $p < 0.18$) (Table 4).

TABLE 4 | Usability testing participants' preparedness to make a decision about participating in a pig kidney transplant clinical trial ($N = 16$).

	Not at all *n* (%)	A little *n* (%)	Somewhat *n* (%)	Very *n* (%)	Entirely *n* (%)
Before reviewing this consent form					
How prepared do you feel to make a decision about participating in a pig kidney transplant clinical trial?	4 (25)	2 (13)	8 (50)	1 (6)	1 (6)
After reviewing this consent form					
How prepared do you feel to make a decision about participating in a pig kidney transplant clinical trial?	3 (19)	1 (6)	7 (44)	4 (25)	1 (6)

4 | Discussion

Our mixed-methods study of information kidney transplant candidates need to provide informed consent for hypothetical first-in-human pig kidney xenotransplant clinical trials revealed five domains of information. Kidney transplant candidates desired extensive information about the trial itself, the trial logistics, the impact of the trial on patient health and quality of life, the pig, and the pig's kidney.

We found that patients desired information about the status of the clinical trial as well as the trial logistics. Specifically, trial status characteristics included the number of participants to date and their outcomes. Trial logistics included the duration of the trial, and the exit plan should the pig kidney not work. Other research on kidney, liver, heart, and lung transplant candidates' information needs for other innovative clinical research corroborates our findings [35].

Our findings about patients' interest in the donor pig's life, death, and health status at the time of organ procurement are novel and may complement two previous recommendations for a xenotransplant trial informed consent form [23, 36, 37]. Neither of those recommendations for consent form information includes conveying the type of information about the pig and pig kidney that our interview participants expressed knowing about. Taking patients' concerns seriously about the pig is consistent with calls for addressing the "moral status of nonhuman animals and humankind's legal and moral responsibility towards them" [38]. Kidney patients' desire to know about the donor pig is similar to some allotransplant recipients' interest in knowing about the donor of the organ they received [39].

We developed an informed consent prototype that should guide the informed consent educational process for prospective xenotransplant trial participants. Our usability testing interviews found that while the prototype was clear, further details were requested. In the absence of trial specifics, placeholders for those details were added to the prototype. The prototype feedback revealed novel insights into patients' trial concerns. Specifically, some felt "uneasy" or afraid after reviewing the prototype but realized how feeling that way was important for recognizing the broad impact that participation in such a trial could have on their lives.

The informed consent process for first-in-human xenotransplant clinical trials should address patients' information needs to facilitate informed decision-making. By providing a patient-centered perspective about information to disclose to prospective xenotransplant trial participants, our findings may guide the development of information guidelines that extend beyond the standard elements of human research informed consent to be disclosed as part of the informed consent process for xenotransplant clinical trials. Moreover, regulatory guidance would be especially valuable to prepare IRBs to review informed consent forms for xenotransplant trials [23].

A systematic review and meta-analysis of participants' understanding of informed consent in clinical trials found that half of the participants understood risks and side effects of trials (51.4%) [40]. Subgroup analysis showed that phase I trial participants had a lower understanding of options after withdrawal, understanding of voluntary participation, and ability to name at least one risk than phase II/III participants; critically ill participants had a lower understanding of study purpose, risks, and benefits compared to non-critically ill participants [40]. Upon initiating first-in-human xenotransplant trials, evaluating comprehension of all informed consent components will be critical to determine whether the disclosure process may need revision to enhance patients' and families' decision-making process. Future research should assess patients' actual decision-making, information needs, and comprehension upon trial initiation.

In the pig kidney xenotransplant clinical trial context, sufficient time will be needed in the consent process to disclose extensive information, support question asking and discussion, ascertain whether the patient has adequately comprehended disclosed information, and assess the patient's voluntariness about trial participation. A multidisciplinary team approach will be valuable for relating the aforementioned desired types of information to facilitate understanding without information overload. A psychiatric consult will be vital for evaluating patient's comprehension and voluntariness. Ensuring that patients have enough time to reflect on the prospect of trial participation in light of their values and life goals may be accommodated through a 1–2 week cooling off period, commonly used among living donors. However, time may be limited amongst patients whose dialysis access has run out. In such circumstances, the time frame may need to be expedited while also protecting patients' voluntariness. An independent patient advocate may help protect the patient's voluntary decision making.

Strengths of our study include the multi-site design, increasing the representativeness and transferability of study findings. Using

a mixed-methods approach generated greater insights than use of a single method. Consultation with our Advisory Committee on the semi-structured interview guide and informed consent prototype enhanced the accuracy and presentation of our informed consent form prototype thereby increasing the validity of our findings. Our sample size of semi-structured interviews was appropriate for deriving themes in qualitative research [30] and for usability testing.

This study has limitations. Participants included waitlisted kidney transplant candidates because, while eligibility for a pig kidney xenotransplant trial remains a topic of debate, emerging opinions during data collection suggested candidates would be optimal trial participants [41–43]. Non-waitlisted patients could have offered other viewpoints. Participants' perceptions reflected consideration of hypothetical xenotransplant trial participation, rather than of an actual trial. While participants were waitlisted for 2 years, on average, it is unlikely that their information needs would differ from patients' waitlisted longer. Waitlist time made no difference in candidates' information needs about participating in other innovative transplant research [35]. The news of two living humans who received a pig kidney at the time of usability testing may have shaped participants' desire for information needs. However, this is unlikely as the two recipients did not participate in a clinical trial that could have generated systematic information about outcomes that participants desired.

5 | Conclusion

Our findings suggest that kidney patients would require extensive information to provide informed consent for participating in a first-in-human pig kidney xenotransplant trial. Transplant programs preparing to conduct trials should address these information needs to optimize the informed consent process.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.