Contextual Vulnerability Should Guide Fair Subject Selection in Xenotransplantation Clinical Trials

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ABSTRACT

Xenotransplant research offers hope to individuals waiting for vital organ transplants. Nascent first-in-human xenotransplantation research trials present unique ethical challenges which may translate into obligations for researchers and special considerations for institutional review boards (IRBs). Contextual vulnerability is an important consideration in reviewing proposed subject selection methods. Some recipients are uniquely prone to receiving an unfair offer to enroll in an experimental clinical trial when excluded from allograft waitlists due to psychosocial or compliance evaluations. These exclusions represent an allocational injustice. Enrolling research subjects subjectively excluded from allotransplantation into xenotransplant research is not a mechanism of fair access but rather an exploitation of an unjustly option-constrained vulnerable group by the clinical transplant system. Carefully considering contextual vulnerability can help researchers and IRBs clarify eligibility criteria for xenograft clinical trials. A requirement for simultaneous allograft co-listing can safeguard the interests of vulnerable potential subjects.

Keywords: IRB, Xenotransplantation, Clinical Trials, Research Ethics, Organ Transplantation, Allograft

INTRODUCTION

In the United States, the supply of allogeneic, or human-derived, organs and tissues from living donors and cadavers available for transplant into critically ill individuals is inadequate.[1] Physicians refer only half of potentially eligible patients for transplant evaluation, and the clinical transplant team ultimately waitlists less than 30 percent.[2] Waitlists are lengthy for those who make it through the evaluation process, and many individuals die while waiting for a transplant.[3]

In contrast to allogeneic transplants, xenotransplantation, from the prefix, *xeno-* meaning foreign, is the process of taking live organs or tissues from an animal for surgical placement into a human recipient.

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Xenografts are typically sourced from porcine animals (domestic pigs) or non-human primates (baboons) and range from simple tissues like corneas to complex vital organs like hearts, lungs, or kidneys. Scientists have explored xenotransplantation methods for decades, but research with vital organ xenotransplants has been in largely haphazard and non-controlled studies, which demonstrated only short-duration survival for recipients.[4] Recent advances using gene modification and improved immunosuppression in single-patient attempts to transplant porcine organs into brain-dead human recipients have presented more realistic human-environment models; however, these modified xenografts have still functioned only for very short durations.[5]

The limited bioethics discourse on xenotransplantation centers primarily on the ethical use of high-order animals and the risks of zoonotic infectious disease spread.[6] Bioethics pays insufficient attention to the potential for exploitation of vulnerable individuals in need of a transplant amid growing interest in phase I clinical trials in living human subjects. Clinician-investigators in contemporary literature repeatedly recommend that these trials enroll subjects who are medically eligible for, but effectively excluded or outright denied access to, an allograft.[7] The Food & Drug Administration (FDA) recommends xenotransplants be limited to subjects with serious or life-threatening diseases for whom adequately safe and effective alternative therapies are not available.[8] The ethically salient difference between the investigator and the regulatory recommendations is why alternatives are not available to potential subjects: because transplant centers have subjectively denied access or because there is a clinical contraindication that proves prohibitively risky. In a notable single-patient emergency use authorization, physician-investigators offered a genetically modified porcine heart to a living male recipient after denying him access to the waitlist for a human-donor heart, citing a history of non-compliance.[9] This case suggests that a person denied access to a transplant waitlist due to subjective compliance criteria is an appropriate research subject. The physician-investigators failed to acknowledge how offering a xenotransplant to a contextually vulnerable subject is potentially unfair. Contextual vulnerability is a specific feature of a research environment that increases a subject's risk of harm. Bioethics discourse must address this vulnerability within the transplant research environment.

This paper describes the current transplant system's use of subjective evaluation criteria, particularly psychosocial support and compliance. Subjective evaluation criteria perpetuate discriminatory medical biases rather than advance the transplant system's goal of additional life-years gained. Researchers designing controlled human subject trials and institutional review boards (IRBs) reviewing and approving proposed protocols must consider how disparate waitlisting practices unjustly preclude some patients from a fair opportunity to access an allograft and impacts their participation in research. It is unethical for physician-investigators to intentionally take advantage of this vulnerability, creating an exploitative and unethical transaction.[10] Protocol inclusion criteria requiring proof of simultaneous allograft listing is a feasible procedural safeguard to protect research subjects' interests.

I. Injustices in Organ Allocation

Solid organ allocation systems are varied but aim for equity and efficiency in granting individuals with similar claims a fair opportunity to access the scarce resource. Allocation decisions attempt to maximize the common good of additional life-years gained.[11] The federal oversight of allograft allocation in the US uses objective clinical metrics like blood type, immune compatibility, body size, and geographic distance to match organs to recipients to increase both graft and patient survival.[12] Transplant centers additionally use their own evaluations to waitlist patients. Although variation exists between transplant center criteria across more objective measurements, such as lab values and concurrent diseases, significant

inconsistencies arise in how they incorporate subjective factors like compliance with medical recommendations, psychosocial support, and intellectual disability into the review process.[13] Only 7 percent of renal transplant programs use formal criteria for subjective psychosocial assessments, while no pediatric solid organ transplant programs use formal, explicit, or uniform review to assess developmental delays and psychosocial support.[14] Failing to establish uniform definitions and inconsistently applying evaluation criteria in the review of potential transplant candidates introduce bias into listing practices.[15] The center they present to and the variable evaluative criteria the center uses may discount an individual's claim to a fair opportunity to access a scarce resource.

Labeling a patient non-compliant can preclude both a referral to and placement on a waitlist for potentially suitable recipients. Compliance considerations presuppose that graft longevity will be jeopardized by an individual's failure to adhere to pre- and post-transplant regimens. It is necessary to distinguish individuals who are intentionally non-adherent to treatment regimens and demonstrate willful disregard for medical recommendations from those who are involuntarily non-adherent due to barriers that limit full participation in care plans. The former would not be offered a spot on the waitlist for an allograft, nor would investigators offer them a spot in a xenotransplantation research study. Significant and repeated refusals to participate in treatment plans would confound the ability of researchers to collect necessary data and perform the safety monitoring required by early-phase clinical trials. Enrolling subjects who are medically eligible for a traditional transplant but denied access requires a population that is suitably compliant to participate in a clinical trial reliably and safely yet judged not worthy of receipt of a standard allograft during the evaluation process.

The latter population is most disadvantaged by compliance judgments and unsubstantiated outcome predictions. Multi-center research studies have found that moderate non-adherence to immunosuppression regimens is not directly associated with poor kidney transplant outcomes.[16] Nor are intellectual and developmental disabilities, conditions for which transplant centers may categorically refuse evaluation, clear indicators of an individual's ability to comply with treatment regimens.[17] Large cohort studies of both pediatric kidney and liver transplant recipients found no correlation between intellectual disability and graft or patient survival.[18] Rather, it is the perpetuation of medical biases and quality-of-life judgments that presumptively label specific populations poor transplant candidates or label their support systems insufficient, notwithstanding data demonstrating their ability to achieve successful transplant outcomes.[19]

Variability in compliance assessments and psychosocial support criteria allows medical biases to persist and disproportionately impedes waitlist access to patients from underserved populations.[20] Low-income Medicaid patients are 2.6 times more likely to be labelled non-compliant as privately insured patients.[21] Additionally, the medical records of Black patients are 2.5 times more likely to contain negative descriptors like non-compliant, non-adherent, aggressive, unpleasant, and hysterical than those of white patients.[22] The higher prevalence of stigmatizing, compliance-based language in the medical records of minority, economically disadvantaged, and disabled persons decreases the likelihood that they will be recommended for a transplant, referred for an evaluation, placed on a waiting list, or ultimately receive a transplant.[23] These populations are at heightened risk of being used in ethically inappropriate ways by xenograft research that capitalizes on this precluded access.

II. Defining Vulnerability

Subjective evaluation criteria in allograft waitlisting disproportionately impact some populations. This precluded access to waitlists increases their vulnerability to experience harm in experimental

xenotransplant research. Fair subject selection requires the development of specific and appropriate inclusion and exclusion criteria designed to address and minimize known subject vulnerabilities.[24] This process begins with physician-investigators designing research trials and IRB review of proposed trials in which some or all potential subjects are vulnerable.[25]

The literature has no consensus on defining vulnerability in the clinical or research setting.[26] Prominent guidelines such as the Common Rule and the Declaration of Helsinki focus on a categorical, consent-based approach to assessing vulnerability. The capacity to provide freely given consent is a necessary prerequisite for ethical human subject research. Still, consent alone is insufficient to establish ethical permissibility or assure that a research transaction is fair.[27] Harm can occur even with informed consent if it results from coercion, undue influence, or exploitation.[28] Subjects have limited ability to avoid exploitation and act as an autonomous moral agents under such circumstances.

Categorical assessments label groups whose members share salient features, such as prisoners or children, as vulnerable. This shared characteristic may compromise their capacity for free consent and autonomous ability to protect their interests. Although widely used, broad categorizations create monolithic views of populations but lack clarity as to why a particular feature makes one vulnerable or what a given characteristic decidedly renders one vulnerable to.[29] Individuals broadly vulnerable in society, such as the severely economically disadvantaged or incarcerated, are not necessarily vulnerable as research subjects in a given proposed trial.[30] Categorical vulnerability is insufficient to recognize that research-related harm is specific to a particular subject potentially participating in a given protocol at a definite time and place.

III. Assessing for Contextual Vulnerability

Ensuring ethical consent, therefore, requires more than an accounting of capacity, competency, and freedom from coercion. This requires looking beyond voluntariness to ask whether the research offer is fair. Contextual vulnerability recognizes and addresses how some subjects are at a heightened risk of being used in ethically inappropriate ways due to research-specific situations and environments.[31] Contextual vulnerability derives from a specific feature of the research environment that increases a subject's risk of harm rather than an intrinsic categorical condition of that subject.

Accounting for contextual vulnerabilities is necessary because it is ethically unsound for a competent subject to give voluntary consent to an offer that is nonetheless unfair or exploitative.[32] Potential subjects excluded from accessing an allograft are contextually vulnerable in a research environment that may view their diminished range of choice as an opportunity for experimental research enrollment. Proposals to exploit or take advantage of this vulnerability places these individuals at a heightened risk of research-related harm.

IV. Exploitative Transactions in Xenotransplant Research

In the landmark single-patient case in Maryland, a genetically modified porcine heart was offered to the subject only because he was denied access to the allograft waitlist due to a history of noncompliance with a recommended medical regimen.[33] Physician-investigators did not define how they evaluated compliance, nor did they elaborate on how this claim demonstrated the subject's clear and convincing contraindication to receive a conventional cardiac allograft. The subject was presented with a so-called Hobson's choice, in which there is the illusion of free choice but ultimately there is no real choice as only one outcome, the acceptance of the experimental xenograft, is permitted; access to other choices, such as pursuing standard of care waitlisting, have been removed.[34] This case set a precedent for researchers and IRBs to view

individuals denied access to conventional allografts as an appropriate subject population without acknowledgment of how this transaction is consensually exploitative.

Consensual exploitation occurs when researchers intentionally and wrongfully take advantage of a subject's vulnerability.[35] In the cardiac xenotransplant case, the application of subjective evaluation criteria created a unique contextual vulnerability specific to transplant waitlist practices. Investigators took advantage of the subject's diminished ability to access the heart transplant waitlist to obtain consent for the xenotransplant procedure. Researchers have no obligation to repair unjust conditions that they bear no responsibility for causing.[36] The wrongfulness in this case is how subjective compliance-based waitlisting criteria precluded the subject from accessing the heart transplant waitlist and denied him fair consideration in accessing the standard clinical option. Then, the transplantation team exploited this disadvantage they were morally responsible for creating. The subject agreed to the terms for an experimental and high-risk xenograft from a place of vulnerability due to the diminished range of choice specifically constructed by the policy and actions of the transplant center. The options offered by the physician-investigators to the patient were manipulated to promote the research system's interests through the production of new scientific knowledge, not necessarily the subject's conception of his own good.[37]

V. Recommendation for Simultaneous Allograft Listing

Ethical research design calls for assessments of which vulnerabilities and in which contexts researchers and IRBs ought to offer additional safeguards. Subjects should be clinically suitable to produce robust, reliable, and generalizable scientific knowledge and be presented with a fair research offer. Researchers and IRBs can achieve this through an inclusion criterion requiring that a subject has previously been placed on and maintains a spot on a waitlist for a conventional allograft.

Investigators and IRBs must ensure that subjects are selected based on scientific rationale, not because they are easy to recruit due to a compromised or vulnerable position.[38] Evidence of simultaneous allograft listing would provide verification that a researcher expects a potential subject to survive the burdens of an experimental xenotransplant procedure. Individuals of advanced age or with severe life-limiting comorbidities separate from their end-stage organ failure are less likely to survive after receiving an allograft or a research xenograft. These subjects would not produce valuable data in service to the study's endpoints or knowledge generalizable to broader patient populations.

Requiring evidence of simultaneous allograft listing fulfills the ethical requirement that subjects who withdraw consent are not worse off than if they had not pursued research enrollment.[39] If a subject withdraws consent before receiving a xenograft, their continued place on a waitlist ensures that their fair opportunity claim to an allograft has been maintained.

Simultaneous allograft waitlisting excludes contextually vulnerable subjects clinically suitable to receive a graft but denied access to a waitlist. This inclusion criteria provides an additional safeguard against unfairly capitalizing on a subject's marginalized status. Requiring simultaneous allograft listing will narrow the potential subject population to those clinically suitable and well situated to receive a fair opportunity to enroll in research: individuals listed for an allograft but significantly unlikely to receive or to benefit from that allograft. This potential subject population includes individuals with broadly reactive antibodies who are unlikely to match to a donor organ and individuals with anatomical contraindications who face prohibitive risks with standard allografts or bridging therapies.[40] This subject population aligns with the FDA recommendation to enroll subjects for whom safe and effective alternatives are not available.[41]

These individuals have not had their claim to a fair opportunity transgressed by a subjective evaluation process, nor has their interest in accessing a scarce resource been unjustly discounted.[42] Neither the individual nor the transplant clinicians are responsible for creating a clinical or statistical disadvantage to receiving a standard allograft. An offer of research enrollment extended to this population has not been manipulated to favor one party over the other, but rather appropriately considers the interests of both parties.[43] Researchers have an interest in identifying subjects capable of producing scientifically valuable knowledge. Potential subjects have an interest in exploring alternatives to the high morbidity of a traditional allograft. This subject population retains the autonomous choice to pursue a standard-of-care allograft or to enroll in xenograft research. Having few treatment options available does not inexorably undermine the voluntariness of research consent or increase vulnerability.[44] The consent transaction is not exploitative or unfair because the transplant system is not responsible for creating this diminished range of choice. Simultaneous allograft listing represents an eligibility criterion that responds to and limits the products of subjective decisions from unjustly impacting trial enrollment.

VI. Counterargument: Is Something Better Than Nothing?

Some may argue that for medically exigent individuals in need of a transplant, any option to participate in research is better than no option. Autonomy and dignity, however, are not advanced when an inability to access the standard of care compels a subject's decision to pursue experimental research. An offer of research enrollment that is unfair or exploitative remains unethical regardless of whether the subject stands to benefit. Nor should benefit be expected in early-phase research. The goals of phase I research are primarily to collect short-term safety, toxicity, dosing, and pharmacologic data, not to provide efficacious treatment.[45] Expanding access to experimental research trials cannot be conflated with fair access to equitable health care.[46] Broadened access alone does not produce a more ethical research environment. Excluding contextually vulnerable subjects from research should not be the end goal, but rather a necessary interim to call attention to the need to redress biases and existing injustices in transplant access. Research that targets a population's vulnerability serves to enable the continuation of unjust systems.

CONCLUSION

In summary, the urgent and significant clinical need for transplantable organs cannot undermine the requirements of ethical research design and conduct. Fair subject selection is a requirement of ethical clinical research.[47] Potential subjects enrolled in upcoming xenograft research must be selected for their ability to answer the scientific objectives of a proposed study and must have the capacity to provide freely given informed consent within a fair research environment. Denying access to allotransplants for subjective psychosocial or compliance-based claims creates contextual vulnerability specific to transplant research that perpetuates the unfairness of the organ allocation system. Ethical research that produces valuable scientific knowledge cannot exploit the rights or interests of subjects in the process. A look beyond categorical vulnerability to contextual vulnerability highlights this currently overlooked area of exploitation.

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