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Pediatric Cardiac Xenotransplantation and Expanded Access: Ethical Considerations

Daniel J. Hurst[1] | Christopher Bobier[2] | Anthony Merlocco[3] | Luz A. Padilla[4] | Daniel Rodger[5,6] | David Cleveland[7] | John D. Cleveland[7]

[1]Department of Family Medicine, Rowan-Virtua School of Osteopathic Medicine, Stratford, New Jersey, USA | [2]Central Michigan University College of Medicine, Saginaw, Michihan, USA | [3]Division of Pediatric Cardiology, Department of Pediatrics, Le Bonheur Children's Hospital, The University of Tennessee Health Science Center, Memphis, Tennessee, USA | [4]Department of Surgery, The University of Alabama at Birmingham, Birmingham, Alabama, USA | [5]School of Allied and Community Health, Institute of Health and Social Care, London South Bank University, London, UK | [6]Department of Psychological Sciences, Birkbeck, University of London, London, UK | [7]Department of Cardiothoracic Surgery, Children's Hospital of Los Angeles, Los Angeles, California, USA

Correspondence: Daniel J. Hurst (hurst@rowan.edu)

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ABSTRACT

Due to the current organ shortage waitlist, alternatives to allotransplantation are necessary. Xenotransplantation is currently being pursued as one such alternative in adults in need of kidney or heart transplantation. Cardiac xenotransplantation of genetically modified pig hearts has been conducted twice in adults under the United States Food and Drug Administration (FDA) expanded access criteria. Because of the shortage of transplantable hearts for children as well as the lack of mechanical circulatory support in this population, pediatric researchers are exploring FDA expanded access in high-risk neonates and infants who lack alternative options for survival. The adult cardiac xenotransplantation experience with expanded access can provide lessons and highlight nuances for researchers preparing pediatric application. This includes aspects of informed consent, biosurveillance, and protection of bystanders from potential xenozoonoses.

1 | Introduction

In addition to increasing the number of donor organs and the improved use of existing organ donor supply, there is the need for alternatives to solid organ allotransplantation to be pursued. One such alternative to allotransplantation is xenotransplantation, specifically, the cross-species transplantation of pig organs, which has been studied for decades but recently has shown more promise due to genetic modifications that confer increased compatibility with human recipients. In January 2022 and September 2023, two patients at the University of Maryland Medical Center (UMMC) underwent cardiac xenotransplantation [1, 2]. Each patient received approval for xenotransplantation under the US Food and Drug Administration's (FDA) expanded access program (i.e., compassionate use) that allows a patient to obtain access to an investigational intervention when clinical trial participation is unavailable and certain other criteria are met.

While patients of all ages suffer the consequences of limited donors, the need for well-functioning transplantable organs

Abbreviations: CDRH, Center for Devices and Radiological Health; DHHS, United States Department of Health and Human Services; ECMO, extracorporeal membrane oxygenation; FDA, The United States Food and Drug Administration; SACX, Secretary's Advisory Committee on Xenotransplantation; UMMC, The University of Maryland Medical Center; US, The United States of America.

may be even more critical for children. In 2021 alone, more than 700 *new* pediatric candidates were added to the cardiac transplant waitlist in the United States, with a *total* of more than 1100 listed according to an annual data report from the US Organ Procurement and Transplant Network [3]. The report concludes that compared with waitlist data for patients < 18 years old from 2010, there was a 40% increase in waitlist candidates by 2021, with nearly 50% being < 5 years of age. Pre-transplant mortality is highest in pediatric candidates < 1 year of age, at 29.8 deaths per 100 patient-years [4]. In this population, limited options for mechanical circulatory support exist [5]. Survival for single and biventricular status is similar, and while the subset of children with failed single ventricle is considered particularly vulnerable, of all congenital heart patients, approximately 50% will die within 6 months when on mechanical circulatory support as a bridge to allotransplantation [6]. Additionally, palliative surgical options for children with complex and life-threatening heart problems often provide unsatisfactory results, as they carry significant co-morbidities and risk of failure [7]. Despite these challenges, once infants and neonates receive a cardiac allotransplant, they generally experience excellent outcomes. Long-term graft survival and rates of rejection are better than in adults, attributable to a potential immunologic advantage conferred by their immature immune systems; importantly though, current survival expectations still do not grant them a normal lifespan [8]. The limited alternatives to allotransplantation, significant waitlist time and mortality, and potential immunological advantages conferring excellent graft survival are all strong arguments that cardiac xenotransplantation studies should be done in children. In fact, the uniqueness of these factors to the pediatric population make a compelling case that children should be first to have access to this novel technology. This is particularly relevant when considering the ability to apply it as a bridge to conventional allotransplantation as opposed to relying on it to serve as destination therapy [7, 9, 10].

There are at least two reasons to consider why pediatric cardiac xenotransplantation expanded access should be considered as a precursor to initiating clinical trials, specifically: (i) the high rates of mortality with current care paradigms and (ii) a precedent set by the FDA for expanded access in adult patients. We consider the specific ethical issues with permitting pediatric cardiac xenotransplantation via the expanded access pathway to require urgent attention due to the following: (i) one biotechnology company has stated an intention to begin pediatric cardiac xenotransplantation clinical trials in the near future [11], (ii) there are active proposals and research by a group seeking to apply this technology to high-risk patients with congenital heart disease [12–14], and (iii) there has, to date, been inadequate attention to these issues.

In this paper, we provide an analysis of the FDA's criteria for expanded access in the context of pediatric cardiac xenotransplantation. We utilize lessons learned from the adult cardiac xenotransplantations performed in 2022 and 2023, as well as ethical guidance on xenotransplantation that has been offered previously to provide recommendations to researchers considering utilizing the expanded access pathway.

2 | Expanded Access Criteria

The FDA provides a pathway for patients to obtain access to an investigational drug, biologic, or medical device for treatment outside the normal confines of a clinical trial. This is termed "expanded access" and is often colloquially referred to as "compassionate use." Expanded access regulations and guidelines were originally developed in 1987 for drugs and biologics in the wake of the HIV/AIDS crisis and for devices in 1996. The current FDA expanded access regulations went into effect in 2009 [15]. The Center for Devices and Radiological Health (CDRH) is the branch of the FDA responsible for the premarket approval of medical devices and for assessing expanded access requests. Between 2018 and 2022, the CDRH granted more than 99% of the expanded access requests that were evaluated [16].

Per the FDA, each of the following criterion must be met for expanded access to *potentially* be appropriate:

1. Patient has a serious or immediately life-threatening disease or condition.
2. There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
3. Patient enrollment in a clinical trial is not possible.
4. Potential patient benefit justifies the potential risks of treatment.
5. Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication [17].

The five criteria cumulatively offer a compelling and *prima facie* ethically defensible allowance for an experimental treatment or medical device. Clinicians should be motivated by beneficence—the obligation of acting for the benefit of the patient—and with the hope of achieving a favorable risk–benefit outcome for patients. If the patient is not at serious risk of death or has an alternative satisfactory therapeutic option, then the risk–benefit analysis is unfavorable when considering a novel and experimental therapy such as xenotransplantation. However, that risk–benefit analysis shifts when the available clinical options are exhausted and there is a possibility of an experimental treatment or device working; clinicians may then be ethically justified in considering such alternatives.

Our critique does not focus on the FDA's expanded access program itself; rather, we question whether the expanded access criteria may require re-evaluation within the specific context of xenotransplantation. As we will explain, the ethical issues that pediatric xenotransplantation researchers should address extend beyond merely *meeting* the expanded access criteria.

3 | Lessons Learned From Adult Cardiac Xenotransplantation

To date, the FDA's expanded access pathway has been utilized twice to allow patients to receive a genetically modified

pig heart. Mr. David Bennett Sr., a 57-year-old male with nonischemic cardiomyopathy and dependent on venoarterial extracorporeal membrane oxygenation (ECMO) received the world's first genetically modified pig heart transplantation in January 2022 at UMMC [1]. Per the research team at UMMC, because Mr. Bennett had been "deemed to have poor adherence to treatment," he was ineligible for either allotransplantation or a mechanical circulatory device [1]. With no remaining therapeutic medical options and death imminent, his clinical team considered cardiac xenotransplantation to be a viable possibility.

Let us use the expanded access criteria to assess this first case. Mr. Bennett did indeed have a serious, immediate life-threatening disease or condition (criterion 1); in this case, Mr. Bennett's medical team had adjudicated that no satisfactory alternative therapy was available to treat his condition, stating that he "was not a candidate for standard therapeutics, including a traditional allograft," [1] and thus fulfilling criterion 2. This point, however, has been brought into question, as an alternative therapy would have been circulatory support with an artificial device such as a total artificial heart or ventricular assist device. It is unclear to us how Mr. Bennett's prior medical non-compliance precluded him from receiving an artificial device. Nonetheless, the FDA seems to have agreed with UMMC's assessment. Next, enrolling Mr. Bennett in a cardiac xenotransplantation *clinical* trial was not a possibility given that none existed (criterion 3) and nor was there an *investigational* trial; thus, there is no interference with a medical product's (xenotransplantation) development or marketing approval for the treatment indication (criterion 5). Lastly, regarding criterion 4, researchers stated that their "belief that the outcome of the experimental transplantation was not likely to be inferior to continuation of medical therapy and venoarterial ECMO" [1] fulfilled this criterion. While experimental xenotransplantation may have been preferable to indefinite ECMO, it is difficult to affirm that is preferable to implantation of a ventricular assist device or compassionate ECMO discontinuation. As such, we do take issue with how researchers sought to fulfill expanded access requirements in this case.

While Mr. Bennett seems to have met the requirements for expanded access (and, of course, it was granted by the FDA), we believe that the FDA expanded access requirements are not the only requirements that should be considered regarding eligibility for cardiac xenotransplantation. In fact, the FDA's own prior guidance on xenotransplantation seems to have been overlooked. For instance, the FDA has recommended the following to researchers regarding patient selection: "You should also consider the patient's ability to comply with public health measures as stated in the protocol, including long-term monitoring." [18] Yet, UMMC researchers have stated that Mr. Bennett had been considered ineligible for allotransplantation and mechanical circulatory support due to having been "deemed to have poor adherence to treatment." [1] The FDA guidance for consideration of the ability to comply is, of course, non-binding but generally seems to require perhaps a higher threshold or at least specific focus on adherence. Because adherence is always a concern prior to *allotransplantation* itself, it is even more surprising that—given the history of debate surrounding the need for post-xenotransplantation biosurveillance—Mr. Bennett was considered a good candidate for xenotransplantation. It may not be the case that any prior adherence concerns should invalidate a potential candidate in the future, but it appears imprudent to deem someone a good candidate when these concerns were so substantive to their current options and without explicitly addressing how this concern will be mitigated. To date, both the UMMC investigators and the FDA have been silent on this issue, which we believe to be a very important one in need of addressing due to the importance of observing post-xenotransplantation biosurveillance.

Mr. Lawrence Faucette, a 58-year-old male with terminal heart disease, received the second genetically modified pig heart transplantation in September 2023 at UMMC [19]. Application of expanded access criteria to Mr. Faucette follows a similar course. Due to pre-existing peripheral vascular disease (criterion 1), Mr. Faucette was deemed ineligible for heart allotransplantation (criterion 2). Enrolling Mr. Faucette in a cardiac xenotransplantation clinical trial was not a possibility as none exist (criterion 3) and as investigational trials also do not exist, interference was not a concern (criterion 5). As with Mr. Bennett, the transplant team at UMMC considered criterion 4 to be met. Surprisingly, as of the time of this writing in mid-2024, detailed information pertaining to Mr. Faucette's death has not been publicly released. His post-transplantation course included reports that he developed renal failure requiring dialysis and ultimately evidence of xenograft organ rejection after 42 days [7]. Thus, given the paucity of information, a thorough analysis of the ethical components of decision-making in Mr. Faucette's case is not possible. At bare minimum, it seems prudent for the sake of transparency and the advance of xenotransplantation that the results of expanded access cases be shared publicly, which has yet to be done in this instance. It remains important that when more is known that we review the application of the expanded access criteria and whether it highlights any *further* criteria that will aid in patient selection.

4 | Expanded Access Within Pediatric Xenotransplantation

Criteria for expanded access in the pediatric population in some cases can be met easier than in adults [14, 20]. Infants born with serious congenital heart defects are at high risk for death with and without currently available interventions. Some children are poor candidates for surgical palliation or repair, making cardiac transplantation their only chance for survival, thus meeting criteria 1. Cardiac xenotransplantation in adults has limited use given the improving long-term outcomes of patients on circulatory support devices [21]. These positive outcomes for mechanical circulatory support have not been realized for infants with cardiac failure, particularly those with complex congenital heart disease. The gold standard for children in this category is achieving cardiac allotransplantation. However, their likelihood of finding a suitable donor is poor given that (1) children under 1-year-old who need heart transplant have the highest waitlist mortality of any solid organ or age group [5] and (2) multiple clinical

criteria must be met for successful organ matching (i.e., low panel reactive antibody, size, etc.). The fact is that there are infants in intensive care units around the United States who will die because they lack the time to allow for successful cardiac allotransplantation, fulfilling criteria 2 and 4 [14, 20]. To our knowledge, there are no clinical or investigational trials in cardiac xenotransplantation in adults or children, thus meeting criteria 3 and 5.

While still learning lessons from adult cardiac xenotransplantation, investigators seem to be approaching cardiac xenotransplantation for pediatrics and, if so, we must recognize nuances specific to this population. Here, we will discuss (i) the additional obligations regarding informed consent for children, (ii) the debate regarding mandatory biosurveillance of the xenograft recipient, and (iii) protection of close contacts and the larger population from the risk of xenozoonosis, which is difficult to quantify at this point but is not zero.

4.1 | Informed Consent for a Pediatric Patient

In 2004, the US Department of Health and Human Services (DHHS) Secretary's Advisory Committee on Xenotransplantation (SACX) issued draft guidelines on informed consent in clinical studies of xenotransplantation, stating that "as a general matter, children should not participate in xenotransplantation protocols." [22] To defend this position, SACX argued (i) that xenotransplantation is in early experimental stages and (ii) that lifelong medical monitoring will be required of all research participants [22]. SACX provided one exception to this recommendation: if "the potential benefit to a child from a xenotransplantation procedure is high given the available alternatives," then proceeding may be allowable, but this must be determined on a case-by-case basis. Since 2004, notable scientific progress has been achieved in xenotransplantation, particularly concerning the pediatric population [23]. One study demonstrated evidence of little to no preformed anti-pig antibodies from exposure to genetically engineered pig organs among infants [24]. Other studies have hinted at the immunological advantages of children over adults as xenograft recipients such as higher chances of tolerance and lower innate cell activity [8, 25, 26]. In fact, it has been proposed that children may benefit more from cardiac xenotransplantation over adults due to several biological factors and their lack of clinical alternatives. However, there is currently a lack of updated guidelines from the DHHS or other bodies regarding informed consent for pediatric cardiac xenotransplantation and what a reasonable benefit and risk assessment might be for each case.

Due to the unknown benefit and risk assessment of the initial first-in-human xenotransplants and that limited alternative therapeutic options may exist for a patient, it is paramount that surrogate decision-makers (e.g., parents) be knowledgeable and have a realistic appraisal of the procedure. While DHHS does not have updated guidelines on informed consent—an element we recommend needs revisiting—other researchers have provided recommendations. Padilla and colleagues have recommended a "cooling off period" be implemented for authorization of xenotransplantation [27]. That is, the surrogate decision-maker(s) could be approached initially regarding the possible clinical xenotransplantation only after the medical and ethics teams have determined the candidate is eligible. Risks and benefits could then be outlined and discussed with the agreement that only after a pre-determined interval would the research team return and formally undertake the informed consent process. This may be a delicate balance, as patient attitudes are not yet fully understood and offering an experimental therapy prematurely may cause distress if ultimately a patient is determined ineligible. Some families may be interested in undertaking the xenotransplant as soon as they are approached, risking that they may not fully comprehend the risks, and others may need considerable time to understand the risks and benefits and many unknowns. Pragmatic concerns will always be present surrounding time sensitivities for the patient. Regardless, further attention to how best to approach patients, families, and decision-makers is pressing to ensure that we support the surrogate decision-maker(s) to adequately understand the potential risks and benefits of the procedure.

4.2 | Biosurveillance

Many guidelines call for long-term or lifelong biosurveillance (e.g., blood tests, imaging, graft biopsies) of the xenograft recipient, even if the xenograft is used as a bridge therapy and later excised [18, 22, 28]. In Mr. Bennett's case, some form of a Ulysses contract was utilized to consent for a future "self" that may be in a different state. Generally, this would be a document (regularly used in psychiatry) in which a patient agrees in advance of a psychiatric episode to specific future medical management when suffering from a psychiatric episode, ignoring any future refusal or withdrawal. Mr. Bennett's case utilized such an approach in order to bind him to post-xenotransplant monitoring requirements [29]. Ulysses contracts have been proposed for decades in regard to adult xenotransplantation, yet they are not without criticism [30, 31]. To our knowledge, Ulysses contracts have not been proposed in the context of pediatric xenotransplantation. We believe this approach would imbalance the interests of a child in having an open future, which would rob the adult (i.e., the former child) of their autonomy. Additionally, Ulysses contracts may be fraught with legal challenges. While every parent who consents to an allotransplantation for their child agrees to some form of immunosuppression regimen and other regular monitoring for the functioning of the graft, this is different from mandatory biosurveillance for xenozoonoses in the context of a clinical trial. Thus, we believe it may be best to refrain from a Ulysses contract approach in children. Nonetheless, if xenotransplantation researchers state in the informed consent documents that a pediatric xenograft recipient should undergo biosurveillance long-term or the remainder of their lives, this creates a situation in which a surrogate decision-maker must consent for the child not only to receive the surgery but also to long-term biosurveillance [32]. Hence, even when the child reaches the age of majority, s/he may need to comply with biosurveillance measures, or even if not legally bound, they may feel an obligation to a decision that they did not make. This may be true of any xenotransplant recipient, as feelings can change over time but is a particular concern for a patient who

has been able only to assent at best, and at worst unaware at all if very young. Since there is currently no mechanism in place to ensure compliance, further work is necessary to delineate an ethically defensible way to ensure compliance as the child ages.

4.3 | Protection of Certain Bystanders

There are many unknowns regarding xenozoonotic risk and what precautions should be taken to mitigate risk. However, the risk of xenozoonotic disease transmission has prompted some researchers to recommend that close contacts, particularly caregivers and members of the same household who may come into contact with the xenograft recipient's blood due to wound and/or line care, as well as sexual contacts, be notified of this risk so that they may consent to assume the risk for themselves [33]. Fishman has recommended that sexual and close social contacts require education on the potential xenozoonotic risks so as to mitigate risk of exposure to bodily fluids even from common items such as toothbrushes [34]. As children will be particularly in need of assistance with daily activities, medical management, and transportation, these activities will put certain bystanders in very close and prolonged proximity to the xenograft recipient which may increase their risk. These persons must not only be informed of the risk they are assuming but should also be aware of the possibility of the need for quarantine measures should the xenograft recipient be suspected of having a xenozoonotic infection.

5 | Conclusion

The eligibility criteria for utilizing the FDA's expanded access program are an important starting point in assessing patient eligibility for cardiac xenotransplantation and may be more easily met within the pediatric population among infants with severe congenital heart disease due to high waitlist mortality, few mechanical support options, and lack of clinical trials. As we have discussed, meeting these criteria merely reveals who *may* be a good candidate for xenotransplantation and justifies its use, but this equation contains additional important considerations, especially in children. That is, the FDA criteria do not capture the breadth of ethical questions that must be satisfied before moving forward with xenotransplantation. As researchers plan investigational studies, numerous other recommendations exist that should be considered. In particular, how best to obtain informed consent of the surrogate decision-maker(s) and additional conversation around biosurveillance and protection of certain bystanders should be thoughtfully considered.

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The authors have nothing to report.

Conflicts of Interest

D.J.H. and L.A.P. are paid consultants to a working group on xenotransplantation ethics at the Division of Medical Ethics of New York University. D.J.H. is a member of the International Xenotransplantation Association Ethics Committee. The viewpoints in this manuscript are those of the authors.

Data Availability Statement

The authors have nothing to report.

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