**Pediatric Cardiac Xenotransplantation: Recommendations for the Ethical Design of Clinical Trials**

**Authors:** Daniel J. Hurst PhD ThM MDiv MSc1\*‡; Luz Padilla MD MSPH2‡; Anthony Merlocco MD MSt3; Daniel Rodger MA4,5;Christopher Bobier PhD6; William H. Gray MD2; Robert Sorabella MD2; David KC Cooper MD PhD7;Richard N. Pierson MD7

1. Department of Family Medicine, Rowan-Virtua School of Osteopathic Medicine, Stratford, New Jersey, USA

2. Department of Surgery, Division of Cardiothoracic Surgery, The University of Alabama at Birmingham, Alabama, USA

3. University of Tennessee Health Science Center, Memphis, Tennessee, USA

4. School of Allied and Community Health, London South Bank University, UK

5. Birkbeck College, University of London, UK

6. Saint Mary’s University of Minnesota, Winona, Minnesota, USA

7. Center for Transplantation Sciences, Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts, USA

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**Abbreviations:**

Congenital heart disease (CHD)

Council for International Organizations of Medical Sciences (CIOMS)

Institutional Review Board (IRB)

International Society for Heart and Lung Transplantation (ISHLT)

Mechanical circulatory support (MCS)

Panel reactive antibodies (PRA)

United States of America (US)

University of Maryland Medical Center (UMMC)

U.S. Department of Health and Human Services (DHHS)

U.S. Department of Health and Human Services Office for Human Research Protections (OHRP)

U.S. Department of Health and Human Services Secretary’s Advisory Committee on Xenotransplantation(SACX)

Ventricular assist device (VAD)

World Health Organization (WHO)

 **Abstract**

For children with complex congenital heart problems, cardiac allotransplantation is sometimes the best therapeutic option. However, availability of hearts for pediatric patients is limited, resulting in a long and growing waitlist, and a high mortality rate while waiting. Cardiac xenotransplantation has been proposed as one therapeutic alternative for neonates and infants, either in lieu of allotransplantation or as a bridge until an allograft becomes available. Scientific and clinical developments in xenotransplantation appear likely to permit cardiac xenotransplantation clinical trials in adults in the coming years. The ethical issues around xenotransplantation of the heart and other organs and tissues have recently been examined, but to date, only limited literature is available on the ethical issues that are attendant with pediatric heart xenotransplantation. Here, we summarize the ethical issues, focusing on (i) whether cardiac xenotransplantation should proceed in adults or children first, (ii) pediatric recipient selection for initial xenotransplantation trials, (iii) special problems regarding informed consent in this context, and (iv) related psychosocial and public perception considerations. We conclude with specific recommendations regarding ethically informed design of pediatric heart xenotransplantation trials.

**Keywords:** cardiac; clinical trials; ethics; pediatric; xenotransplantation

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**1. Introduction**

 Alternatives to solid organ allotransplantation are needed to address the persistent shortage of healthy, well-functioning human hearts relative to the number of patients who might benefit if donor supply was not limiting. Transplantation using organs from other species, or ‘xenotransplantation,’ is one potential solution. Xenotransplantation of organs from pigs genetically-engineered to make them more compatible with humans has been studied for decades with improving outcomes, through setbacks and incremental advancements.1 In January 2022, cardiac xenotransplantation from a genetically-engineered pig was performed in a 57-year-old male—the first procedure of its kind—at the University of Maryland Medical Center at Baltimore (UMMC). The cardiac xenograft recipient died from graft failure on postoperative day 60.2 A second pig heart transplant was performed at UMMC on September 20, 2023. The second recipient, although doing well initially after surgery, died 6 weeks post-surgery, possibly from rejection.3 Cardiac xenotransplantation has also been studied in deceased human recipients, where life-supporting function of the heart was demonstrated for up to 3 days.4 Recommendations for the ethical advancement of adult xenotransplantation—especially kidney5-7 and heart8 xenotransplantation—have been offered at length in the published literature. While renal and cardiac xenotransplantation may surely be valuable for adults once xenotransplantation proves safe and effective, cardiac xenotransplantation may be even more impactful for children than adults to reduce wait-list mortality, expand access, and add quality-adjusted years of life.9,10

Attempts at pediatric cardiac xenotransplantation date back to 1984 when, in a landmark event, an infant with hypoplastic left heart syndrome (HLHS)—“Baby Fae”—received a baboon heart transplant.11 Baby Fae would die 20 days post-transplant when her body’s immune system rejected the heart (administration of a blood product incompatible with the baboon heart that triggered rejection). This event would prove seminal for xenotransplantation as it attracted increased interest in the ethical issues and ignited new debate.11 Pediatric cardiac xenotransplantation has not been attempted again, and the particular ethical considerations related to xenotransplantation in this age group have received little attention in the literature in the 40 years since this case.

Meanwhile, the science that supports pediatric cardiac xenotransplantation has made significant recent progress. Blood from infants with congenital heart disease (CHD) with or without a history of prior cardiac surgery contain no anti-pig antibodies towards cells of the gene-edited pig source for the hearts.12 Additionally, several experiments have been carried out in a pre-clinical model for pig-to-baboon pediatric heart xenotransplantation. Meanwhile, in ‘adult’ preclinical models, consistent survival of heterotopic pig heart grafts (in the abdomen and non-life-supporting) in baboons has been reported, in one instance for >2 years.13 Orthotopic pig hearts have provided life-supporting function in immunologically mature baboons for up to 8 months.14

In July 2023, eGenesis, a biotechnology company producing genetically-engineered pigs for xenotransplantation, announced plans to initiate pediatric cardiac xenotransplantation clinical trials as soon as 2024.15 Children have a critical need for increased access to healthy, durable transplantable organs. In 2021, >700 pediatric candidates were added to the heart transplant waitlist, bringing the total to >1000.16 Neonates and infants experience the highest waitlist mortality when compared to any other solid organ group, and there exist limited options for mechanical circulatory support (MCS) for these children.17 Half of infants who are on MCS awaiting a cardiac allograft die within six months.18 Allotransplantation has to date proven incapable of serving all children who need it. Transplantation offers the best chance for the child to survive into adulthood;19 in our estimation there is a great need for effective alternatives such as xenotransplantation.

Although there is enthusiasm for the use of cardiac xenotransplantation for children, from an ethical perspective little has been written on potential clinical trials in this population.20,21 In a 2022 consensus statement on cardiac xenotransplantation in children from experts in the field, the authors list five relevant issues for clinical translation of cardiac xenotransplantation to pediatric patients: (i) recipient selection; (ii) optimal technique for heart transfer and transplantation; (iii) immunosuppression and monitoring; (iv) development of tolerance; and (v) potential need for re-transplantation.10 While these represent an excellent starting point for implementation, the authors did not focus on the ethical issues.

Here we consider the ethical dimensions of pediatric xenotransplantation, and whether they may impede or even prohibit translation into children. We (i) assess what we foresee as the pressing ethical considerations relating to pediatric xenotransplantation, clarifying where gaps exist and which areas need further consensus prior to initiating clinical trials, and (ii) provide initial recommendations on how the field might proceed. While we write from the context of the United States (US) and its regulatory landscape, we believe some of these principles have global application.

**2. Ethical considerations for pediatric xenotransplantation**

 The Belmont Report serves a foundational role for research ethics in the US. Its three principles—respect for persons, beneficence, and justice—have been expanded and codified into the US Code for the protection of research participants.22 When applied to children, the Belmont Report notes the principle of beneficence creates an essential conflict for medical research that presents greater than minimal risk without the immediate prospect of direct benefit:

Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.22

Beneficence can be understood on both an individual and/or a societal level. In xenotransplantation research, especially in Phase 1 clinical trials, beneficence to individual participants is uncertain, as it is unknown whether the first individuals to undergo xenotransplantation will receive any direct benefit. While certainly there is *potential* benefit of prolonged life, it is also unknown if this is balanced by potential harms including pain, additional procedures, and possible death from failure of the heart (‘rejection’) or from a complication related to the treatment regimen (infection, drug toxicity). While similar harms including death may occur without xenotransplantation, given the unknown physiological and functional capacity of the organ or how the prescribed treatments will be tolerated, suffering may be worse and death come more quickly than in the natural course of the native heart disease. At a societal level, however, knowledge from initial clinical trials is an essential step for medical advancement. Regulators, sponsors, investigators, and patients will need to agree if children are to be allowed to be enrolled in cardiac xenotransplantation trials prior to establishing safety and efficacy in adults. If xenotransplantation were successful and available timely, children may benefit more from this novel clinical alternative than adults by reduced waiting list mortality, improved cardiovascular health through critical phases of physical, mental, and emotional maturation, and improved access to other established treatments including subsequent receipt of a heart allograft. If either bridging to an ‘elective’ allograft or durable support as ‘destination therapy’ seemed probable based on available evidence, withholding advancement of its use in children until adult data prove to be successful may itself be unethical. In this section we discuss several ethical issues that merit attention and summarize recommendations for responding to each in Table 1.

*2.1 Cardiac Xenotransplantation in Children or Adults First?*

*a) Regulatory guidelines*

 Until outcomes for adult subjects become better defined by exploratory ‘pilot’ clinical experiences, uncertainty regarding risk/benefit will continue to confound clinical trial design and thus delay advancing the field for adults. Prior authors uniformly agree that, if possible, novel therapies should be studied in adults prior to children. For instance, The Belmont Report states that it can be considered a matter of social justice that adults precede children in research. The Council for International Organizations of Medical Sciences (CIOMS) guidelines provide recommendations based upon whether the proposed research has the potential to benefit the participant or not:

For research interventions or procedures that have the potential to benefit children or adolescents, the risks must be minimized and outweighed by the prospect of potential individual benefit.

For research interventions or procedures that have no potential individual benefits for participants, two conditions apply:

* the interventions and procedures should be studied in adults first, when these interventions and procedures target conditions that affect adults as well as children and adolescents, unless the necessary data cannot be obtained without participation of children or adolescents;
* and the risks must be minimized and no more than minimal.23

Regarding xenotransplantation generally, Pierson and colleagues have noted:

Internationally accepted ethical guidelines generally discourage inclusion of children in “first-in-man” trials, particularly for high-risk interventions, unless testing in adults is not feasible. For this reason, inclusion of minors in an initial clinical cardiac xenotransplantation trial would be controversial.8

Similarly, the Nuffield Council on Bioethics recommended that the first xenotransplantation trials should involve adults rather than children because “it would be difficult to justify the involvement of children in major and risky trials as recipients of heart xenografts, for example, before some of the uncertainties have been eliminated in trials involving adults.”24 Nuffield does not completely rule out proceeding with cardiac xenotransplantation in children but argues that, if clinical trials in adults prove successful, then this may inform our assessment of the benefit-to-risk ratio for xenotransplantation in children. However, in our view justification for cardiac xenotransplantation trials among adults may be less compelling compared with children due to availability of competing therapeutic options and proportionately lower mortality on the wait list for adults. For example, for an adult, the risk-benefit ratio of unknown xenotransplantation outcomes relative to well-defined MCS options would likely be considered ethically suspect in most circumstances, whereas for a child whose anatomy complicates or precludes an MCS option a ‘bridge-to-allo’ heart xenograft might be judged ethically defensible. However, should the studies not prove beneficial to the patients, approving pediatric cardiac xenotransplantation under US Food and Drug Administration (FDA) expanded access guidelines or in the context of a clinical trial without prior testing and positive outcomes in adults might risk leading to diminished public acceptance of xenotransplantation.

*b) Clinical advantages of children*

Data generated from adult cardiac xenotransplantation may not necessarily be useful for predicting success in children due to biological differences.25-27 First, infants may have an immunologic advantage for accepting a xenograft when compared to adults.25 Within the first 6-12 months of life they have low or no preformed anti-pig antibodies to organs from the gene-edited pig that are likely to be the sources of hearts. Infants also exhibit less robust complement systems and reduced innate immune cell activity, additional factors which are expected to decrease the risk and severity of heart xenograft rejection, particularly for neonates, a population for whom MCS options are most constrained.12,25 Unlike with adults, during cardiac allotransplantation in infants the thymus is routinely removed, theoretically decreasing cell-mediated responses that could favorably affect xenograft survival (although regulatory cells that mediate graft protection and immunological tolerance might also be adversely affected).26

Younger patients, particularly infants, have a greater likelihood of developing B cell immune tolerance to an allograft, though this does not allow them to discontinue immunosuppressive medication.28,29 Currently, limited data exists on xenotransplantation tolerance though strategies are being designed.12,30,31

Secondly, neonates have superior survival after cardiac allotransplant when compared to older children and adults, with a median graft survival of >25 years; it is conceivable that similar results for xenotransplantation could occur in the immature immunologic environment of an infant.32 Thirdly, utilizing xenotransplantation as a bridge to allotransplantation may be judged ethically appropriate in pediatric patients, due to the high mortality of infants on the donor heart waitlist and the poor outcomes of MCS, and in light of the fact that some pediatric hearts go unused due to lack of a size-matched recipient. In contrast bridging with a xenograft is more difficult to justify in adults where the overall supply of usable human donors is limiting and MCS is more often a reasonable bridging option.27,33

If the 8-month survival of pig-to-baboon heart transplantation described above can be consistently achieved pre-clinically and then replicated in the initial stages of clinical trials in children, the use of cardiac xenotransplantation in children may be valuable as a bridge, for as many as 90% of children with single ventricle die within months, even on MCS.27 In contrast, 70% of adults with ventricular assist device (VAD) placement for bridging to transplant can survive up to 3 years.34 The background of pediatric cardiac waitlist mortality and few available alternatives to cardiac allotransplantation in this population with life-threatening CHD presents an ethical dilemma: is it ethical to delay clinical trials in neonates and infants while awaiting safety and efficacy data in adults? What threshold of preclinical ‘success’ would be needed to satisfy the equipoise stipulation that underlies clinical trial ethics – that is, when would we judge that the benefit-to-risk ratio justifies beginning heart xenotransplant trials in children?

For some CHD populations where conventional clinical options are exhausted and the child is unlikely to survive to allotransplantation, the only current alternative is palliative or hospice measures while awaiting death. Initial xenotransplantation clinical trials may not have definable risk-benefit ratios for the experimental subject due especially to uncertain efficacy, but nonetheless would likely generate knowledge that can scientifically advance the field for future individuals.

Other examples exist in pediatric cardiology supporting this approach, including the initial investigation of the arterial switch procedure for transposition of the great arteries, which has now largely supplanted the atrial-level switch procedures,35-37 or balloon valvuloplasty for fetal aortic stenosis, for treatment of hypoplastic left heart syndrome.38,39 Both of these advances had unknown short- and long-term risks when first introduced but were justified by unsatisfactory long-term morbidity or mortality associated with then-established treatment paradigms. As with those procedures, the outcomes associated with initial cardiac xenotransplantation clinical trials in children (and adults) are unknown. While in our estimation initial pediatric cardiac xenotransplants are likely to be associated with short- and long-term results that are inferior to allotransplantation, but hold the promise of yielding transformative new knowledge, and eventually changing the treatment paradigm for future pediatric CHD patients.

To identify pediatric CHD patients who are medically and ethically appropriate to participate in initial xenotransplantation activities, we believe that the FDA, the DHHS, and/or the National Institutes of Health (perhaps in partnership with other nations’ health care and research agencies) should convene a body of stakeholders: providers, patients, transplant recipients, scientists, etc. in relevant fields. We propose that this body be tasked with producing a report that explores and examines the existing data, statistics on need, risk/benefit ratio and the current clinical alternatives that is specific to children in need of a heart. The report should have arguments for and against the inclusion of children in cardiac xenotransplantation clinical trials and set forth the minimum requirements needed to initiate cardiac xenotransplantation.

Some existing documents, such as the First and Second WHO Global Consultations on Regulatory Requirements for Xenotransplantation Clinical Trials,40,41 do not specifically address children. A 2023 report from a National Heart, Lung, and Blood Institute workshop on xenotransplantation ethical considerations does address children but does not address how pediatric patients for xenotransplantation should be chosen.42 However, in the report by the International Society for Heart and Lung Transplantation (ISHLT) in 2000, the Xenotransplantation Advisory Committee stated that “The disproportionately high mortality for infants on the waiting list, particularly those with ductal-dependent physiology who have very limited life expectancy, provides a compelling reason not to exclude these patients from consideration.”43 Importantly, the limited ethical recommendations that have been offered are not empirically grounded from pediatric population studies, but rather derive from existing research ethics frameworks and/or empirical work completed in adult xenotransplantation particularly in kidney.

*2.2 Pediatric Recipient Selection*

After heart allotransplantation, age-related survival is better in neonates and infants relative to older children and adults after heart allotransplantation. In a report from the registry of the ISHLT—the largest source of worldwide heart transplant data—median survival for infants who underwent heart allotransplantation was 22.3 years, which is longer than any other age group.44 Hence, the longer cardiac allograft survival of neonates and infants has stimulated optimism that cardiac xenotransplantation may work best in this population.9,27 It has been suggested that severe cardiac failure in infants may represent a scenario in which cardiac xenotransplantation could be ethically defensible.27

Irrespective of age within the pediatric spectrum, it is important to try to estimate a risk/benefit balance with the selection of initial candidates for cardiac xenotransplantation. The ideal candidate will still have the possibility to clinically benefit from a xenograft: sufficiently critically ill to justify taking an unknown risk of early graft failure, but with sufficient physiologic resilience to tolerate the surgery and related treatments, and no viable therapeutic alternative. We imagine that the xenograft may initially be used as a bridge until a matching allograft becomes available. Importantly, MCS use in pediatric patients itself is constantly evolving and thus how MCS alternatives or MCS and xenotransplantation use in concert may develop may be dynamic and will require ongoing re-evaluation. As MCS options evolve, the beneficence and non-maleficence evaluation of xenotransplantation as an alternative may change. Nonetheless, some patients for whom MCS is a poor option due to anatomical limitations could likely benefit from xenotransplantation.

Criteria for selecting pediatric patients as candidates for cardiac xenotransplantation need to be established. One model that could be followed by an Institutional Review Board (IRB) considering a xenotransplantation study would be to submit the case to external review following a similar process for approval for compassionate use devices. The field of pediatric cardiac xenotransplantation is nascent and so a community must be established from which to draw expert opinion and consensus. From that community, two independent physicians in a field of relevance to pediatric cardiac xenotransplantation (pediatric heart surgeon, pediatric cardiologist, pediatric cardiac critical care intensivist) from different institutions should review the patient and provide a written letter that verifies that the potential candidate has exhausted his/her clinical alternatives and could potentially benefit from the xenograft and demonstrates a favorable risk-benefit profile.

Furthermore, as for xenotransplantation in adults, minimum and ‘optimal’ sets of gene edits for a pig heart donor need to be evaluated, the optimal recommended size and acceptable size range of the heart for various clinical circumstances must be determined, and the immunosuppressive treatment regimen to be used for the xenograft recipient will need to be defined. The principles of beneficence (i.e., risk-benefit; benefit to the individual patient; benefit to society) and justice (i.e., how the clinical trial is justified; how the inclusion/exclusion criteria are justified)—important in any biomedical research—must be applied in a deliberate fashion, include multidisciplinary stakeholder perspectives, and provide independence from any singular biotechnology company.

Selection of candidates who are unlikely to benefit due to noncompliance, frailty, or medical comorbidities will constrain our ability to evaluate the efficacy and therapeutic potential of xenotransplantation. Evidence of harm to the recipients, from known or previously unknown infections or from failure of the graft, would be devastating to further progress and subsequent public and regulatory approvals, especially if the early participants include ‘vulnerable’ children and these risks could have been discovered in adults.

*2.3 Informed Consent*

In 2004, the DHHS Secretary’s Advisory Committee on Xenotransplantation (SACX) issued draft guidelines on informed consent in clinical research involving xenotransplantation. SACX holds that “as a general matter, children should not participate in xenotransplantation protocols,” citing (i) that xenotransplantation is in very early experimental stages, and (ii) that lifelong medical monitoring will be required of all xenotransplantation research participants.45 SACX does provide an 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. SACX concluded that additional study of these points was needed. Since 2004, xenotransplantation has made significant scientific advancements specific to the pediatric population, yet no updated guidelines for pediatric consent exist.

The safety and efficacy of the initial pediatric cardiac xenotransplantation trials will be speculative until such trials are completed and analyzed. However, the hoped-for patient benefit and avoidance of predictable harms, which will be necessary to establish a favorable benefit-to-risk ratio relative to other available treatments, may not be demonstrated in the first patients. Based on preclinical results and initial clinical experience in the decedent model and in 2 pig heart recipients, we predict that the risks from early graft failure and adventitious infection during a pediatric heart xenotransplantation trial are likely greater than ‘minimal’ to inform our recommendation regarding the DHHS category that should guide the protocol review process for studies in children. Under 45 CFR 46.407, research that may help in “understanding, preventing or alleviating a serious problem affecting the health or welfare for children, and that doesn’t meet the other children’s risk level categories”, is allowable.46 Under this section, the importance of adhering to sound ethical principles and of obtaining child assent and parental consent is affirmed. Of note, child assent may differ by site, but it would not be possible in children younger than around 7 years. Under §46.407 the DHHS Office for Human Research Protections (OHRP) may review the request and will notify the institutional review board if they agree with the determination. In addition, the FDA is notified since their regulations will also apply due to the use of an investigational product (the pig organ is categorized as both a device and a drug under current regulations). OHRP in coordination with the FDA must then organize a “consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law).” After allowing for public review and comment, it will be determined if the research can be approved.

The difficulties for informed consent in xenotransplantation in adults have been discussed elsewhere.47,48 In adults, a significant issue complicating the consent process centers on whether xenograft recipients should be able to withdraw from the rigorous post-transplant monitoring requirements, with differing viewpoints, recommendations, and considerable lack of consensus, revealing the complexity.49-51 A surrogate for the pediatric patient will be required to consent for the initial surgical procedure as well as any subsequent xenozoonotic disease monitoring.52 Monitoring might be required for life, which could take the form of periodic blood tests, imaging, and graft biopsies. If lifelong monitoring is required, this creates a scenario in which a pediatric xenograft recipient who never consented to xenotransplantation and its attendant mandatory monitoring would be required to continue being monitored into adulthood. Monitoring xenograft recipients for infectious disease has been a contentious issue within xenotransplantation, with no consensus on whether, or how, to do this.47,50,53 Whether effective and complete monitoring is even possible is an open question. In addition to required monitoring for the xenograft recipient, recommended monitoring for third parties, such as caregivers and close contacts may be needed.54

Informed consent, especially in the context of unknown xenozoonotic risks presents a complex question of (i) how to approach consent/assent in the recipient, and (ii) who is an obligated third-party who must consent. More deliberation is needed on these points as well as how best to counsel surrogate decision-makers who must consent on behalf of the recipient. As parent/guardians may be in a desperate state to try any potential means to save their child’s life, great attention will need to be given to ensuring that they understand the research nature of xenotransplantation to avoid therapeutic misconception, the risks (including unknown risks) involved, and the potential need to carry out re-transplantation of the heart at a later time, should the xenograft be utilized only as a bridge or should it fail.

Parents/guardians will need to be informed of the potential effects that participating in initial trials may have on the privacy of their lives and their child’s, including potential implications for health insurance. Industry and researcher influence and interests must be divested completely from the consent process. As parents/guardians may be overly trusting of the recommendations of the treating physician(s), it may be wise to have consent obtained by another qualified individual who is not participating directly in their child’s care.

Lastly, we should not assume that the OHRP, FDA and IRBs are familiar with applications for research under 45 CFR 46.407, as they are rare. Agencies should be certain that reviewers are educated and prepared for this type of research application within these agencies. DHHS should also consider convening a multidisciplinary panel of experts who can judge the science and ethics of pediatric cardiac xenotransplantation clinical trials as applications arise. As mentioned above, one company has already announced that it hopes to initiate a pediatric cardiac xenotransplantation clinical trial in 2024. Establishing a plan for who might comprise such an expert panel, and how protocols and research documents will be reviewed to protect pediatric (and adult) human subjects, would be prudent.

*2.4 Psychosocial and Public Perception Considerations*

 Psychosocial risks to the patient, family, and caregivers merit consideration before pediatric xenotransplantation is undertaken, and careful monitoring after xenotransplantation clinical trials are initiated. Potential stigmatization may be encountered by xenograft recipients in the schoolyard or later in their life. This concern was voiced in focus groups on xenotransplantation particularly by parents of children with CHD.55 Another study found that parents are concerned that, if their child is a pig heart recipient, this might change how other people view or interact with the child; this would have psychosocial implications and impact the child’s social life.55 Current perceptions of inert pig tissue such as heart valves appears not to manifest in this way; however an entire organ with the concomitant attention in the media makes xenotransplantation unique. Pediatric patients are particularly vulnerable to social isolation, insecurity, anxiety, shaming, and post-traumatic stress; anticipating these vulnerabilities and providing focused emotional and spiritual support would be prudent to detect and minimize the impact of these predictable psychosocial risks.

These concerns about stigmatization of children with pig hearts are greatly decreased if the pig heart is implanted in infancy simply as a bridge to cardiac allotransplantation. In the USA, under these circumstances the pig heart is likely to be replaced by an allograft within 4-8 months, and so children will unlikely be at risk of stigmatization. Their peers, and even the child, may be unaware that they had ever been the recipient of a life-saving pig heart.

As for allotransplantation and potential kidney xenotransplantation candidates, psychosocial support services (social workers; counselors; psychologists; chaplains) should be offered to parents/guardians at all times. It will be necessary for parents/guardians to undergo psychosocial evaluation to assess their: (i) emotional wellbeing, (ii) health literacy, and (iii) understanding of the risk-benefit ratio and the implications for their child.

In 2008 the World Health Organization (WHO) recommended that xenotransplantation clinical trials and procedures need effective regulation due to potential community risks that may present from xenozoonosis. The WHO recommended that: “The regulatory system should be transparent, must include scientific and ethical assessment and should involve the public.”40 Indeed, the public should be involved in assessing the regulatory system for xenotransplantation, and we believe it has an even wider role in accepting its development. To date, only limited viewpoint studies of the public’s attitudes toward xenotransplantation have been published.56,57 Viewpoints of adult patients who may benefit from xenotransplantation—such as those on dialysis awaiting a kidney transplant—have only been minimally studied.56 The empirical data on viewpoints of pediatric heart patients who may need a cardiac xenotransplant and their parents or guardians of pediatric patients are especially sparse.55,58

In two studies of pediatric cardiac surgeons, pediatric transplant cardiologists, pediatric cardiac nurses, and parents of children with CHD, acceptance of xenotransplantation was high as long as xenotransplantation had similar outcomes to allotransplantation.58,59 Acceptance fell if results were anticipated to be inferior to those of allotransplantation. More viewpoint studies, especially of key stakeholders, will reveal important attitudes about xenotransplantation, concerns and reasons for hesitancy, and how these may be mitigated.

**Recommendations:**

1) A national (e.g., FDA, European Medicines Agency) and/or international (WHO) regulatory body, with input from scientific (e.g., National Institutes of Health), regulatory (FDA), and professional societies (e.g., International Xenotransplantation Association, The Transplantation Society, American Society of Transplantation, American Society of Transplant Surgeons) should form a multidisciplinary group of essential stakeholders (clinicians, ethicists, social workers, parents/guardians of children with CHD) to parse the issues at stake, identify pediatric CHD patients who are medically and ethically appropriate to participate in initial xenotransplantation activities, and how best to study them.

2) Viewpoint studies with the pediatric CHD population should be undertaken, particularly incorporating the viewpoints of parents and guardians.

3) Public education initiatives, population assessments, and/or xenotransplantation education campaigns should be conducted to gauge and promote public acceptance.

4) Guidelines for informed consent specific to cardiac xenotransplantation in children is needed given the intention of commencing these trials soon. Bystander risk, including a plan of education and/or monitoring for infectious diseases, should be considered.

We believe that interval scientific advances coupled with the results of these four initiatives are likely to provide an ethically sound basis for ‘pilot’ and then IND-qualifying xenotransplantation trials.

**Limitations:**

Additional considerations in xenotransplantation (e.g., the ethics of the use of animals) are beyond the scope of this manuscript.

**3. Conclusions**

Xenotransplantation is an advancing field with potential to alleviate the shortage of organs needed for transplantation. Pediatric CHD patients, particularly infants, may potentially benefit from this clinical alternative by better aligning availability of a graft with clinical need, reducing mortality while waiting, increasing utilization of available human donors, and thus decreasing the morbidity and mortality associated with the current organ shortage among children with end-stage heart failure. Ensuring the clinical success of xenotransplantation involves not only medical and scientific advances, but also due attention to the ethical issues discussed here, particularly in relation to this vulnerable patient population. Our recommendations are designed to strengthen the ethical foundations for pediatric cardiac xenotransplantation, and we suggest should be acted on prior to initiating clinical trials.

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**Table 1: Recommendations to consider regarding pediatric cardiac xenotransplantation clinical trials**

|  |  |  |
| --- | --- | --- |
| **Topic** | **Item(s) to consider** | **Recommendation(s)** |
| **Proceeding with pediatric cardiac xenotransplantation prior to adults and regulatory considerations** | -Should we wait until safety and efficacy is established in adults? Or, because of the need for improved or additional therapeutic options in children and their mortality while on the waitlist, can we begin with infants and children prior to adults?-Withholding a potential beneficial option for anyone is unethical. It may take too long to conduct clinical trials in adults before producing results to advance to clinical practice. Few cases justify the use of cardiac xenotransplantation due to existing clinical alternatives for adults.-Results from adult cardiac xenotransplantation clinical trials ultimately may not generalize to children due to biological differences. | -Guidance specific to cardiac xenotransplantation in children should be drafted/updated. Guidance should contain minimum requirements (scientific, regulatory, etc.) that are needed to satisfy that a sufficient benefit-to-risk ratio has been reached to begin trials in children. |
| **Pediatric patient selection** | -Principles of beneficence (benefit to the patient; benefit to society) and justice (justification for a particular inclusion/exclusion criteria) will have to factor into discussions of patient selection.-Several details outside of undergoing the procedure itself will also require examination. For example: selection of pig and size-matching of organ for the recipient and immunosuppression regimen. | -Patient selection inclusion and exclusion criteria need refining.-Deliberation should take place from a multi-stakeholder perspective rather than that of a singular biotechnology company.-Centers participating in clinical trials should identify appropriate pediatric candidates and submit the case to outside review following a similar process for approval for compassionate use devices. External review should verify in writing that the potential candidate has exhausted their clinical alternatives and could potentially benefit from the xenograft and demonstrate a favorable benefit-to-risk profile. |
| **Informed consent** | -Guidelines on informed consent for cardiac xenotransplantation in children are lacking.-Procedures for properly obtaining consent from parents/guardians and assent from child when able to assent.-Assurance that parents/guardians have weighed the benefit-to-risk ratio for their child as a heart xenograft recipient. | -Xenotransplantation has made significant scientific advancements specific to the pediatric population. Guidelines for informed consent and the process specific to cardiac xenotransplantation in children is needed given the intention of commencing these trials soon.-Assure that OHRP, FDA and IRBs are prepared and aware of procedures regarding 45 CFR 46.407.-DHHS should consider establishing a multidisciplinary panel of experts who can judge the science and ethics of pediatric cardiac xenotransplantation clinical trials as applications arise. |
| **Psychosocial and public perception considerations** | -The long-term psychosocial outcomes of xenotransplantation are unknown. Previous studies have shown concerns from parents. Potential stigmatization may be encountered by xenograft recipients throughout their life. | -Parents/guardians should undergo psychosocial evaluation to assess their: (i) emotional wellbeing, (ii) health literacy, and (iii) understanding of the risk-benefit ratio and the life-long implications for their child.-Parents/guardians should be informed during pre-surgical consults of the potential for social stigmatization/bullying towards the recipient. -More viewpoint studies are needed to examine attitudes, hesitations, concerns, and how to mitigate these so that cardiac xenotransplantation in children may succeed from a parental and societal perspective if it were to become available as a clinical option. |