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Title: Governance, Regulation and Public Trust in Xenotransplantation

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Structure Abstract

Purpose of review

Across the world, several solid organ xenotransplants have been reported as being provided to deceased people and to living patients. In the US, xenotransplants to living patients have been authorised under the Food and Drug Administration's Expanded Access program, and clinical liver and kidney xenotransplants have also been reported in China. During 2025, the first clinical trials of kidney and liver xenotransplants have been approved in the US. These developments make it necessary to understand the regulatory and governance issues and challenges raised by clinical xenotransplants.

Recent findings

Key regulatory and governance issues remain to be addressed before xenotransplant clinical trials begin, including identifying the responsible regulator, drafting informed consent protocols, and establishing long-term monitoring regimens. International cooperation and collaboration are key to establishing appropriate and effective regulatory regimes and frameworks which enable science to proceed while offering the necessary protections to those involved. Public awareness, education and trust are central to the success of clinical xenotransplantation.

Summary

Starting xenotransplant clinical trials too soon without appropriate regulation and governance, may affect public trust in this biotechnology specifically and science more generally. The possible risks of xenotransplantation necessitate exploration of global harmonisation and regulatory frameworks for clinical xenotransplantation.

Keywords

Clinical xenotransplantation, regulation, law, governance, public trust,

Introduction

During this decade, the long-anticipated move of xenotransplantation from the lab to the clinic may come to fruition, following significant advances in gene-editing techniques [1]. In preclinical studies in China and the US, genetically modified pig solid organs have been xenotransplanted into people who have been declared brain dead (the 'decedent model') [1-6]. Living patients have also received genetically modified pig hearts, livers and kidneys in China and in the US [1,4-5,7-8]. In 2025, the US Food and Drug Administration (FDA) approved the first kidney and liver xenotransplant clinical trials [8-10].

This review discusses regulatory and governance matters raised by human preclinical and clinical xenotransplants, including clinical trials. Access and patient selection, consent and information, infection risks and monitoring are considered. Monitoring is likely to extend beyond the xeno-recipient, to family members and close contacts, raising additional issues. To secure public trust in xenotransplantation specifically, and science more broadly, public engagement, awareness and understanding of this emerging biotechnology is considered [1].

Preclinical xenotransplants to deceased patients

The decedent model was developed because of difficulties in conducting safety and efficacy studies of genetically modified pig organs designed for humans in non-human animals [2,11]. Such research is not formally regulated in the US as institutional review boards are only concerned with research involving living humans [2,12-13]. Cognisant of concerns that might be raised by this research, some centres in the US established their own committees to assess

and review the research [2,12]. In China, brain death is medically but not legally recognised as a basis for declaring death and so the decedent model is even more controversial [14]. Whole body donation for research purposes is also not covered by existing legislation but may be permissible with the written consent of the surviving spouse, adult children and parents [14]. The legality of decedent research must be ascertained wherever it is proposed [14], and such research raises ethical questions too [15-16].

The suitability and reliability of the decedent model has been questioned because of the physiological changes which follow brain death, and the limited times available for monitoring and studying the recipient post-xenotransplant [3,17-18]. Data collected might thus not translate to clinical xenotransplants and so be of limited use to researchers and regulators [21,19]. Other models, including humanized non-human animals and organoids, might be more useful in preclinical studies [3].

To preserve public trust in donation practices, research and health care as a whole, if the decedent model is to be used for preclinical xenotransplants matters to be considered include responsibility for regulation and oversight, responsibility for maintaining the deceased's body during the study, the duration of the research, infection prevention and control, information disclosure and seeking authorisation for whole body donation [12-13]. The views of all stakeholders are essential to ensure that ethically appropriate research involving deceased people is conducted, overseen by a suitably composed committee [13].

Preclinical xenotransplants to living patients

By August 2025, all clinical xenotransplants performed in the US have been approved under the FDA's Expanded Access pathway (also known as compassionate use). To qualify for this,

the patient must have a serious or life-threatening illness, there is no comparable or satisfactory alternative, and there is a favourable benefit-risk ratio for the patient [20]. Accessing xenotransplants in this way offers a chance of increased life expectancy, but the pathway may be being misused, with data being collected as a precursor to clinical trials [20-22]. Xeno-recipients under this pathway could be equivalent in number to those who could be included in a phase 1 clinical trial, but the xenotransplants are not provided within the regulatory framework and mandatory safeguards provided for clinical trials. There is also no obligation to publish the results of expanded access xenotransplants [11,20,23].

Information on relevant biosurveillance measures adopted for expanded access xenotransplants have not been routinely shared, although the recipient, close contacts and clinical staff involved in the first living kidney xenotransplant were educated on the biosurveillance procedure [24]. Nevertheless, it is not known how potential individual and public health risks were addressed in other xenotransplants. There are access and equity issues too [25-26], including providing a xenotransplant to someone who had failed to comply with previous medication regimes and was deemed unsuitable to receive an allotransplant or durable mechanical support [21,27]. Greater transparency and explanation from the FDA is essential to ensure public trust in xenotransplantation and the regulatory regimes, including the rationale for authorising xenotransplants under the expanded access program [20].

As with decedent xenotransplant research, data from expanded access xenotransplants might not translate to the clinical trial context because of the medically complex health status of those involved. Furthermore, the results may not be comparable to those achieved in

preclinical research involving non-human primates [25]. Potential xeno-recipients must be told this [28].

Xenotransplant clinical trials

Calls for appropriately designed and regulated xenotransplant clinical trials have followed preclinical research with humans [23,29-32]. The US FDA has approved two xenotransplant clinical trials to start during 2025 [9-10]. Before trials commence, remaining issues include clinical equipoise, risk-benefit calculations, and whether the risks and costs of, and alternatives to, xenotransplantation have been appropriately considered [33-36]. Further preclinical research involving decedents, including children, might also be necessary [37-38].

Effective institutional and governmental oversight of clinical trials is essential [13], with a robust regulatory framework providing important safeguards for potential participants, researchers, sponsors and the wider public. Compliance can be encouraged by appropriate sanctions, such as financial penalties, suspension or termination of the trial. Transparency will help to increase public trust in xenotransplant clinical trials, including recording and timely sharing information on the trials, their results and public health concerns [13,40].

Such frameworks are not universal and at least two clinical xenotransplants have been performed in China [4]. There is no expanded access program in China, and the regulatory framework, if any, under which these surgeries were performed is not known [41]. Regulatory oversight, including ethical review, is required in any country seeking to perform clinical xenotransplants [32,41], and the government will have a role in funding the research and leading on the development of standards, guidelines, rules and policies [41].

The proposed clinical trials highlight regulatory and governance issues regarding access and selection, consent and information, and infection risks and monitoring.

Clinical trial selection criteria

Selection criteria and staged trials are ways of engineering equity into xenotransplant trials [39], which is a well-noted concern [1,11,13,37,42-43]. A wider range of less seriously ill patients will be eligible for inclusion in the FDA approved clinical trials than under the expanded access pathway [9-10]. Six patients will initially be enrolled in the kidney trial [9], and an external pig liver will filter the blood of four patients will for 72 hours over two weeks [10]. Each trial will be paused to allow the results to be reviewed by monitoring committees and may subsequently be expanded to include up to 50 kidney recipients [9] and 20 liver participants [10]. The liver trial will have two stages, with safety data reviewed after the first two recipients' blood has been filtered, and another review after the second two [10].

Criteria for providing allotransplants as treatments are well-established but may not be relevant to xenotransplant clinical trials [11,37]. The inclusion of those with diminished capacity [44] or under 18s in xeno-clinical trials is contested [11,26,29,37,45-49]. Proposed criteria for cardiac xenotransplant trials include medical need, the ability to benefit, patient choice, and expected compliance with post-xeno regimens [47,50-54]. Selection criteria are legally, ethically and medically important. Outcomes can be affected, and scientific advances possibly delayed, if only those with limited chances of benefit [11,26,37] or 'healthier' recipients are included in trials [55].

Consent and information in xenotransplant clinical trials

Consent to involvement in, and information about, a clinical trial are common legal requirements. Providing relevant information may be challenging as much is still unknown about clinical xenotransplants in terms of rejection, infection risks, and there may be unforeseen complications too [1,35]. These are matters that must be addressed in the consent process [28,56]. Information on infection control measures will also be needed in the trial protocol and shared during the consent process.

Attention should be paid to who recruits potential xeno-recipients and obtains consent because of possible conflicts of interest [37]. Time will be needed to explain the information, and for potential xeno-recipients (and others) to consider and understand it [56]. The amount of information and detail potential xeno-recipients might want should not be underestimated [56], as knowledge of xenotransplantation may be limited, including amongst kidney transplant recipients and candidates [57]. Information on alternatives, including palliative care, will be important [11,53]. Uncertainty about the risks and benefits of xenotransplantation may make it harder to meet the legal and ethical requirements for 'informed' consent [11]. Information provision to health professionals involved in xeno-clinical trials also needs careful consideration, and some may have a conscientious objection to being involved [58].

Linked to the selection criteria for a clinical trial, is the question of whether a seriously ill potential xeno-recipient can give their informed consent to participate [40,43]. Specifically, whether their consent can be voluntary if they have no other alternative is debated [21,37,43,47,51-52,59-60], and such patients are in a particularly vulnerable position. The health status of a potential xeno-recipient may affect the voluntariness of their decision and may make them less risk averse and more open to therapeutic misconception or optimism

[28,60-61]. Some patients on the waiting list for a kidney allotransplant have recognised that they might feel pressured to agree to participating in a xeno-clinical trial if no other choice is available to them [59-60]. As first-in-human clinical trials are necessary but inherently risky, paying participants might address some of the ethical concerns regarding their involvement [62].

Monitoring post-clinical trial

The nature and extent of post-xeno infectious risks remain unknown [63], but it is agreed that the source non-human animals will need to be bred in particular conditions and monitored [27,63-65], and some form of long term (possibly lifelong) monitoring of xeno-recipients will be required [1,27,30,35,66]. Remaining questions include what this monitoring will involve, who will undertake it, and how long it will be required [55]. Details of the monitoring after the two FDA approved xeno-trials are limited, but the kidney recipients will be monitored for about six months, with lifelong follow up [9], and the liver recipients will for a year [10].

An important legal and ethical concern with long-term monitoring is that participants have the right to withdraw from a clinical trial. The need for post-xenotransplant monitoring challenges this right [13,37,45,60,67-69]. Ulysses contracts (also known as advance directives or advance decisions) have been proposed to ensure compliance with monitoring, but their efficacy will depend on enforcement which will require both resources and legal authority [27,45,67,70]. The legality of enforcing necessary monitoring is unclear and jurisdiction specific. Public health laws tend to require confirmed illness relating to specific communicable diseases rather than mere potential for infection [66-68].

Monitoring of family members and close contacts (including involved health professionals) is likely too, raising additional legal and ethical questions and concerns [27,67,71]. It should not be assumed that potential recipients will accept a xenotransplant if this means that their family members will also be monitored [28]. At a minimum, family members and close contacts will need to be educated about the risks of a xenotransplant clinical trial [13,24,71-72]. Whether their consent or assent to the risks of xenotransplantation is also required remains at issue [13,71], but if they are to be subject to any form of monitoring their consent will be needed. A particular issue with paediatric xenotransplantation is that children may put more people at risk because they are likely to come into contact with a wider selection of people as they grow up than [45]. The legal ability of parents to consent to long-term (possibly lifelong) monitoring for their child is unclear [45,49].

Global harmonisation of regulations and governance

The global regulatory landscape is complex and there is a myriad of legislation, regulations, guidelines and guidance which may apply to clinical xenotransplants, depending on the relevant country or region [4,30,35,41,50,73-76]. The International Xenotransplantation Association (IXA) has produced guidelines, but these have no legal force, compliance with them is unknown, and their effectiveness is unclear [30,50]. An update of the WHO and IXA's Changsha Communique is proposed, including an expert review of existing guidelines [30].

Global harmonisation of regulatory frameworks can encourage collaboration and coordination of trials, prevent unnecessary delays, and enable multinational trials [1,30,41,50,73,77]. It might also result in sharing best practices and treatments, aid the cross-border supply of xeno-organs, and the acceptance of trial results [1,30,41,50,73,77].

Regulatory harmonisation may foster public trust and help protect public health as it can ensure that there are safeguards to protect the recipient, close contacts, and the wider public from the potential risks of infection [1,35]. The World Health Organization (WHO), International Xenotransplantation Association (IXA), and Transplantation Society (TTS) are well placed to lead on harmonisation, streamline international approval processes, ensure equitable access to xenotransplant clinical trials, and evaluate safety, efficacy and infection risks [1,27,30,39,54,71,73,76,78]. An IXA Clinical Trial Advisory Committee, supported by the TTS, could be established to advise and direct clinical trials, and provide up-to-date information for institutions and regulators considering clinical trial applications [73].

A global registry of xenotransplant procedures, accessible to all researchers (and possibly the public too [79]) is important [1,30]. This could be a new registry, or an expansion of the IXA's registry to include information on the source of the organ, the recipient of it, and the type of immunosuppression used, as well as information from the Global Observatory on Donation and Transplantation [30,80-81]. Any registry must be appropriately financed and supported [30,81]. Transparency will be critical.

Cultural nuances and religious and faith differences regarding the acceptability of xenotransplantation may make global harmonisation harder to achieve [66,78,82-83]. Health infrastructures differ across the globe, and allotransplantation is not routinely accepted in all countries [66]. It should not be assumed that 'one-size-fits-all' or that accepted norms in the Global North necessarily translate to the Global South. The significant commercial interests at play in xenotransplantation might also mean that it is harder to establish a consensus [41]. Global legislation might seem a way to prevent xeno-organ trafficking and other

unscrupulous practices [73], but this would be unprecedented and difficult (if not impossible) to draft, implement and enforce.

Public engagement and trust

Public engagement can help to foster public trust and societal acceptance of xenotransplant clinical trials, and create flexible, adaptable and effective standards [1,13,26,41,72,77,84]. Dialogue with stakeholders is necessary because of differences in scientific perceptions and societal ethical standards, and religious beliefs might affect attitudes to xenotransplantation [11,13,26,58,66,73,78,82-83,85-89]. Diverse representation is critical for effective public engagement, with a range of voices heard and influencing decision-making [30,39,66,79]. Ideally, proactive public consultation, engagement and education would precede clinical trials [30]. Health professionals should be educated too, as some may not be as knowledgeable about xenotransplantation as might be assumed [85,90].

Conclusion

Clinical xenotransplantation raises complex regulatory and governance questions and further consideration of these matters is required [22,91]. Starting xenotransplant clinical trials without public education, consultation and engagement, as well as research on attitudes to xenotransplantation [27,92], may affect societal acceptance of this biotechnology and its attendant risks.

Global harmonisation of regulatory frameworks is vital for the conduct of safe and effective trials. Further work on the costs of xenotransplantation as compared to allotransplantation is important [27,93], as well as on the wider effects of xenotransplantation on healthcare systems and health inequalities more broadly [87,94].

Key points:

- Despite the imminence of xenotransplant clinical trials, key regulatory and governance issues remain outstanding.
- Global harmonisation is essential to secure public trust in xenotransplantation and to help to protect public health.
- Public engagement, consultation and awareness is needed prior to the start of xenotransplant clinical trials.

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