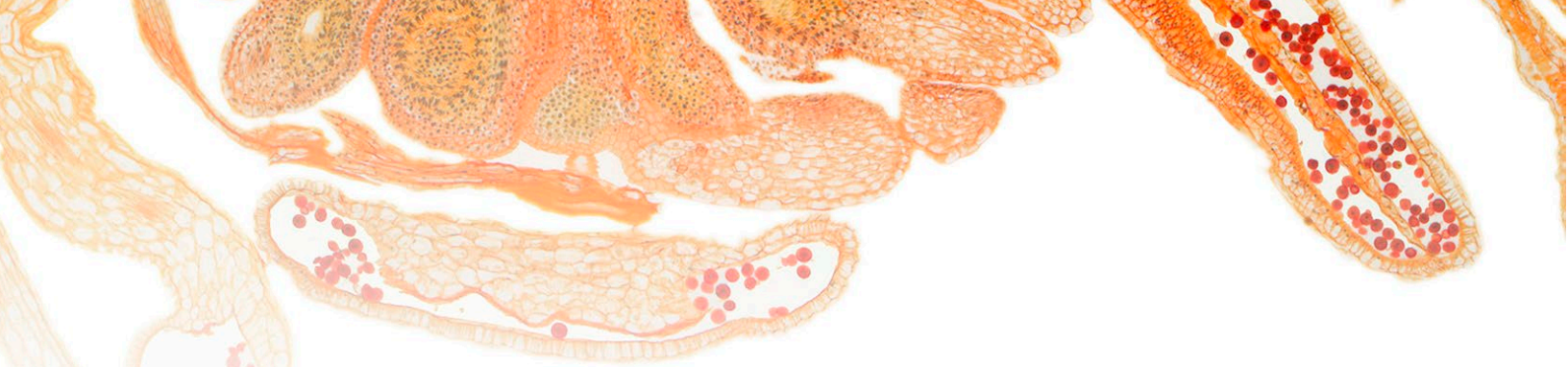

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POLICY FORUM: PEER-REVIEWED ARTICLE

Should Xenotransplantation Surgeries Be Authorized Under the Food and Drug Administration's Expanded Access Pathway?

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Abstract

This article examines use of the US Food and Drug Administration's (FDA's) expanded access pathway to permit cardiac xenotransplants. This article first argues that, although data are collected from cardiac xenotransplant surgeries authorized through the FDA's expanded access pathway, uses of preclinical trial data do not align with the FDA's stated aims of expanded access. This article also argues that potential risks of xenotransplantation merit greater caution than risks posed by devices and that it is unclear how caution about such risks is regarded and operationalized during the FDA's expanded access authorization processes.

Risk, Data, and Expanded Access

We are concerned about the use of the US Food and Drug Administration's (FDA's) expanded access pathway to permit 2 recent cardiac xenotransplants. We argue that (1) preclinical trial data are being collected from these uses as a precursor for clinical trials, which does not align with the FDA's stated aims for expanded access, and (2) the potential public health risks associated with xenotransplantation merit greater caution compared to other medical devices; it is not clear how precautions are being applied under the expanded access authorizations to date. Importantly, our concerns are not with the acceptability of the expanded access pathway per se, but only with its use for the specific practice of xenotransplantation. The FDA should clarify its rationale for and use of these one-off xenotransplant authorizations.

Compassionate Use of Xenotransplantation

In January 2022, a team of clinicians and researchers at the University of Maryland Medical Center transplanted a genetically modified pig heart into a severely ill patient, David Bennett Sr, in an operation that was granted emergency authorization through the FDA's expanded access, or compassionate use, for implanted devices program.[1,2] This program grants patients and clinicians access to experimental devices, and, between 2018 and 2022, more than 99% of the device requests evaluated were accepted.[3] To qualify for compassionate use, 3 conditions must be met: "(1) the patient has a life-threatening illness; (2) there is no therapeutic alternative; and (3) the benefit-risk ratio is favorable."[4] Mr Bennett was 57 years old with end-stage heart failure and on

venoarterial extracorporeal membrane oxygenation support (condition 1). Because of a history of prior medical nonadherence, he was deemed ineligible by 4 organizations for a heart allotransplant (condition 2). With no other clinical options and death imminent, his clinical team considered heart xenotransplantation to be the most promising option (condition 3). Despite the xenograft, Mr Bennett began deteriorating suddenly 49 days after transplantation, and he died 11 days later.[1]

Now it has come to light that the same team transplanted a genetically modified pig heart into another severely ill patient, 58-year-old Lawrence Faucette, on September 20, 2023, under the same FDA provision.[5] Faucette had end-stage heart disease, and, due to preexisting peripheral vascular disease and other comorbidities, he was deemed ineligible for a heart allotransplant. Because he was experiencing symptoms of heart failure and deemed ineligible for an allotransplant (conditions 1 and 2), the team considered cardiac xenotransplantation to be the most promising option (condition 3). However, similar to the outcome in the first heart xenotransplant, Faucette died just 6 weeks after transplantation on October 30, 2023.[6]

For someone who meets eligibility criteria, participating in the expanded access program can be a welcome opportunity, and there is considerable public support for the program.[7] The families of both cardiac xenograft patients expressed a sentiment that the extra days with their loved ones meant incredibly much to them.[8] However, we need to ask whether the FDA is using the expanded access pathway as a proving ground for xenotransplant phase 1 clinical trials.[4] As yet, there are no formal cardiac xenotransplantation clinical trials under consideration, and the FDA states that, despite recent advances, "more studies are needed to ensure safe and effective xenotransplantation,"[9] which suggests that the FDA is looking for more preclinical and decedent data to justify approving formal cardiac xenotransplant trials. David Cooper has written that before formal cardiac xenotransplant clinical trials can begin, "consistent survival … needs to be achieved."[10] It is unclear what the benchmarks are that should be met for approving a cardiac xenotransplant clinical trial, but this much is clear: although the expanded access program allows "devices that are not being studied in a clinical investigation" to be used, the program is not intended to be a proving ground, or a de facto clinical trial.[11] That is, expanded access is not envisioned as a pathway for providing evidence of efficacy and/or safety to initiate a clinical trial. And yet, in the absence of cardiac xenotransplant clinical trials, it seems as though it is being used in this way.

This use of the expanded access pathway for xenotransplantation is troubling. If several heart xenotransplants are permitted via the expanded access program that would be equivalent to the number of participants acceptable for a phase 1 trial, then the reasons for not permitting a formal clinical trial are prima facie redundant; the expanded access program could potentially end up being used as a de facto clinical trial in violation of the spirit of the expanded access program. Let's suppose that the FDA does not permit a phase 1 trial within the next 5 years but that several more cardiac xenografts are permitted via the expanded access program. While the data gained would be valuable, they would not be equivalent to those obtained from a phase 1 trial. Because equivalency will depend on the entry criteria used for a clinical trial, the expanded access and clinical trial patient groups could be dissimilar: Bennet and Faucette were both medically fragile, leading to the question of whether this preclinical use data will support clinical trials. Regardless, there must be a threshold achieved whereby either no more compassionate access uses should be permitted or formal trials must be initiated.

Perhaps this is the FDA's plan: once *x* "compassionate uses" have been permitted or *y* results have been achieved, these data would count as sufficient evidence to justify initiating phase 1 clinical trials.

This leads to our second point that there has been a general lack of transparency regarding the use of the expanded access program in the context of cardiac xenotransplantation, which may present a public health risk. The FDA's guidelines and information for the public emphasize the risk to public health through possible zoonotic infection and the requirement for lifelong biosurveillance of xenograft recipients,[12,13] and yet, in both of the compassionate use cases, it remains unclear how public health was being protected, as the transplant teams have not disclosed this information. We therefore recommend greater transparency from the FDA regarding the criteria it is seeking before approving a cardiac xenotransplantation clinical trial,[4] clarification on why expanded access has been the approved mechanism for cardiac xenotransplantation to date, and greater transparency regarding public health protection, such as biosurveillance protocols for xenograft recipients and possibly their close contacts. By clarifying its rationale for and use of these one-off xenotransplant authorizations, the FDA can help advance the field.

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Conflict of Interest Disclosure
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