Research Ethics: Must Subjects Waive the Right to Withdraw from a Xenotransplant Clinical Trial?

Ana S. Iltis, PhD,¹ Henry J. Silverman, MD, MA,² Robert M. Sade, MD³

¹Wake Forest University, Department of Philosophy and Center for Bioethics, Health and Society, Winston-Salem, NC
²University of Maryland, School of Medicine, Department of Medicine, Baltimore, MD
³Medical University of South Carolina, Department of Surgery, Division of Cardiothoracic Surgery, Charleston, SC

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Corresponding Author: Robert M. Sade, MD
Distinguished University Professor
Professor of Surgery
Medical University of South Carolina
30 Courtenay Drive, MSC 295
Charleston, SC 29425-2950
robert.m.sade@gmail.com; 843 876 0182 (office); 843 345 0480 (cell)

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Central Picture Legend: An infectious agent could be transmitted from pig to human.

Introduction

Robert M. Sade, MD

The advent of cardiac xenotransplantation has reinvigorated controversies engendered by animal-to-human transfer of living tissue. Among those controversies is the long-term potential for zoonotic infection that could lead to a public health crisis. Zoonoses have led to crises such as an epidemic (e.g., human immunodeficiency virus) or pandemic (e.g., severe acute respiratory syndrome-coronavirus 2). The risk of a serious zoonotic disease arising from swine-to-human transplant that could lead to a major public health problem is believed to be small but real, and could arise at any time. Lifetime surveillance of research subjects who receive a heart transplant from a pig is believed to be necessary, but how can such follow-up be ensured? One possibility is to require potential subjects to sign a waiver of the right to withdraw from surveillance, but this would conflict with the fundamental ethical requirement of freedom to withdraw from a study at any time. This question was explored in a debate between two scholars: a philosopher-ethicist, Ana Iltis, and a physician-ethicist, Henry Silverman, focusing on the following vignette.

Case: A Problem of Consent

Transplant surgeon Dr. Fern Zuckerman has finally received clearance from her department chair and the hospital’s medical executive committee to proceed with a clinical investigation of cardiac xenotransplantation. She has worked in her laboratory on a pig-to-primate model and feels confident that her program is ready to move into a clinical trial. In developing the informed consent form, however, she is uncertain how to deal with the problem of zoonosis risk. She is sure that the risk of late transmission of a porcine virus to a graft recipient that produces a transmissible disease with epidemic potential is quite low, but is not zero. Dr. Zuckerman plans to include lifetime virological surveillance of xenotransplant recipients in the study. She is certain that some patients will tire of the surveillance routine after a few years and will fail to appear for their follow-up studies, in essence, withdrawing from the study.

The right to withdraw from a study is a fundamental research ethics principle. The long-term public health risk of a zoonotic epidemic is unknown and is likely very small, but is potentially catastrophic if it occurs. One way to reduce the chance that a recipient will stop participating in
surveillance is to add to the consent form a requirement that the potential subject must waive the right to withdraw from surveillance. Dr. Zuckerman understands that enforcing such a waiver would be problematic, but at least it would put potential recipients on notice that long-term surveillance is a gravely serious expectation. She wonders about a critical issue: would such a requirement even be ethically permissible? She asks two colleagues, who she knows have differing opinions, for their ethical analysis.

**Pro**

**Ana Itis, PhD**

Dr. Zuckerman should require potential xenotransplantation subjects to waive the right to withdraw from long-term monitoring (LTM).

The probability, timing, and scope of harm of xenogenic infection risk (XIR) are unknown. Most experts hold that the risk is low but not negligible, even using animals bred in pathogen-free environments, and that some infections could have years-long latency. Xenotransplantation clinical trials may justifiably and, consistent with national and international guidelines, require LTM for XIR.

Public health and research concern individuals and populations, and both sometimes involve balancing competing interests and rights. Their guiding ethical principles are relevant to xenotransplantation research. Requiring LTM is in tension with the right to withdraw from research that many research ethics codes and regulations stipulate. Public health interventions that are not aimed primarily at individual benefit and that interfere with liberties are justified when the intrusion is proportionate to the risk of harm to be prevented, necessary to prevent it, and the least restrictive effective measure available. Xenotransplantation research involves great uncertainty about potential benefits to participants and risks to recipients and society. Many research ethics codes and regulations hold that risks to participants must be minimized and reasonable relative to the potential benefits to participants and society. They often are silent on third-party risks, and the literature is limited. Drawing on the general obligation to avoid harming others, third party risks should be minimized. Currently, LTM for XIR is necessary to
make the risks to society acceptable and proportional relative to the potential benefits. Over time, new information could make the requirement unjustified or provide greater justification for it. Xenotransplantation research that requires LTM should include routine evaluation of available evidence to assess XIR. Specifying the acceptable risk level and what constitutes sufficient evidence are separate matters. LTM is justified because it is reasonable, necessary, and the least restrictive effective measure to protect public health. A more burdensome and restrictive option, for example, would be to quarantine recipients for long periods or even for life.

Seven possible objections are considered. First, the right to withdraw is absolute and not one that persons may waive, override, or balance because: it is necessary to protect bodily integrity or prevent unwanted intrusions on the body; individuals may not be asked to make irreversible decisions of this sort; persons may not revoke their future freedom or undermine their status as autonomous agents; this right helps individuals to protect themselves from harm; it limits possible abuse or exploitation; uncertainty regarding the risks, burdens, or other aspects of research makes it impossible to give informed consent to long-term participation; or researchers must give participants the space to attempt to avoid terrible outcomes by taking on small risks or burdens. People have the right to make permanent, life-altering decisions that carry risks and burdens, including in some jurisdictions the right to consent to be killed. People have the right to make irreversible decisions that later could become inconsistent with their values, including becoming gamete donors. That is part of the price of autonomy. There are exceptions to sacrosanct, autonomy-based rights, such as the right to refuse treatment. While precisely what may be required of whom and under what circumstances is debated, various guidelines and principles govern these practices.

Second, requiring LTM denies people the fair opportunity to participate in potentially beneficial studies, violating the fair opportunity requirement. The LTM requirement does not unfairly deny access to participation or deny people a benefit to which they are otherwise entitled. People regularly are denied research participation if they are unwilling to meet study requirements, including requirements aimed at protecting others, such as using specific contraception. Requiring LTM does not target any group for exclusion, and it would not result in unfair distribution of potential benefits and burdens of research.
Third, requiring LTM undermines voluntary informed consent. Xenotransplantation candidates have exhausted treatment options and xenotransplantation is their only chance at survival. Forcing them to agree to LTM to access xenotransplantation is exploitative or coercive. People routinely consent to medical care and research participation under similar circumstances. Voluntariness does not require a menu of palatable options but rather freedom from coercion, undue influence, and deception. Requiring LTM is not coercive. It does not involve “an overt threat of harm,” “a threat to put someone below their baseline,” or a threat to violate a person’s rights or a threat that an existing obligation will not be fulfilled for failure to comply with the demands. There is no pre-existing right to participate in xenotransplantation research. As long as the requirement is clearly disclosed, it does not involve deception. It is not exploitative because requiring LTM does not involve taking unfair advantage of participants.

Another concern might be that candidates lack information necessary to consent to LTM. Informational asymmetry regarding the implications of research participation is typical. If this makes consent uninformed, then consent to xenotransplantation itself and to most research and even to much medical care is not informed, which deflates the claim.

Fourth, LTM is unnecessary because the risk of xenogenic infection is low. According to many experts, zoonosis remains a concern and, while the probability is low, the magnitude could be great. Especially on heels of pandemic, substantial disagreement regarding acceptable risk is expected. A related argument is that studies in which participant withdrawal would pose serious concerns should not be done. If withdrawal would not cause serious problems, e.g., because risk of xenogenic infection is low or sufficient LTM for XIR is possible without requiring it, then requiring LTM is unjustified. It remains unknown whether sufficient LTM would occur without a requirement. Given the potentially devastating effects of zoonoses for society, doing everything reasonable to monitor recipients, including sending a strong signal that LTM is critical, might be worthwhile.

Fifth, if LTM is necessary to protect public health, then public health officials will have the authority to monitor xenograft recipients. Researchers need not require it, preserving the right to withdraw while still requiring LTM. Potential mandatory public health surveillance must be
disclosed as part of the informed consent process.\textsuperscript{13} Essentially researchers would be saying that a condition of participation is agreeing to LTM by public health officials, resulting in many of the same objections to the LTM requirement. Furthermore, it is unclear whether public health law in all countries would confer the authority necessary for LTM.\textsuperscript{1,13} If it does not, some might argue that LTM is unwarranted. It is worth considering whether the risks researchers and participants create might be different from the kinds of unavoidable threats that public health law has traditionally addressed and thus might be subject to a higher standard. We also might be understandably skeptical about the capacity of public health systems to monitor for zoonosis effectively or argue that they should not bear the costs and burdens of this monitoring for xenotransplantation research.

Sixth, coordination or enforcement issues render the LTM requirement ineffective.\textsuperscript{22} Many requirements are imperfectly fulfilled, including routine vaccination and taxation, yet we do not abandon them. Enforcement objections sometimes imply that requiring LTM is inappropriate in a liberal society because it would involve aggressive physical force.\textsuperscript{1,24} Enforcement mechanisms are on a spectrum, from sending military or police at one extreme to repeatedly contacting participants when they fail to adhere to monitoring to using clinically acquired biospecimens to monitor for zoonosis. Tactics to foster adherence to LTM should focus on minimizing the risk of withdrawal through improved consent processes, participant selection, persuasion, and incentives.\textsuperscript{23} Nevertheless, enforcement measures proportional to the risk may be appropriate and effective.

Seventh, waiving or overriding the right to withdraw could decrease public trust in research.\textsuperscript{12,16} If so, an alternative is to explore ways of increasing trust. Other aspects of research design also could undermine trust, such as withholding potentially beneficial interventions from some participants, also could undermine trust yet are routine. Furthermore, failure to monitor for risk also could undermine public trust in xenotransplantation research.\textsuperscript{23}

The arguments here are necessarily broad and many questions remain, particularly regarding children. Nevertheless, requiring LTM for XIR is part of an appropriate strategy to minimize risks associated with xenotransplantation research.
Dr. Zuckerman should not require potential xenotransplantation subjects to waive their right to withdraw from long-term surveillance.

A first-in-human pig heart xenotransplantation occurred on January 7, 2022, at the University of Maryland Medical Center. The patient survived for over two months before succumbing to heart failure. This attempt at investigating an alternate source of hearts for transplant provided an opportunity to examine several ethical issues to guide selection criteria for future xenotransplant clinical trials. The ethical issues that need to be considered in such trials include: acceptable risk-to-benefit analysis, appropriate selection criteria, whether patients on the waitlist for an allotransplantation should be eligible for a heart xenotransplant, the conditions for informed and voluntary informed consent, and ensuring equitable access to xenotransplant clinical trials. Another controversial ethical issue regards whether participants should have the right to withdraw without penalty from the clinical trial at any time. The significance of this issue emanates from the expectation that research participants will need to undergo life-long surveillance procedures to decrease societal risks from virulent porcine viruses (zoonosis), which amounts to being in a life-long clinical trial. Therefore, to enhance the protection of society from human-transmitted viral infections, there might be an inclination to condition enrollment in clinical trials on a patient’s promise of fidelity to remain in the research. However, surveillance procedures might be burdensome; hence, participants might desire a right to withdraw at some point in the clinical trial. Undeniably, a recognized ethical requirement of clinical research is that research participants should not be denied their right to withdraw from the study at any time. The right to withdraw from participation in research is recognized in virtually all national and international guidelines for research including the Nuremberg Code. The principle of “respect for persons” articulated in the Belmont Report provides further justification for such a right.
Nevertheless, one cannot merely rely on international statements to substantiate a claim for a right to withdraw. Indeed, there has been little justification in the literature for such a right. Hence, arguments for and against a right to withdraw from xenotransplantation clinical trials are worth considering.

Arguments for limiting a right to withdraw rely mainly on utilitarian arguments based on the concept that society should achieve the “greatest aggregate welfare to the more significant number of individuals.” Zoonosis can harm individuals close to the patients (e.g., family members and friends), society in general (i.e., the occurrence of pandemics), and harm participants themselves. Also, allowing participants to withdraw will threaten the integrity of the data and hence, compromise the reliability of the research results. A waiver of the right to withdraw health data gains importance in genomic research where large databases are needed in genome-wide association studies. Data withdrawal that threatens data integrity can significantly diminish the scientific value of the research and lead to a waste of invested societal resources. Hence, allowing a right to withdraw in xenotransplant trials can fail to protect society from research harms, and hinder necessary research, which together can compromise the public trust in science.

Arguments for maintaining a right to withdraw rely mainly on deontological arguments, which include the intrinsic value of respecting participants’ autonomous choices, a right to bodily integrity, their interest in liberty, and their right to privacy. A right to withdraw also provides research participants an “escape hatch” from onerous surveillance procedures not foreseen at enrollment. Furthermore, although there might be compelling arguments to waive the right to withdraw a participant’s health data in genomic research, surveillance procedures in xenotransplant clinical trials might include blood drawing and other invasive bodily procedures. Hence, a right to withdraw relies heavily on the more general right to bodily integrity in xenotransplant trials that do not apply to genomic research health data.

In contrast, Edwards argues that “the relationship between researcher and subject should be contractual [and….] Such a relationship would allow the researcher to impose a penalty …for
Edwards contends that the possible imposition of penalties would make it less likely for participants to withdraw from research. However, courts would unlikely enforce such contracts, and researchers’ attempts to proceed with any penalties would weaken public trust in medical research.\(^{23,29}\)

As this controversy involves casting individual rights vs. public health, a final analytical approach would entail using a public health framework.\(^{32,33,34}\) Containing or preventing a catastrophic pandemic sometimes requires drastic measures against the core of civil liberties.

A public health framework focuses on when the extent of measures is used to protect public health “reasonable” to the infringed moral considerations. The relevant moral considerations include respecting autonomous choices and actions, including liberty of action, protecting privacy, ensuring procedural justice, and maintaining trust.

A public health framework generally considers the following principles: evidence of the effectiveness of the intervention, necessity, proportionality, and least infringement measures on the relevant moral consideration. The issue is how to balance these competing concepts. What follows is a discussion of applying these principles to waiving the right to withdraw from xenotransplantation clinical trials.

Regarding “evidence of the effectiveness of the intervention in achieving its goal,” is waiving the right to withdraw essential to protect public health, or is it based more on beliefs and conjecture than facts? Preclinical data indicate that widespread zoonosis from patients with transplanted pig hearts is believed to be rare.\(^{35}\)

Concerning “proportionality,” public health interventions' degree of infringement on individual rights should be proportional to the degree of expected benefits. The greater the burden imposed by a program, the greater must be the expected public health benefit. A disproportionate action would involve a minimal chance of significant benefit at the cost of harm, deprivation, or rights. As the risk of zoonosis from individuals with xenotransplants is believed to be low, waiving the right to withdraw is disproportionate to the expected benefit.
Regarding “necessity,” not all policies and interventions are necessary to realize the sought public health goal. Proponents must have supportable reasons that an invasive approach is necessary.

To further address this “necessary” requirement, discussing the “least infringement” principle is essential, which entails that the contemplated action should be the least restrictive and least intrusive to protect public health. In other words, one must ask whether waiving the right to withdraw represents a more substantial measure necessary to solve a problem.

According to Fernandez-Lynch, there are preemptive or less restrictive approaches to minimize the risk of withdrawal and methods available to encourage participants not to withdraw. These include:

- Carefully select study participants who appear reliable enough to complete the entire course of participation.
- Seek insight into prospective participants’ competing considerations to remain in the clinical trial and help participants address their competing considerations.
- Use persuasive approaches at the time of the participant’s withdrawal request.
- Encourage participants to consider the range of potential harms that may result.
- Inquire about the presence of financial constraints.

To conclude, the use of a public health framework currently does not justify an infringement on the right to withdrawal mainly due to:

- Scarce evidence for its effectiveness.
- The expected benefit is not proportional to the deleterious means used against significant autonomy, liberty, privacy, and bodily integrity values.
- Waiving the right to withdraw does not represent the “least restrictive means”, as there are other pragmatic approaches to consider.

Finally, a waiver of a right to withdraw is neither legally nor ethically enforceable and would threaten public trust in medical research.
Our support for one side or the other of this debate could be colored by our own and the world’s recent experiences with the COVID-19 pandemic, which might lead us to favor Iltis’s position: advise Dr. Zuckerman to go with the public health approach by requiring xenograft recipients to waive the right to withdraw from the study’s long-term surveillance program. In the long term, however, as memories of our recent experiences fade, we might take a more uncolored approach to answer the question of whether to require a waiver, giving more weight to the position that supports protecting the subjects’ autonomous right to withdraw from a clinical investigation without penalty. Both essayists present persuasive arguments, so investigators designing xenotransplantation clinical trials should consider both sides before deciding which approach ought to be the norm for such trials.
Declaration of generative AI and AI-assisted technologies in the writing process.

During the preparation of this work the author(s) used DALL-E in order to generate the central picture. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.


