**Xenograft recipients and the right to withdraw from a clinical trial**

**Abstract:** Pre-clinical xenotransplantation research using transgenic pigs has begun to show some promising results and could one day offer a scalable means of addressing the organ shortage. While it is a fundamental tenet of ethical human subject research that participants have a right to withdraw from research once enrolled, several scholars have argued that the right to withdraw from xenotransplant research should be suspended because of the public health risks posed by xenozoonotic transmission. Here, we present a comprehensive examination and critical evaluation of the claim that xenotransplant recipients should be required to waive their right to withdraw from lifelong bio-surveillance. We conclude that, *if* xenotransplantation requires participants to waive their right to withdraw, then clinical trials may not be justifiable given the ethical and legal obstacles involved with doing so. Consequently, *if* clinical trials are permitted with a right to withdraw, then they may pose a significant existential and public health risk.

**Keywords:** public health, zoonosis, patient rights, xenotransplantation

Recent xenotransplant research using transgenic pigs has been promising and a phase I clinical trial has been registered in the United States (US) (Locke, 2022; Porrett et al., 2022; Montgomery et al., 2022). Xenotransplantation raises numerous ethical and legal concerns (Caplan & Parent, 2022; Johnson, 2022; Bobier et al., 2022; Hawthorne et al., 2022; Entwistle et al., 2022; Sade & Mukherjee, 2022), one of which is whether research participants who receive xenografts can withdraw from the study protocol. It is a fundamental tenet of ethical human subject research that subjects be able to withdraw from research once enrolled, but it seems that the right to withdraw from xenotransplant research should be suspended due to the public health risk posed by xenozoonotic transmission (Reese et al., 2023; Entwistle et al., 2022; Sade & Mukherjee, 2022; Spillman & Sade, 2007). González (2020) has argued that there is a growing scholarly consensus that, because of the overriding public health concerns, recipients should not be permitted to withdraw their consent to life-long health surveillance. Though rebuttals to such a proposal have been offered in the past, we present a fuller examination, critically assessing the claim that xenotransplant recipients should be required to waive their right to withdraw from lifelong bio-surveillance. Whilst we limit our discussion to the adult context, similar principles could apply in the pediatric context and the ethical issues around the right to withdraw from a clinical trial for pediatric patients has been addressed elsewhere (Hurst et al. 2020).

**The case for waiving the right to withdraw**

Transplanting organs from transgenic pigs poses several potentially serious risks, one of which is xenozoonosis—the transmission of an infectious disease from the host animal to the human recipient via the xenograft. This is not merely a theoretical concern—the vast majority of emerging infectious diseases are zoonotic and are estimated to account for more than 2.5 million deaths every year (Salyer et al., 2017). Whilst the infection risk posed by xenotransplantation is considered to be low, transgenic pigs may still present an infectious disease risk due to various swine-derived pathogens (Fishman 2022). For instance, pigs are carriers of a group of unique swine pathogens known as porcine endogenous retroviruses (PERVs), which have become integrated into the pig genome. As Łopata et al. (2018) explain, due to their evolutionary role in protecting porcine health, ‘PERVs constitute an integral part of the porcine genome and are present in various proportions depending on pig breed, tissue type, and retrovirus subtype’ (1). There are three types of PERVs, two of which are polytropic viruses that infect cells of different species and are present in all pigs (Denner, 2016; 2021). That PERVs are in the porcine genome means that they cannot be mitigated through rearing practices or embryo selection, and while they are generally harmless to pigs, they may be fatal in other species (Denner, 2021).

There is thus the ever-present concern that a xenograft recipient may become infected with a swine-derived pathogen, including but not limited to PERVs, that could go undetected (Fishman 2022). A PERV could, Sade and Mukherjee (2022) explain, ‘infect human cells, mutate, and cause cancer, or combine with other viruses to cause novel infectious diseases’ (pg. 713). A xenozoonotic disease could express itself soon after transplantation, as seems to have happened in the severely ill recipient of a transgenic pig heart, David Bennett Sr., who died two months after the transplant; it is believed, but still unconfirmed, that a previously undetected xenozoonosis—porcine cytomegalovirus—was partly to blame (Fischer & Schnieke, 2022). Because many zoonoses have long latency periods before expression, a pathogen could be transmitted but remain dormant within a recipient before ever becoming symptomatic (Denner, 2022; 2016). The xenograft recipient is thus always at risk, even if the transplant fails and the xenograft is removed.

Xenozoonotic transmission could theoretically spread from the xenograft recipient to others, and at least theoretically could result in an epidemic or pandemic. As Johnson (2022) explains, ‘everyone in the world is at risk from an XTx-related [xenotransplantation-related] infection, not merely the individual xenograft recipient’ (p. 360); she goes on to say the ‘unknown and unquantifiable risks of [xenotransplantation] include the possibleunleashing of zoonotic diseases that could potentiallyaffect the entire world’ (p. 364). Generally, xenotransplantation researchers believe there is a low risk of xenozoonotic infection occurring in a xenograft recipient and then spreading to the broader public; however, many unknowns remain and the possibility of unknown unknowns. In reality, only formal clinical trials can determine the true nature of this risk—the potentially global scale of the risk warrants obvious caution and whether or when they should begin rightly remains contentious and the source of ongoing debate (Rodger, Hurst, and Cooper, 2023).

Given the third-party risks associated with xenozoonoses, and the fact that zoonoses may have years-long latency periods, it has been proposed that xenograft recipients must undergo lifelong bio-surveillance (Table 1). That is, to safeguard public health, there must always be an aspect of the clinical trial from which xenograft recipients cannot withdraw. This proposal seems to be an enactment of the precautionary principle, which foregrounds caution and restricts an activity until it can be proven safe, even if there is uncertainty about the actual risk the activity poses. The appeal of the precautionary principle grows when the potential for harm is significant. Lifelong bio-surveillance is thought necessary even if the xenograft is excised from the patient. Sade and Mukherjee (2022) explain that ‘the patient must understand the necessity for lifelong clinical and laboratory surveillance for xenogenic diseases, as well as certain invasions of privacy, such as mandatory reporting of sexual contacts’ (pg. 713). The bio-surveillance may include reporting of sexual contacts, blood sampling at regular intervals, and autopsy upon death. Jorqui-Azofra (2020) is more descriptive of what recipients might be expected to do:

[R]egular postclinical checkups and testing schedule, informing about possible changes of address/contact numbers, timely reporting of all unexplained illnesses, following specific behavioral guidelines with respect to exchanges of body fluids with intimate contacts, education of family members and intimate contacts about their need to take precautions associated with infectious disease risks, possible isolation and quarantine, travel movements, etc. (pg. 324)

Though post-xenotransplantation follow-up visits may become less frequent as time progresses and without any xenozoonotic risk presenting, the follow-up is still intrusive, not passive, and would need to occur at regular intervals. The requirements for lifelong bio-surveillance risk being or becoming onerous and to encourage long-term engagement will need to be minimally burdensome. For example, remote monitoring and periodic self-reporting should be considered.

That recipients of transgenic pig organs are at risk for xenozoonotic disease is not taken by itself to justify mandatory lifelong bio-surveillance. Generally, patients are permitted to accept some degree of risk to themselves so long as they do so freely and voluntarily. Allotransplantation, for example, poses serious risks for recipients, enough to warrant lifelong follow-up (Neuberger, 2020); but there is no call for mandatory lifelong bio-surveillance of allotransplant recipients and their wider contacts. What is taken to justify mandated lifelong bio-surveillance of xenograft recipients is the risk to public health. Reese et al. (2023) claim that ‘some loss of liberty involved in infection monitoring is reasonable in light of public health risks imposed by potential zoonoses’ (pg. 241). The enforcement mechanism is unclear, with some proposing fines and others proposing something more forceful (Spillman & Sade, 2007; Florencio & Ramanathan, 2004). However, this position is grounded in the idea that researchers have an ethical duty to ensure bystander risks are minimized and that public health concerns trump individual liberty in *some* cases, especially cases that pose a significant risk to the wider population.

**Ethical problems with mandated lifelong bio-surveillance**

Rights are beneficial for possessors, for they protect the possessor’s interests from consequentialist considerations by generating *prima facie* obligations on others to respect them. A person’s right to life entails a *prima facie* moral obligation on others to not kill her, even if killing her promises to save the lives of five other people. An ethical tenet of human subject research is that subjects have the right to withdraw without penalty. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research’s (1979) *Belmont Report* states that patients be informed that they have the right “to withdraw at any time from the research” (Part C, 1). This right is reaffirmed by the Code of Federal Regulations’ (2023) *Common Rule*, which states that a basic tenet of informed consent is a statement “that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled” (45 CFR 46.116.b6). United States federal rules align with the World Medical Association’s (2008) *Declaration of Helsinki,* whichstates that ‘The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal’ (26). There is no indication that this right can be waived, for this would mean that a human research subject must participate in research and the force of this ‘must’ is reminiscent of unethical prison experiments of the previous century (Hurst et al., 2022; McConnell, 2010).

There are at least five compelling benefits that result from research participants having the right to withdraw from a study without punishment. First, research may involve the intimate use of one’s body and individuals have the right to bodily autonomy and integrity, viz., they get to choose what happens to their body (Capell et al., 2021; Fernandez Lynch, 2020; Holm, 2011; Schaefer & Wertheimer, 2011). If a person does not want something to happen to her body, others should respect that person’s wishes. Rare exceptions aside, researchers cannot force people to do something they do not want to do. Second, the right to withdraw protects subjects from undue influence and information asymmetry (Holm, 2011; McConnell, 2010). If a subject agrees to undergo a medical procedure about which they do not fully understand the impact of, they should be allowed to withdraw upon learning the impact more fully. Or, if it comes to light that a patient was coerced into a study, the patient should be allowed to withdraw. Third, the right to withdraw protects patients from undue harm (Fernandez Lynch, 2020; McConnell, 2010). For instance, forcing a patient to continue in an unwanted long-term study or procedure may be financially challenging for the patient. As we are discussing the right to withdraw in the context of research, it might be assumed that bio-surveillance costs would be covered by the trial sponsor. Yet, this cannot be assumed apart from knowing the terms and conditions of an actual clinical trial. Even if the protocol and informed consent documents of the trial promise coverage, there is the possibility that the trial sponsors may go out of business and default on their financial obligations. Fourth, the right to withdraw protects patient privacy (Capell et al., 2021). If a patient does not want to disclose personal, perhaps compromising, information to a researcher, that person should be free to do so. Finally, the right to withdraw has a role in promoting public trust in science (Schaefer & Wertheimer, 2011). Public trust in science is put at risk when people perceive scientists or law enforcement officials forcing healthy-looking people to undergo invasive, intrusive, and unwanted procedures.

Some rights can be waived or transferred through a voluntary and informed decision. One waives their right to control what happens to a piece of property when it is sold to another through a valid transaction. One waives their right to control all aspects of a piece of property for a time one leases to another through a valid, time-limited contract. Others waive what they are otherwise entitled to secure some other good they are entitled to or are free to pursue (e.g., documentation of informed consent for the sake of medical privacy). The question before us is this: can one “waive” one's right to bodily integrity and medical privacy to secure a potential benefit offered only in the context of clinical research? If we consent by waiving our rights, then is our right to control our bodies either given up, suspended or set aside for the sake of receiving the benefit? Some appear to think so. Applied to xenograft recipients, Entwistle et al. (2022) explain that ‘because of the public health implications of zoonotic disease, recipients may be required to waive their right to withdraw from infectious disease surveillance’ (pg. 989). The argument goes that requiring would-be xenograft recipients to voluntarily waive their right to withdraw respects their autonomy while protecting public health at the same time (Chwang, 2008; Spillman & Sade, 2007). More specifically, if would-be xenograft recipients are adequately informed about what lifelong bio-surveillance requires and its importance to them and others, then they could voluntarily “waive” their right to withdraw in the sense that it is permanently suspended.

Support for this authority-suspending act can be drawn from Appelbaum et al.’s (2009) account of the conditions for involuntariness: “a decision is involuntary only if it is subject to a particular *type* of influence that is external, intentional, illegitimate, and causally linked to the choice of the research subject” (pg. 33). An external agent, they explain, must intend to influence the choice illegitimately, i.e., against generally accepted norms. A researcher proposing xenotransplantation as an option to a would-be recipient is not illegitimately influencing the decision, for, as Spillman and Sade (2007) highlight, there are other options for would-be xenograft recipients, e.g., they can remain on dialysis, accept death, or wait for a human donor. Voluntary and informed consent is therefore possible.

Granting for the sake of argument that this is the proper interpretation of consent (which is questionable, see below), the case can be made that the influence is illegitimate and causally linked to the choice of the research subject, thereby, undermining the voluntariness of the consent to waive one’s right to withdraw. The American Medical Association (2017), following guidance from the Food and Drug Administration (FDA), recommends limiting xenotransplant recruitment to “patients with serious or life-threatening conditions for whom no adequately safe and effective alternative therapies are available” (sect. d). Current guidelines favor the selection of individuals who are disadvantaged or otherwise excluded from receiving a human organ (Hurst et al., 2022). Would-be xenograft recipients thus lack medical options and are invited to participate in a study that promises treatment for their condition. Since recruitment is targeted to individuals with a serious, possibly life-threatening, condition and who have few or no alternatives, they are presented with an illegitimate choice: waive their right to withdraw or likely die (McConnell, 2010). This kind of forced decision is not acceptable in other medical contexts. For instance, it would be illegitimate for doctors to require would-be allograft recipients to waive their right to withdraw from post-transplant follow-up to receive an organ, and Appelbaum et al. (2009) agree that patients who otherwise lack medical care should not be recruited to studies that promise to treat their illness because that would render the decision to participate involuntary.

There is also a concern about whether xenograft recipients would be able to comprehend or understand what is being asked of them. The World Medical Association’s (2008) *Declaration of Helsinki* states that ‘each potential subject must be adequately informed of…post-study provisions’ (26). There is a significant amount of information would-be recipients have to process (Silverman & Odonkor, 2022), and given the invasiveness and duration of post-xenotransplant follow-up, it is doubtful whether a would-be recipient can appreciate how, in the words of Millum and Bromwich (2021), ‘normative boundaries are being redrawn by the speech act of consenting’ (pg. 55). When presented with the choice of waiving their right to withdraw or not receiving an organ, subjects are likely going to be attentive to the immediate goal of surviving. They are not likely going to appreciate what mandated bio-surveillance will entail—that decades later, they will be required to disclose the name of their new sexual partner(s) to researchers; that they will have to seek approval to move to another country and ensure bio-surveillance can be established there; and that they will still have to meet with medical personnel even if they lose their job, transportation, and insurance coverage. Clinical trials may be covered by the sponsor, but this remains uncertain and it is possible that a sponsor, e.g., a company that makes transgenic pigs, goes out of business in the future. The situation might be different if the follow-up were passive and non-invasive (Capell et al., 2021); but as it stands, proposed follow-up protocols are invasive and demanding for subjects, involving intimate access to the body and personal information (Rodger & Cooper, 2022).

One might respond that the right to withdraw in this case poses a significant public health concern, and so, it should be waivable. But there are three problems with this line of argument. First, the risk is largely theoretical and unknown, and the evidence that we do have from pre-clinical and animal studies suggests that it is low. Joachim Denner (2022) observes that so far ‘there is convincing evidence that no PERV has been transmitted in any transplantation or infection experiments in small animals, as well as in non-human primates’ (pg. 8). Research is progressing on better detection and genetic deletion of PERVs in transgenic pigs. Xie et al. (2018) were able to gene-edit pigs resistant to classical swine fever virus, while Niu et al. (2017) were able to inactivate all 25 PERV copies, which were then used in somatic cell nuclear transfer to produce piglets—no reinfection was observed. Yang et al. (2015) succeeded in inactivating 62 copies of proviruses in the pig genome, creating PERV-inactivated pigs. Moreover, certain antiretroviral drugs and vaccines are available and could be used to prevent PERV infection, as well as RNA interference technologies (Denner, 2021). So, while xenograft recipients are at risk of zoonoses, the risk remains unknown but is likely low, due to advancements in screening, detection, and prevention (Yuan et al., 2022).

Second, there is something curious about the argument in favor of waiving the right to withdraw from considerations of public health risk. As McConnell (2010) notes: if there is such a danger to the public, then individuals do not need to waive their right to withdraw, for in such cases, rights can be overridden. In general, when an individual poses a significant risk to others, we do not require them to voluntarily waive their rights; the state or other actors are justified in overriding their rights. One’s right to life can be overridden by a police officer if they are actively threatening the life of another. So, if xenotransplantation poses such a great risk, the risk is enough to override a patient’s right to withdraw regardless of whether the patient has voluntarily done so. After all, if someone initially waives the right to withdraw and then reneges, the third-party risk justifies the invasive violation of autonomy.

Third, “waiving” the right to bodily integrity begs the question as to whether one’s authority over what happens to one’s body can be voluntarily suspended or given up. Indeed, the language of “waiving one’s right to bodily integrity” involves a paradoxical view of autonomy insofar as it appeals to the autonomous choice of research participants to vacate their authority over what happens to one’s own body and defer it to investigators until the investigators think it appropriate to give back. Presumably, that autonomous choice is to be respected. Yet respecting this particular choice is to undermine the respectability of autonomous choice altogether since subsequent autonomous choices of the participant after the deferral need not be respected by the investigators if those choices are inconsistent with the investigator’s goals. In other words, asking one to autonomously waive their right to bodily integrity is to treat what is to be respected as something that can undermine itself as an object of respect. In fact, the concept of consent as waiving one’s rights is misleading, because it does not account for the dynamics of permission-giving that is grounded in *authority-retaining* consent (Liberto 2022). It is widely recognized in research ethics that informed consent is a process, not an event, that involves a give-and-take relationship with the participant with whom the researcher interacts at the participant’s discretion. This is simply a function of the authority-retaining character of consent, which not only grounds respect for autonomous choice within biomedical ethics, but also within sexual ethics and other domains, legal or otherwise, that involve rules against assault (Liberto 2022).

While forced bio-surveillance might be morally justifiable in rare cases where an individual poses an immediate public health risk, this is much less clear in the context of clinical trials for xenotransplantation and the problem that an uncooperative participant presents. A more accurate example might be that of Mary Mallon or ‘Typhoid Mary’ who refused to cooperate with medical treatment that could have cured her and instead was forced into quarantine for a total of 26 years (Marineli et al 2013). Let's say that after five years, a participant in a clinical trial for xenotransplantation is no longer willing to cooperate and complete any health surveys or undergo any invasive or non-invasive test that they originally consented to. That participant is not necessarily an *immediate* risk to the public and presumably as time moves on, the risk to public health decreases, and therefore the justification for forcing them to undergo the requirements of bio-surveillance decreases. Importantly, the language of *mandatory* bio-surveillance risks obscuring what this could potentially entail. If the requirement is mandatory, who exactly is going to ‘force’ an uncooperative participant to have a blood test against their will? After all, this may require sedating or anaesthetising a competent individual and seems *prima facie* morally absurd. Therefore, *if* a clinical trial entails that mandatory bio-surveillance is necessary, then one must question whether the risk posed from beginning clinical trials can be morally justified to begin with.

**Legal problems with mandated lifelong bio-surveillance**

Aside from the ethical challenges, there are pressing legal challenges with mandated lifelong bio-surveillance in the United States, which is currently illegal and unenforceable. First, while the U.S. Supreme Court has ruled that individual rights can be suspended in the interest of public health when the risks are subject to scientific assessment, there is no legal precedent for mandated bio-surveillance of individuals who do not show signs of illness (Padilla et al., 2022; Florencio & Ramanathan, 2001). Second, public health laws tend to be specific, directed to particular communicable diseases such as HIV and tuberculosis, and as Holland (2007) explains, some state health codes allow for measures to be taken to prevent the spread of a contagious disease but only when informed of its presence. For an individual’s rights to be overridden by the government, there needs to be proof that an individual is sick with a contagious disease and poses a risk to public health. But, as it currently stands, the risk to public health of xenotransplant zoonosis is too unspecific and unknown to be legislated.

There are two constitutional hurdles a proposed mandated life-long bio-surveillance protocol must pass in the United States (Fernandez Lynch, 2020; Lynch, 2014; Holland, 2007; Florencio & Ramanathan, 2004). First, the Fourth Amendment protects citizens from unreasonable searches and seizures. According to *Skinner V. Railway Labor Executives’ Ass’n*, a case in which railway workers sued the federal government for authorizing policies of taking, sometimes requiring, blood, urine, and breath samples; the court found that the government may compel the taking of bodily tissue and fluids when there is a special need that justifies such action (Florencio & Ramanathan, 2004). Researchers may argue that the undisclosed public health risk justifies a special need for government intervention at the expense of xenograft recipient freedom. However, as Holland (2007) explains, the “fact that the monitoring involves repeated, invasive procedures for the duration of the individual’s life would likely outweigh the argument of a legitimate government interest”, especially given the unspecified nature of what is being looked for (pg. 160). Second, the Fourteenth Amendment protects citizens’ right to privacy and liberty, as guarded by due process (Maclin, 1993). Government interference or infringement of liberty, life, and property is carefully scrutinized, and forcing subjects to unwanted invasion of their body and personal information for possible, not actual, risk is likely not going to pass legal muster (Holland, 2007; Florencio & Ramanathan, 2004). In *Hancock v. County of Rensselaer*, a case in which plaintiffs sued their employer–the Rensselaer County Jail–for accessing their medical records without consent in violation of the Fourteenth Amendment, the court affirmed the right to medical privacy and cautioned against a multiplication of exceptions. Of current importance, the court ruled that exceptions to this right may occur during a pressing emergency, which is not the case in xenotransplant research, or (possibly) through legislative action.

The best route, therefore, would be to legislate an exception to the right to withdraw for xenotransplant research (Padilla et al., 2022). But practical questions abound. Who could issue such an exception and on what legal grounds? Who would enforce mandatory bio-surveillance? On what grounds might officials legally enforce it? These are not insignificant questions, even though defenders of requiring recipients to “waive” their right to withdraw—already a dubious notion—tend to gloss over them. One suggestion would be to fashion consent to xenotransplantation along the lines of an employment-like contract (Lynch, 2014): in exchange for an organ, the recipient agrees to waive their right to withdraw. However, as Fernandez Lynch (2020) notes, employment contracts assume bodily autonomy of both parties, since otherwise there would be forced labor; accordingly, a U.S. court is unlikely to enforce an employment-like contract in this context.

Another suggestion is a Ulysses Contract, which is sometimes used in psychiatry: patients with a psychiatric illness but who are competent and in remission may authorize their psychiatric team to provide a certain treatment even if they refuse at a later time (Reese et al., 2023; Spillman & Sade, 2007). Patients would be required to waive their right to withdraw from surveillance, with the form that they sign outlining, in the words of Spillman and Sade, ‘the surveillance schedule, as well as the proposed penalties for non-compliance’ (pg. 270). But Ulysses Contracts in psychiatry are disanalogous to xenotransplantation for at least three reasons: (i) the goal of the advance directive in a psychiatric context does not apply to xenotransplantation, (ii) enforcing Ulysses contracts in xenotransplantation is infeasible, and (iii) the ethical and regulatory hurdles such enforcement would require make binding enforcement impractical (Hurst et al. 2023; McConnell, 2010). Psychiatry patients enter into them for benefit *to* themselves, whereas xenograft recipients would enter into them for the benefit *of* themselves (i.e., it gets them an organ) and third-party benefit (i.e., protects public health from infectious disease). Accepting lifelong biosurveillance is part of the “cost” of receiving an organ, whereas the restrictions stipulated in a Ulysses contract are perceived as “benefits” worthy of choice. In psychiatry, such a contract is freely entered into, whereas this would not be the case in xenotransplantation: they are given the option of agreement or not receiving an organ. Such a set of perceived options may unduly influence one’s decision. The contract is enforced when the psychiatric patient is manifesting a mental illness, whereas the contract may be enforced on xenograft recipients who are exhibiting absolutely no signs of illness but who opt out of bio-surveillance protocols. Most importantly, a justification for Ulysses Contracts in psychiatry is that the patient’s decision-making capacity is compromised, which is not the case in xenotransplantation. There is no legal precedent for forcing a healthy person with competent decision-making capacity to do something they otherwise do not want to do.

**Conclusion**

Xenograft recipients, like allograft recipients, will need life-long follow-up and monitoring. The growing scholarly consensus that—because of the overriding public health concerns—recipients should not be permitted to withdraw their consent to lifelong health surveillance faces serious ethical and legal hurdles. We conclude that, if xenotransplantation does require participants to waive their right to withdraw, then clinical trials may not be justifiable given the ethical and legal obstacles involved with doing so. Consequently, if clinical trials *are* permitted with a right to withdraw then they may pose a significant existential and public health risk.

Table 1: Biosurveillance Proposals

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| [UK Nuffield Council](https://www.nuffieldbioethics.org/publications/xenotransplantation) (1996) | ‘6.36: It should be a requirement of clinical trials that the need for monitoring is explained to the patient and that it is made clear that consent to the operation also implies consent to subsequent monitoring.’ |
| [FDA/PHS (2001](https://www.fda.gov/media/73803/download)) | ‘The informed consent discussion… should address, at a minimum, the following points relating to the potential risk associated with xenotransplantation:2.5.7. The importance of complying with long-term or life-long surveillance necessitating routine physical evaluations and the archiving of tissue and/or body fluid specimens for public health purposes even if the experiment fails and the xenotransplantation product is rejected or removed.2.a.iv. The informed consent document should contain information about the proposed life-long surveillance for all recipients and the need for clinical and laboratory monitoring throughout. You should explain, to the extent possible, the schedule for such clinical and laboratory monitoring.’ |
| [European Commission: Health & Consumer Protection Directorate-General](https://ec.europa.eu/health/ph_risk/committees/scmp/documents/out38_en.pdf) (2001) | ‘Some of the measures that may need to be taken in a surveillance system may have legal implications as they could be in violation of the Declaration of Helsinki and other guidelines for research on human subjectsIn the recent EC directive for conduct of clinical trials, the right of a subject to withdraw from a clinical trial is explicitly stated (EC 2001), and this could be a problem for prolonged surveillance in xenotranplantation clinical trials. As xenotransplantation has implications for public health, it may be that certain rights may have to be modified in such a way that surveillance can be continued. Patients (and others?) could therefore have to agree to waive some of their human rights.’ |
| [American Medical Association, Code of Medical Ethics, Opinion 6.3.1](https://www.ama-assn.org/delivering-care/ethics/xenotransplantation-and-ama-code-medical-ethics) | ‘Physicians who choose to participate in clinical research that involves transplantation of organs or tissues from nonhuman sources should: (c) Ensure that research in which they participate is adequately funded to assure lifelong surveillance of xenotransplant recipients and treatment of medical complications related to transplantation.’ |
| WHO Changsha Communique (2008) | ‘Participation in xenotransplantation will usually require the long term storage of animal and patient samples, pre- and post-treatment, as well as records. It will require life-long follow up of recipients and possibly their close contacts.’ |
| [FDA (2016)](https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Source-Animal--Product--Preclinical--and-Clinical-Issues-Concerning-the-Use-of-Xenotransplantation-Products-in-Humans--Guidance-for-Industry.pdf) | ‘You should limit candidates to those patients who have potential for a clinically significant improvement with increased quality of life, following the procedure. You should also consider the patient’s ability to comply with public health measures as stated in the protocol, including long-term monitoring.’ |

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