# Xenotransplantation and Informed Consent

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## Introduction

At the time of this writing in early 2022, a pig heart was just transplanted at the University of Maryland Medical Center into a living adult male who did not meet criteria for an allograft [1–3]. While this incident of xenotransplantation (XTx) was not a clinical trial but implanted under an emergency use authorization by the Food and Drug Administration (FDA) in the United States (US) regulatory sense of the term,[1] other medical centers have plans to conduct XTx clinical trials, which are likely on the near horizon. However, before clinical trials may commence, regulatory and ethical issues surrounding the trials must be adequately considered. To date, there is little in regard to systematic considerations regarding informed consent for XTx clinical trials. Padilla et al. recently approached this subject offering the most comprehensive and updated account of factors that will need to be addressed, such as a research participant's ability to withdraw from the clinical trial, restrictions on participants' reproductive rights, and the possibility that a participant may need to quarantine for some length of time if there is a perceived risk of xenozoonosis [4]. Additional commentary has been provided on regulatory issues that Institutional Review Boards (IRBs) should be made aware of before an approval is granted [5], but the literature on practical consent issues is scant.

[1] Researchers at The University of Maryland had applied to the FDA to begin a clinical trial of pig-to-human cardiac transplants but were not approved due to lack of non-human primate studies. The FDA granted an emergency authorization for this particular procedure.

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Informed consent straddles both regulatory and ethical realms; it is an ethical obligation that is codified into law. Hence, with the uptick of research in XTx, combined with the approaching trials that are planned, the dearth of recent literature on the subject of informed consent is surprising considering the notable differences that exist for informed consent in XTx clinical trials compared to other trials. This chapter provides an overview of the topic of informed consent within XTx clinical trials. Rather than focusing on regulatory matters that may differ between nations, this chapter focuses on philosophical and practical matters that will affect XTx programs regardless of locale and that are deserving of further consideration. The first section will provide a brief history of informed consent as a concept within medical research, then informed consent within the context of XTx is examined. The notion of community consent, distinguishing it from the individual consent of the research participant, is presented. Finally, the research participant's right to withdraw from a XTx clinical trial is explored.

## Early History of Informed Consent

The history of modern informed consent is not lengthy. Distinctions can be made between consent for medical procedures in normal practice and consent provided by research participants in the context of a clinical trial. A modern understanding of informed consent is not found in classic medical texts, such as the Hippocratic Oath (ca. fourth century BC) or Thomas Percival's *Medical Ethics* (1803) [6]. The term "informed consent" would not be used extensively until the 1950s and many early decisions about the usefulness of informed consent—what physicians needed to disclose, what a patient had a right to know—played out in the courts [6, 7].

In the context of medical research, which is the focus of this chapter, informed consent took center stage in the aftermath of World War II. The medical research atrocities committed by Axis forces on their captives are well known [8]. After the Allied forces secured victory they established the Nuremberg tribunals (1946–1947), which brought forth charges and resulted in convictions for many of those involved in the Nazi medical experimentation [9]. Additionally, the Nuremberg tribunals are noteworthy due to the landmark establishment of what would be known as the Nuremberg Code—a set of ten research ethics guidelines regarding human clinical trials. The very first principle of the Nuremberg Code points to the importance of the principle in the minds of those who wrote it:

> The voluntary consent of the human subject is absolutely essential.This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter

> element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity [10].

The Nuremberg Code was designed to protect the rights and welfare of those who participate in human research. Other ethics guidelines for human research would follow, such as the Declaration of Helsinki (1964) and the Belmont Report (1979), each reiterating the need for the true informed consent of the research participant prior to research activities commencing.

## Informed Consent and Xenotransplantation

This discussion begins in the 1960s with the pioneering surgeon James Hardy. In 1963, Hardy would perform the world's first lung allotransplant at the University of Mississippi, receiving much public acclaim. Hardy was also determined to carry out the first clinical heart transplantation and in 1964 decided to acquire some chimpanzees as potential "donors" in case he could not identify a deceased human donor. Hardy found a patient who, reportedly, was already in a state of dying and was a less than ideal candidate for transplantation [11]. Furthermore, the commentaries that exist on this event are not entirely clear if adequate consent was gained by the patient and/or surrogate decision-maker for the transplant. Regardless, Hardy transplanted a chimpanzee heart into his patient. Hence, from this event we have at least two serious ethical issues at hand: (a) the ethics of performing a xenotransplant—a very risky experimental surgery—on a patient who was unlikely to benefit due to their already declining state, and (b) the question of whether adequate consent was obtained. Granted, the concept of informed consent during the 1960s was not as developed as in today's medicine, yet the standard that a patient or their surrogate must agree to the procedure did exist [12, 13].

The reception by the public toward Hardy's xenotransplant was not welcoming. David Cooper has described that the ill public and medical professional response toward the heart XTx dissuaded Hardy from further attempts [11]. Unfortunately, it is not entirely clear in the existing literature what specifically the public and medical community found objectionable.

**Box 6.1: Summary of 45 CFR 46.116(a)**
The regulations require that the following information must be conveyed to each subject:

(a) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
(b) a description of any reasonably foreseeable risks or discomforts to the subject;
(c) a description of any benefits to the subject or to others which may reasonably be expected from the research;
(d) a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
(e) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
(f) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
(g) an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
(h) 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.

In US regulations governed by the Department of Health and Human Services, specific requirements exist as to the content of informed consent, which can be found in 45 CFR 46.116(a). These requirements are summarized in Box 6.1 [14].

From the requirements listed in Box 6.1, issues are immediately encountered in point (a) within XTx. As will be discussed further in a section below, the expected duration of a research participant's involvement in XTx is for their lifetime, which may even be mandated for the participant and possibly other close contacts. This conflicts with (h) as the participant would have no recourse to fully discontinue their participation. Furthermore, describing foreseeable risks and discomforts as required in (b) proves difficult because of the novelty of the therapy and the risk of xenozoonotic infection. There are known risks in XTx, such as possible graft failure. There are known unknown risks, such as the level of risk posed to the participant from xenozoonosis. However, there are also unknown unknowns—those unknown risks that are not likely to be known until XTx clinical trials proceed.

Patient selection for initial clinical trials of XTx has been discussed. Cooper et al. posit that elderly patients who may not survive on a waitlist long enough to receive a suitable deceased human donor organ could be considered for initial clinical trials as long as they are otherwise in stable health [15, 16]. A concern may arise within XTx that, for those patients who are either not candidates for a deceased human donor organ or will more than likely not survive on the waitlist long enough for transplant, a patient may believe they have limited options and accept the xenograft because of this (i.e., the alternative is death or continued dialysis with poor and/or declining quality of life). That is, the paucity of options may exert pressure upon the individual to consent to the xenograft. This is not a completely unique experience. We can make analogies to oncology clinical trials in which new therapies are being tested on patients who may have exhausted existing clinical therapies. The informed consent process must clearly explain the risks and potential benefits of the procedure but will have to do so in a way that does not seek to unduly influence the decision.

## Community Consent

The unique risks of XTx clinical trials—primarily the unknown risk of xenozoonotic infection spread from the pig organ to the human recipient—has spurred some commentators to argue that the individual consent of the trial participant is inadequate. What is needed in addition, it is argued, is the consent of the community and perhaps the globe. While the risk of xenozoonotic infection in the human xenograft recipient is now thought to be low (compared to earlier research), the risk is not null and may not be able to be fully understood in the absence of clinical trials [17–19].

Abdallah Daar has written on the vexing issues with consent in XTx clinical trials. Daar was perhaps the first person to question whether, because of the unique risks that a community may bear from XTx trials (mainly risks in the form of possible xenozoonotic disease transmission in the xenograft recipient and then to other persons in the community), some form of community consent for clinical trials should be obtained [20]. Daar was quick to point out that a methodology for this is unclear as no model existed for it. These short lines, appearing in a special section of a 1999 *Bulletin of the World Health Organization* dedicated to topics of animal-to-human transplants, seem to be little more than a thought in Daar's writing. Nonetheless, others would more fully develop this idea in response articles. Fritz Bach makes the case that community consent may be possible via a public referendum that would allow a country's citizens to have a voice. If not a referendum, Bach states that a national committee composed of a heterogeneous assortment of persons could try to reach consensus that would represent the viewpoints of the public [21].

National referendums may be a fine option for gathering viewpoints on a country-level issue that will have minimal or no effect outside a nation's borders. However, let us remember that what is forcing this question is the issue of possible xenozoonotic disease transmission within the community. Infectious diseases are no respecter of borders and can become uncontainable in short order. Hence, a national

referendum does not seem to achieve the result that advocates for community consent are looking for. Regarding Bach's second point of a national committee, the same hesitations could be said for this solution. That is, having one nation's committee decide on an issue that may impact the globe is not sound.

Robert Sparrow has written one of the most thorough analyses on the concept of community consent for XTx clinical trials [22]. Sparrow notes that the relevant community that must be considered is global in scope due to the potential for spread of infectious diseases. With this in mind, he notes that no institution exists to establish such consent. The United Nations or one of its institutions, such as the World Health Organization (WHO) or United Nations Educational, Scientific and Cultural Organization (UNESCO) come to mind. Both institutions have been effective in gathering viewpoints from Member States on particular issues. For instance, the WHO has the World Health Assembly as its decision-making body which includes delegates from all Member States. Similarly, UNESCO in 2005 published a set of ethics guidelines, the Universal Declaration on Bioethics and Human Rights, that were approved by its Member States. A democratic process through these channels could be possible, but it still does not get to the core of what advocates of community consent seem to want, which is true consent by all those who may be affected (harmed) by the research.

In Sparrow's view, the major concern seems to be based on the distribution of risks and benefits that exists from XTx globally. High-income countries will be the sites of the clinical trials, will see XTx as a clinical option first, and will be better prepared than a low- or middle-income country to mitigate any infectious disease that is propagated by the procedure. Low- or middle-income countries, on the other hand, will continue to suffer from an organ shortage and will be less prepared to handle an infectious disease that may spread as the result of XTx. Hence, per Sparrow, the vast majority of the global population have very little to gain from XTx (at least in the immediate near-term) and a lot to lose.

Solutions out of this impasse have been offered. Martine Rothblatt has recommended that global surveillance programs for new xenozoonotic infections be established [23]. This may be relatively simple in countries with robust national health systems. For those countries without such infrastructure, Rothblatt states it will be necessary to establish networks of medical stations and surveillance systems to monitor for new pathogens. This would also include basic healthcare for the approximately one billion persons globally who currently do not have access to basic healthcare. To pay for such a schema, high-income countries would need to tax themselves—likely a tax on each xenotransplant that is performed—which would also create global buy-in for XTx, Rothblatt posits. Access to basic healthcare remains scarce in many places globally. The United Nations' 2015 Sustainable Development Goals set a target to achieve universal health coverage for all by 2030 (Goal 3.8)—a target that will not be met even in places of resource abundance who play major roles in the United Nations agenda (e.g., the United States) [24]. The political willpower here seems to be lacking.

In addition, Sparrow worries that tying the offer of access to basic healthcare in low- or middle-income countries to their willingness to consent to XTx calls into

question how free such a consent decision is and if this could constitute exploitation [22]. Sparrow thinks it does constitute exploitation, as the vulnerability of the low- or middle income country is being used to secure consent. The only way out of this quandary, per Sparrow, is to eliminate the inequalities in access to healthcare that endure globally.

While approaches to community consent for XTx exist, what is clear is that community consent in the sense of global consent is a minority opinion. The topic is not one that seems to be supported by a majority of researchers, likely because of its pragmatic difficulty. Nonetheless, the WHO has recommended that regulatory systems for XTx should involve public input [25]. The recommendation is nebulous, and some researchers have interpreted this as seeking the input of the local community in which clinical trials are likely to occur [26]. Nonetheless, the public's attitudes towards XTx is certainly an area in which further research is needed [27], and it seems unlikely that a true global community consensus is possible at this point.

## The Right to Withdraw

The right to withdraw has been a persistent topic within XTx. As with community consent, the issue of a research participant's right to withdraw arises from the unknown xenozoonotic risk that is present. Since the Nuremberg Code was published, an established tenet in medical research is that persons participating in research should have the ability to withdraw from a clinical trial at any time and for any reason. In modern informed consent forms there is standard language that communicates this, and it should also be part of the conversation that a research team has with potential participants prior to the person agreeing to participate in the trial.

As noted above, the risk of xenozoonotic disease brings about the ethical dilemma here. If there is some unknown risk of xenoozoonosis post-transplant, then regular monitoring should—perhaps must—accompany follow-up care for the remainder of the patient's life. This would include if the xenograft is excised. Because novel pathogens could spread to close contacts, such as close family and intimate partners, these persons could also be subject to some form of monitoring. Many guidelines agree with this. The US Department of Health and Human Services, in its 2001 guidelines on XTx, stated that informed consent discussions should address the importance of the xenograft recipient complying with long-term or life-long monitoring, which could include items such as blood and other tissue samples and imaging [28]. Similarly, the WHO in the Changsha Communiqué (2008) noted that XTx would require the life-long follow-up of xenograft recipients and possibly their close contacts.

It would seem that not allowing a research participant to wholly withdraw from all aspects of a clinical trial (i.e., the infectious disease monitoring portion) counters the principles of research ethics that dictate a participant should be able to do so. The ethical implications of this have been written on in both adult and pediatric populations with still no resolution [29, 30]. In the US, regulations on these issues are woefully behind. Standards need to be implemented for the monitoring of

xenograft recipients, and perhaps their close contacts, prior to the conduct of clinical trials and, ideally, before more emergency procedures are conducted. Mechanisms for monitoring xenograft recipients, including courses of action that will be taken when a patient does not meet their scheduled monitoring appointment, should be clear in consent documents and conversations with potential recipients. With the unknown risk of disease spread, consent to the XTx should also imply consent to subsequent follow-up monitoring which the patient must comply with for the safety of the public. Mechanisms for doing this need development without further delay.

## Conclusion

Informed consent is a vital part of the clinical trial process. In highly novel, experimental medicine such as XTx, there are many aspects of consent that have not been fully explored and are deserving of more attention. Additional stakeholder consultation on a number of these items seems appropriate, as well as more regulatory guidance to direct those research centers who are actively preparing for XTx clinical trials.

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