Position Paper of the Ethics Committee of the International Xenotransplantation Association

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Xenotransplantation (XTx) provides a potential solution to the shortage of human organs and tissues, and has several advantages over other possible solutions to this problem. However, a number of scientific and ethical barriers exist, and need to be addressed in order to advance the field of XTx in a manner that optimizes its potential to benefit society and minimizes its risk. Some of the most pressing ethical issues are discussed, and the position of the Ethics Committee of the International Xenotransplantation Association is presented.

Keywords: Ethics, Guidelines, Infectious risk, Pig, Porcine, Religion, Retrovirus, XTx.

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The subject of ethics in relation to xenotransplantation (XTx) has been widely explored (*1–7*). The purpose of this paper is not to reiterate these discussions in detail, but to provide an overview of the major issues and a brief statement of the International Xenotransplantation Association (IXA) Ethics Committee's present position on these issues. The paper is not meant to be the "final word" of the IXA on all aspects of ethics in XTx, but instead it is intended to present a few conclusions and recommendations that are felt by the IXA Ethics Committee to be warranted and of highest priority at the present time. A draft document has been circulated to the IXA Council and membership at large, and numerous thoughtful comments have been received in response. Many of these have been incorporated into the final document. While the overwhelming majority of these responses were supportive of the views expressed herein, some were not, and we have attempted to defend our views in these instances. Thus, the final document does not represent a unanimous viewpoint of the IXA, but represents the best consensus from the responses received, and has been agreed upon by the Ethics Committee and endorsed by the IXA Council. We thank all of those who have taken the time to comment on the draft, and we hope that the paper will continue to stimulate thought and engender further responses from within and outside the IXA membership. We encourage written responses via letters to this journal, and we look forward to participating in an ongoing dialogue on the topics discussed herein.

The inadequate supply of organs for transplantation is well established and widespread. The number of patients dying while waiting for allogeneic organ transplants is unacceptably high, and new solutions to the problem are needed. For example, approximately 75,000 individuals were on the American UNOS waiting list in March 2001, and less than one-third of those were transplanted that year. These figures represent just the tip of the iceberg, as many more individuals with organ failure who could benefit from organ or tissue transplants, if these were available, are not on transplant waiting lists or are withdrawn prior to their death.

Xenotransplantation provides a potential solution to the organ shortage. Other potential solutions include the use of artificial organs, as well as organs and tissues engineered from stem cells. While the latter possibilities are attractive and promising, many workers believe that the solution closest to clinical application is XTx of organs, tissues and cells; XTx of tissues and cells and ex vivo perfusion of natural and bioartificial porcine livers have already entered into clinical trials (*8–12*). The potential benefits of XTx to mankind are enormous. In addition to solving the organ shortage problem, XTx offers a number of other potential benefits (*13*):

1. In countries where human organ donation has not been accepted for ethical or cultural reasons, XTx might provide an acceptable alternative.

2. In several respects, xenogeneic organs would offer advantages similar to those associated with the use of human live donor organs - the transplant procedure can be scheduled; recipient pretreatment is feasible; the quality of the organs will be known in detail; there will be minimal warm and cold ischemia times; the influence of the various pathophysiologic consequences of brain death on organ quality will be avoided.

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3. With ready access to organs, recipient selection criteria could be broadened.

4. Xenogeneic transplants might not be susceptible to the human autoimmune diseases or viral infections that caused organ failure in the first place and which often limit the survival of allogeneic organ transplants.

5. The use of inbred, immunologically standardized source animals would facilitate pretransplant tolerance induction. Source tissue could also be modified by genetic engineering to minimize its rejection, optimize its function and provide other potential advantages to the recipient.

However, a number of scientific and ethical barriers to XTx exist, and these will need to be properly addressed in order to move the field of XTx forward in a manner that optimizes its potential to benefit society and minimizes its risk. The ethical considerations include some that are unique to XTx and others that apply to any experimental therapy. Our considerations will focus mainly on the ethical issues that are unique to clinical research in XTx, including the potential risk to society that it imposes, and considerations relating to the use of non-human source animals. While the discussion below focuses mainly on organ and cell transplants from non-human animal sources, similar considerations apply to XTx as defined by the United States Public Health Service, i.e. any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live cells, tissues or organs derived from a non-human animal source, or of human body fluids, cells, tissues or organs that have had ex vivo contact with live, non-human animal cells, tissues or organs. However, the level of potential risk to the patient and society must be considered on a case-by-case basis and taken into account in decision-making regarding each XTx trial.

Ethical Considerations Relevant to Xenotransplantation

It is widely accepted that certain ethical principles must be applied to experimentation conducted in humans, and these have been outlined in the Belmont Report (*14*). They include respect for persons, beneficence, and justice, which call for certain ethically required actions or applications. Respect for persons requires informed consent. Beneficence (the duty to benefit others) calls for an assessment of risks and benefits. Justice requires an equitable selection of research subjects. An ethical review is done for the purpose of ensuring that studies are conducted according to these principles and their applications (*15*, *16*).

Beneficence and Risk/Benefit Analysis

In most types of human research, assessment of risks applies mainly to the research subject, whereas the potential for benefit may be to others in society, with or without potential benefit to the research subject. In the case of XTx, both the risk and the benefit may be to society as well as to the subject, and the nature of the risk to society raises special considerations that are discussed below.

First, risk assessment is based on the principle that the possible harm of the research must be outweighed by its probable benefits. In other words, research must be justified on the basis of a favorable risk/benefit assessment (*16*). In instances involving significant risk to the research subject or society, there must be significant potential for benefit. This is an especially important consideration in the field of XTx, in which there is considered to be a potential risk of introducing new infections into the human population, and in which major barriers to success still exist.

Thus, clinical trials of XTx must be scientifically sound and associated with significant expectation of benefit to the transplant recipient and hence, ultimately, to society. There should be adequate preclinical, including, whenever possible, nonhuman primate data, to support the possibility that the xenotransplant has the potential to succeed. It is noteworthy that a similar viewpoint was expressed in The Transplantation Society's ethics statement in 1997 (*7*). Expectation of benefit is particularly important because the possibly extensive benefits of XTx can be undermined if its potential risks to society are not controlled or because positive public perception of XTx is not maintained. Public perception must always be considered in an overall risk/benefit analysis because, as public awareness of the potential infectious risks of XTx has increased in recent years, society - through governments and other legal institutions - will ultimately decide whether or not the potential benefits of XTx justify the risk (and cost) to society. Maintenance of a positive public perception requires restraint on the part of enthusiastic investigators and biotechnology companies, who must refrain from statements that may be interpreted as a promise for clinical success before adequate scientific data have demonstrated that the major obstacles have been overcome.

The benefits that result from positive perception also raise the required level of expected potential benefit of any clinical trial that is conducted, because one or two highly publicized failures may be sufficient to severely damage the image of XTx research. Thus, it is particularly important that clinical trials be initiated only with supporting preclinical scientific data. Furthermore, it would be desirable for patients included in trials to be in sufficiently good condition that there is a chance that they will survive the procedure for more than a few days or weeks. A xenotransplant procedure that provides a short prolongation of survival to already moribund patients would be difficult to justify in terms of the risks to society and to public perception of XTx. On the other hand, the risks associated with XTx mandate that the procedures be evaluated in patients who lack reasonable alternatives. Both of these considerations must be balanced in order to identify the most suitable candidates for XTx trials.

Secondly, for any ethically conducted trial, risks to the patient and to society must be minimized. Major efforts have been carried out by national and international bodies to develop guidelines for minimizing the infectious risks of XTx. It is widely agreed that animals used for XTx should be bred in closed colonies in captivity, to permit the exclusion from the colony of known potential pathogens to humans. However, potential pathogens which have not been previously identified and which therefore cannot be screened for, and particularly those that do not cause disease in their natural non-human hosts, still impose a potential risk to humans under such conditions. Viruses that do not cause disease in their original hosts may modify themselves once transmitted to humans and become severely pathogenic. If such modifications occur and an infected xenotransplant recipient spreads the infection to human contacts, society could be placed at

risk of an epidemic from an unidentified pathogen, particularly if the clinical manifestations of the infection have a long latent period, as is the case for HIV-1. In part because of the high risk of unknown infections being transmitted from non-human primates (*17*), as exemplified by the HIV pandemic, these animals have largely been removed from consideration as source animals for XTx. While these risks are reduced with the use of porcine source animals for XTx (*18*, *19*) because of their greater phylogenetic distance from humans and the ability to breed them in specific pathogen-free, closed colonies, the risk associated with unknown infectious agents cannot be quantitatively assessed.

In considering pigs as potential xenograft source animals, particular concern has been focused on the potential for endogenous retroviruses, which are vertically transmitted and cannot readily be excluded by breeding procedures in a closed colony. The demonstrated potential of porcine endogenous retroviruses (PERV) to infect human cells in vitro (*20*) has increased the concern that these could infect xenotransplant recipients, who are likely to be susceptible because of immunosuppressive therapies they are given and because the xenogeneic tissue is introduced directly into the body. PERV could potentially recombine with human endogenous retroviruses, or become modified in other ways to become pathogenic in their new hosts. These risks could be further potentiated by genetic modifications of the porcine source, such as removal of the Gal epitope by genetic engineering. Gal sugars on retroviral envelope proteins may be a target for natural antibody-mediated viral resistance (*21*), and this initial form of resistance will disappear if Gal-knockout porcine donors are used. While no examples of PERV infection have yet been documented in human (*22–25*) or non-human primate (*26–28*) xenotransplant recipients, and recombination events between endogenous retroviruses in a recipient's genome and others introduced exogenously have not been documented, the magnitude of the potential risk to society if such an event were to occur mandates vigilance. The extensive human experience with *short-term* exposure to porcine materials, including patients receiving porcine insulin and clotting factors and temporary skin grafts, and more recently, those receiving islet or neural cell transplants or blood perfusion through pig livers, is reassuring. However, none of these situations involves the *long-term* presence of large numbers of porcine cells or organs in an immunosuppressed individual, in which the potential for unknown porcine viruses to spread is increased.

The optimal way to avoid the introduction of new infections from animals to humans via XTx has been considered by both international and national health agencies in countries such as the United States, Canada, Australia, New Zealand and Japan, and in Europe. Most of these agencies agree that extensive monitoring of such recipients is necessary, and specific guidelines for such monitoring have been developed. Examples include the guidelines of the United Kingdom XTx Interim Regulatory Authority (*29*), the United States Food and Drug Administration (*30*), the standards-based risk management regulatory framework developed by Health Canada (available at http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/btox/standards/xeno std e.html), and those of the World Health Organization (*31*). However, there is still considerable uncertainty about the costs, location and appropriate time to archive patient specimens. Another issue is the degree to which close contacts should be monitored and have their specimens archived. Furthermore, the assays for PERV have been under continual development and, as assay sensitivity and specificity improve, the necessity of re-analyzing previously studied samples should be considered. The development of a standardized assay for PERV is an important goal.

Despite the above limitations, existing guidelines and the lack of evidence for PERV transmission to humans so far, and evidence that some pigs may be incapable of producing PERV particles that can infect human cells (*32*), are encouraging. These developments lead the IXA Ethics Committee to conclude that, when such monitoring practices are followed, it is appropriate to move forward with XTx trials that also satisfy the other ethical principles discussed in this paper.

Respect for Persons and Informed Consent

The potential risk of XTx to society brings some special conundrums to the development of an appropriate informed consent process. The purpose of informed consent is to ensure that research subjects have as full an understanding as possible of the potential risks and benefits of the medical procedure, and that they affirmatively agree to participate in the research in the absence of undue influence or coercion (*14*, *15*). Normally, the burden of risk is borne largely by the research subject. In the case of XTx, however, the burden of risk is also carried by close contacts and medical caregivers and by society, which may reasonably insist that the research subject agrees to life-long monitoring, avoids blood donation, informs close contacts about the xenotransplant and its potential risk of infection, and follows patterns of behavior with his or her close contacts that will minimize infectious risks. Asking a subject to agree to life-long monitoring effectively denies him or her the right to withdraw from the study at any time, a fundamental right which is delineated in the Declaration of Helsinki and the US Code of Federal Regulations.

Another difficulty is whether or not current and future close contacts of xenotransplant recipients could be expected to refrain from blood donation and agree to monitoring if this were deemed necessary. Notification of close contacts and caregivers about the potential infectious risk surrounding a xenotransplant recipient could violate principles of confidentiality, another fundamental right to which human research subjects are entitled. Furthermore, even if an individual agrees to all of the above in order to undergo the procedure, there is currently no means by which he or she can be forced to comply. In the event that a new infectious agent is introduced into the human populace through XTx, and initiates a new epidemic, who will be held responsible? The research subject, his or her close contacts, the organization sponsoring the study, the Ethics Committee of the institution that allowed the study to proceed, and the government and its regulatory agencies which approved the study could all arguably be held responsible. While there is no clear solution to these questions, it will be essential to select research subjects who appear capable of fully understanding the potential impact of their behavior on the rest of society, and who seem genuinely motivated to minimize these risks. Government-level approval of XTx procedures may be seen as an implicit form of social acceptance that the potential risks will be outweighed by its potential benefits. For this reason, public input

into the decision as to whether or not a country will proceed with XTx studies is necessary, and governments may consider whether research subjects should be informed that certain government services will be withheld from subjects who do not honor their original promises to abide by practices that will minimize infectious disease risks.

The Problem of "Xenotourism": Fairness in Safety Precautions

The potential risks of XTx will not be confined to the country in which the transplant is performed. Even the most assiduous safety efforts of any nation or group of nations may be ineffective in the absence of internationally agreed regulations and monitoring procedures for XTx. This problem arises because patients are mobile and could receive a xenograft in one country, which may or may not have appropriate regulatory and monitoring processes, and later leave that country and enter another without ever having to state that they are the recipient of a xenograft. In ethical terms, the principle of justice requires all nations to bear their fair share of responsibility regarding the control of infectious disease risks.

At present, no country's immigration authorities routinely ask a question that would reveal that a particular person is a xenograft recipient. The scale of such "casual" xenotourism is likely to be small. However, there is a risk that entrepreneurial xenotransplanters may deliberately set up business in countries with minimal or no regulation and set about attracting foreigners with organ failure to come to be transplanted and then return home. The absence of questioning about XTx upon re-entry, and the absence of a mechanism for bringing such patients into surveillance programs in their home countries almost guarantee that such patients will avoid surveillance when they return home.

There is no simple solution to this problem. It can probably only be managed by having as complete as possible international agreement on regulations covering XTx, and for each country to institute appropriate questioning of entrants. It may be necessary to have XTx gazetted in a manner similar to a notifiable infectious disease so that physicians who may see such patients are obliged to register them with a national authority.

Securing Benefit over Harm through Preclinical Studies

What level of preclinical data should be required before proceeding to a clinical XTx trial that is likely to benefit patients and society? The criteria by which animal studies should be judged before deeming it appropriate to move forward with clinical studies have been strongly debated. It is our position that these criteria should not be predefined, but should be determined on an individual basis, with an appropriate assessment of the preclinical data that are available at the time, the limitations of the data and of the models used, the potential to obtain more specific and relevant preclinical data, and the expectation that conditions in a human recipient will be more favorable than those in non-human primates receiving similar transplants in preclinical studies. The latter may be the case because of improved monitoring and supportive care available to humans than to animals used in preclinical studies, and because of the superior ability of human transgenes inserted into the porcine genome to interact functionally with other molecules in a human compared with a non-human primate. These limitations do not, in our view, override the need for encouraging preclinical data before proceeding to clinical trials; they must simply be taken into account in the decision-making process. Although perhaps outside the scope of this paper, it is our view that an infusion of funds into the development of core facilities for measuring drug levels and producing biological reagents that are specific for non-human primate species used in XTx research, and into non-human primate research facilities with more sophisticated monitoring techniques, could go far in improving the quality of data obtained, avoiding unnecessary duplication of resources, and improving the clinical applicability of data obtained from non-human primate studies. In any case, an unbiased assessment of the potential for benefit and of the need for more preclinical studies that can realistically be performed, should be obtained before any clinical study proceeds.

The fact that clinical trials of cellular XTx have been previously conducted in the absence of non-human primate preclinical data (*8*, *33*) does not justify continuation of this practice. Since the time these trials were initiated, we have obtained information regarding the potential of PERV to infect human cells and to infect immunodeficient mice in vivo (*34*, *35*), raising the level of scientific and public concern about the possibility of PERV transmission to humans. Thus, the requirement for non-human primate data to demonstrate the potential for significant benefit to the xenotransplant recipient is currently of greater importance in order to justify proceeding with clinical trials of XTx. Although the procedures associated with islet XTx are less potentially risky to the recipient than solid organ XTx, the level of benefit demonstrated in the previous clinical trial (*8*) and in previous non-human primate studies of porcine islet xenografting is not, in our view, sufficient to justify further clinical trials using the same approach. While we acknowledge that success in non-human primate studies does not guarantee similar success in humans, we believe that promising data would be needed in a non-human primate study of porcine islet XTx before a clinical trial using a particular approach could be justified. We will not attempt to define the duration of survival considered "promising" in this paper, as we believe this is a determination that must take into account the strengths and limitations of the particular nonhuman primate studies performed, as is discussed above.

Ethical Issues Regarding the Use of Animals

First, there are a variety of emotional, personal identity issues associated with the transplantation of an organ from another human being in a recipient, and even stronger reactions might be associated with the implantation of organs and tissues from non-human source animals. This is a risk that should be discussed with the individual xenotransplant recipient, and should be considered as thoroughly as possible in advance of the transplant and managed appropriately if it does occur. We do not believe that these concerns and other social taboos against XTx are a priori reasons to remove XTx from consideration. They are individual issues that can be addressed with candidate recipients, who should be encour-

aged to talk with a counsellor or religious advisor if concern is expressed.

Secondly, the rights of the xenograft source animals are a consideration that has generated controversy. For many members of society, these issues vary according to the species under consideration as a source animal. Non-human primates such as baboons have complex social behaviors, and there are many ethical concerns about their use, including the fact that those closest in size to humans are protected species. In addition to these ethical issues, financial and practical problems, relating to the breeding of large numbers of these animals in captivity for use as organ-source animals, and increased safety concerns about viral transmission, which is more likely to occur between closely related species, essentially rule out non-human primates as useable organ sources.

The use of pigs, which are widely bred in captivity and used for food in many societies, as potential organ-source animals is considerably less controversial. Although it is not necessary for humans to eat meat in order to survive, ethical concerns do not override desire and do not prevent most people from eating meat. Therefore, most non-vegetarians will consider a life-saving organ or tissue transplant from a pig to be ethically acceptable. The special considerations relating to religious beliefs that exclude pork from the diet are discussed below. Various animal rights advocates, however, maintain that humans do not have the right to breed and use other animals for our own needs because animals have the same rights as humans. While this viewpoint must be respected, it is not a mainstream view in societies in which meat is eaten, leather goods used, etc. It has also been suggested that the crucial factor in deciding whether or not it is appropriate for humans to use animals should be the question of whether or not the animal has sufficient awareness to be capable of suffering (*36*). There is, however, room for considerable debate on which species are capable of suffering.

It is an accepted ethical principle that animals used for research or clinical XTx must be treated respectfully and humanely, the minimum number should be used, and their use must not occur without institutional approval (*37*). Genetic modifications of xenogeneic source animals are considered to be acceptable as long as they do not change the overall character of the animal species.

Religious Views on Xenotransplantation

Whereas ethics deals with what is right or wrong in terms of common experiences and rational argumentation, religious beliefs distinguish between right and wrong actions based on boundaries set by God, the transgression of which may be seen as sacrilegious or sinful (*38*). As religion plays a major role in the day-to-day life of many individuals, and may indeed influence and restrict lifestyle choices and actions, including which food may be eaten or which medical treatment may be undertaken, we will briefly examine religious views of XTx.

Monotheistic Religions

The three major monotheistic religions, Christianity, Judaism and Islam, have many things in common, and it has been argued that these commonalities result in similar approaches and responses to the issues raised by XTx (*39*). The three specific religious issues raised by XTx are: (i) the acceptability of intervention by humans in the order of creation; (ii) the acceptability of using animal organs to improve the chances of survival and well-being of humans; and (iii) the impact of the xenotransplant on the identity of the human recipient.

Intervention in the Order of Creation

As discussed above and elsewhere, genetic modification is probably required to develop suitable source animals. Does man have a right to do so and what are the limitations? For the three major monotheistic religions, man alone was created in "the image and likeness of God" and "has dominion over all other creatures and all the earth". All three religious doctrines have a hierarchy in the order of creation, in which Man has a special place and is different from the rest of creation. The Roman Catholic Church has further ascertained that Man has a mandate to guide the life of creation toward the integral good (*40*). Therefore, genetic engineering of animals, if used for the benefit of mankind, does not conflict with Catholic theology, but does indeed represent an opportunity for "creative responsibility in making reasonable use of power that God has given to him". Similar arguments could be made for Judaism and Islam, as these religious laws permit animal use for practical benefits to mankind (*39*, *41*). Therefore, XTx does not contravene the order of creation.

Acceptability of Using Pig Organs

As both Judaic and Islamic laws forbid the raising and consumption of pigs, it has been suggested that transplanting pig organs into observant Jews and Muslims would be prohibited. However, using pig organs for XTx is not regarded as eating pork, but as deriving a substantial benefit from pigs. Furthermore, both Judaic and Islamic laws allow for exceptions to dietary laws, particularly when it comes to saving a human life (*39*, *41*). Therefore, all three major religions justify the sacrifice of animals only if there are to be significant benefits to humans; the preservation of a human life would justify XTx. Nevertheless all three religions prohibit cruelty to animals, and insist on humane treatment and that suffering be minimized (*39–41*); the ethical issues relating to the use of animals have been discussed above.

Identity of the Human Xenograft Recipient

Another religious issue raised by the prospect of XTx is whether the xenograft will affect the recipient's personality or identity and, more importantly whether pig DNA will enter the human genome, particularly in germ cells, and thus be transferred to offspring. For some time now, all three religions have accepted the use of pig heart valves and insulin to treat humans. Furthermore, allotransplantation is now acceptable to all three religions, with the allograft being viewed as purely a functional organ without affecting the recipient's identity. Therefore the use of pigs as a source of functioning organs should not present a major problem and should be seen as being acceptable. The Catholic Church view is that all pig organs, with the exception of brains and gonads, are acceptable (*42*).

Non-Monotheistic Religions

Non-monotheistic religions are widely embraced in some countries, such as Japan and India, where cadaveric allotransplantation is virtually non-existent for either religious or cultural reasons, and successful XTx would therefore have a significant impact.

Buddhism

Like the three monotheistic religions discussed above, Buddhists require proper ethical conduct to reduce hurt and suffering in non-human animals and humans, all of which are capable of feeling pain. In regard to allotransplantation, Buddhists believe that organ and tissue donation is a matter of individual conscience and indeed place high value on acts of compassion. The fundamental teachings of Buddhism regarding the protection and minimization of injury to animals would make XTx unacceptable, but there is no law precluding individual Buddhists from availing themselves of XTx in accordance with their "stage of perfection." There is no written resolution on this issue and Buddhists believe this is a matter that should be left to an individual's conscience.

Hinduism

Hindus believe that the body must remain whole to pass into the next life, and therefore do not believe in transplantation - either allotransplantation or XTx. However, religious law does not prohibit Hindus from donating their organs or accepting an organ, both of which are an individual's decision. There is nothing in the Hindu religion indicating that parts of animals cannot be used to alleviate the suffering of humans, with the exception of the cow, which is sacred to Hindus. Pigs would be acceptable. As with Buddhism, there is no one view, and it is an individual choice whether or not to accept a xenograft.

The IXA Position on Selected Ethical Issues Relating to Xenotransplantation

Urgent Need to Control for Infectious Disease Risks

While guidelines on informed consent and monitoring procedures are still under development, considerable effort has already been made toward the development of guidelines for husbandry of source animals and monitoring of xenograft recipients. It is the position of this Committee that XTx trials in humans should only be performed with oversight from a governmental regulatory agency with guidelines similar to those developed by the agencies mentioned above. These trials should include the use of source animals housed in closed colonies from which known pathogens and potential pathogens have been excluded, as well as monitoring procedures for XTx research subjects and, where deemed appropriate, their close contacts. The development of a national repository for holding specimens from these human subjects is desirable in countries in which such trials are conducted. If this is not possible, specimens must at the very least be properly and routinely obtained, tracked, analyzed and stored. In the absence of such oversight and monitoring, clinical XTx should not be performed.

Given that many countries around the world are beginning XTx efforts, and that individuals may freely travel from one country to another to undergo XTx procedures, this Committee strongly emphasizes the urgent need for international cooperation to develop universally accepted oversight procedures and standards, including guidelines for monitoring xenotransplant recipients. The committee recommends that the IXA should take leadership in its capacity as an international organization to encourage the development of a cooperative international effort to develop universal guidelines for XTx. Without such cooperation, the efforts of individual nations to minimize the potential risks of XTx may be thwarted by travel of prospective recipients from countries with regulation to those without for the purpose of undergoing XTx, or by the entry into other countries of individuals (or their close contacts) who have received a xenotransplant in a nation that does not have regulatory guidelines for XTx. In addition, the IXA should encourage the public health authorities in countries with regulations on XTx to consider developing questions to screen entrants into the country to identify those who have had xenotransplants abroad, monitoring (and/or exclusion or quarantine) procedures for such individuals, and public health reporting requirements for physicians seeing patients who have undergone XTx in foreign countries. We have witnessed the worldwide spread of the HIV-1 epidemic in our lifetimes, and we must do everything in our power to prevent a similar scenario from developing as a consequence of a promising therapeutic strategy such as XTx.

Ways to Uphold the Integrity of Clinical Trials

It is the position of this committee that ethical principles and their application should be upheld in the conduct of all XTx research, including, of course, clinical trials. As the topic of this paper is clinical XTx, we will summarize the principle-based actions that we believe must be followed for the conduct of clinical studies in XTx:

1. There must be adequate preclinical data to justify the trial, that takes into account the risk to the research subjects and to society imposed by the trial. It follows that the limitations in our knowledge of infectious risks currently mandate a relatively high expectation of benefit to the research subjects on the basis of sound preclinical data.

2. The trial must be conducted with regulatory oversight from a national body that ensures that source animals are derived from closed colonies that are free of known pathogens. If possible, this should include the use of pigs that have been shown to be incapable of transmitting PERV to human cells. The oversight must also ensure that routine monitoring of the research subjects (and possibly of close contacts) is performed, and that proper facilities for archiving of specimens are available.

3. The trial must be conducted with approval and oversight from an institutional panel to ensure the ethical conduct of human research.

4. The trial must be conducted with approval and oversight from an institutional panel to ensure the ethical and humane treatment of non-human animals. The committee advocates the exclusion of non-human primates as source animals, because it is felt that the infectious risks and ethical concerns override the potential benefits of using them for this purpose.

The Committee recommends that the IXA adopt a policy of a priori rejection of abstracts submitted for presentation at its biennial international congress or to its journal *XTx* if there are significant concerns that the above principles may

have been violated in a clinical or preclinical study. While implementation of such a policy may not be simple, the following procedures should be feasible:

1. Authors should be required to document institutional and, in the case of clinical XTx research, ethical approval and oversight of the research by a competent regulatory authority, in the submitted abstract or paper.

2. A questionnaire should be provided to reviewers asking if there is concern about violation of the above principles in the reported studies. If concerns are raised by a reviewer, the abstract or manuscript in question should be brought to the attention of the IXA Ethics Committee for review and discussion with the IXA Council as a whole.

All of the considerations and concerns discussed above are balanced by the enormous potential benefit to society of XTx. It is the position of this committee that the potential of XTx to alleviate the organ shortage as well as to alleviate diseases not currently treated by transplantation mandate continued preclinical and, when appropriate, clinical efforts in this area. Nevertheless, the possible risks to society imposed by this work mandate a proactive leadership role for the IXA membership to ensure the minimization of these risks and the responsible, ethical conduct of all XTx research.

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