

Starting clinical trials of xenotransplantation—reflections on the ethics of the early phase

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Abstract

What kind of patients may be recruited to early clinical trials of xenotransplantation? This is discussed under the assumption that the risk of viral infection to the public is non-negligible. Furthermore, the conditions imposed by the Helsinki declaration are analysed. The conclusion is that only patients at risk of dying and with no alternative treatment available should be recruited to xenotransplantation trials in the early phase. For some of the less dangerous cell or islet cell xenotransplantation other categories might be recruited. The risk of cell and islet cell xenotransplantation should, however, be weighted against the development of other technologies. In order to safeguard the public, the opt-out clause in the Helsinki declaration should not be fully applied. Legally binding rules on obligatory monitoring and restrictions should be imposed—before clinical trials start.

(Journal of Medical Ethics 2000;26:231–236)

Keywords: Xenotransplantation; ethics; clinical trials; risk

At present there is a shortage of human organs for organ transplantation. The use of animal organs for transplantation, that is, xenotransplantation, would greatly increase the number of organs available. Other forms of xenotransplantation (living cells, islet cells and tissue) open up new possibilities of treatment. For various reasons the pig is the designated donor animal.¹

It is not known how successful we will be in overcoming the physiological and immunological compatibility problems of organ transplantation from animal to man, but progress has been made in overcoming the very first hyperacute rejection.² In contrast to solid organ xenotransplantation, transplantation of pig cells or pig islet cells seems to give no immunological adverse reaction.³

Hopes and fears surround the new technique. The fears are concentrated around the risk of the spread of new infections of a porcine genesis among the general public. This risk has been widely debated and demands for a moratorium have been made.⁴ The hopes are concentrated on new and more widely available treatments. In the short run, xenotransplantations using cells or cell islets look promising and patient organisations are urging a move to the clinical phase.⁵

This paper will focus on the ethical problems of risk to the public and under what circumstances research subjects might be recruited for early trials. Animal ethics problems will not be discussed in this paper.

Risk to the public

The possibility of transmission of porcine endogenous retrovirus (PERV) to human cells in vitro has been demonstrated.⁶ There is a risk (the extent of which is at present unknown) that the porcine retroviruses will infect the transplanted patients and spread to the general population. There is also a risk that the retroviruses will mutate or recombine in their new human surroundings and transform into a dangerous human pathogen that may cause an epidemic. Porcine endogenous retrovirus cannot be eliminated from pigs as the virus is incorporated into the porcine genome.

Arguments have been advanced that some retroviruses which can infect cells of other species (such as PERV infecting human cells) may give rise to two possible effects: mutagenesis and immunosuppression.⁷ The first may induce cancer. The second will damage the human immune system and "... in analogy to HIV and SIV, high titer virus replication may cause an AIDS-like disease in the immunosuppressed human transplant recipient".⁸ Obviously, if the patient is at the same time receiving immunosuppressive drugs the risk is increased. Given the above arguments about the effect of retroviruses one would regard the spread of a xenotransplantation-induced infection to other persons by blood and other bodily fluids as the most probable way of transmission.

Studies of two groups of Swedish patients who had participated in xenotransplantation showed no sign of PERV infection.⁹ Caution was, however, recommended in the comments of one of the leading medical journals.¹⁰ The results from a recent study of about 160 patients who have undergone xenotransplantation with living pig cells or extracorporeal connection to a pig organ show no sign of PERV infection.¹¹ Two findings are of special interest (apart from lack of evidence of infection). Pig cells can survive for many years in the human body and microchimerism has been detected. (In microchimerism the pig cells in the human body contain PERV but—if no infection has occurred—no virus particles have been incorpo-

rated in the human genome.) These results are encouraging, but the risk that the xenotransplantation may cause PERV infection can still not be ruled out. Whether one can really distinguish between microchimerism and an infection is not clear.¹² The real test of the danger of PERV in humans will obviously arise when there is long term survival of xenografts of solid organs in patients.

Furthermore, the risk of PERV has been discovered only recently. Obviously, there may be more viruses around and more, as yet unknown, risks.

Should there be a moratorium?

In a paper by Fritz Bach *et al* a moratorium has been proposed based on the perceived risk of infections spreading to the public. Risks to the public should be decided by the public. The authors want to have some kind of "... public mechanism for determining the acceptability of, and method of consent to, the risk".¹³ They claim that: "The level of risk for such infections to the recipient and the likelihood that such infection will spread to others is unknown".¹⁴

The worst case scenario is, of course, of there being a mutation of a porcine virus that turns it into a murderous human one, which then spreads widely through the human population. Is this a serious risk? Obviously, if the worst case scenario materialises and we have a new deadly plague, we will all agree that it was a very great risk indeed and that, sad to say, very few took it seriously. The problem is that we do not know the probabilities for the various outcomes, nor is there reason to believe that we know all the risks.

The ultimate test will be to search for signs of viral infection following long term survival of xenografts in transplanted patients. This is also recommended by Bach and his co-authors. They want small-scale clinical trials to start, but not before public deliberation on how to monitor and issue restrictions for the participants has taken place. These small-scale clinical trials should go on for a couple of years. After that there should be a break and the results should be evaluated—presumably also for a number of years. Bach *et al* are aware that this break could be difficult and stress that it is important in this evaluation phase to stop further xenotransplantations. After the evaluation phase, the length of which again should be decided by public deliberations, if the danger has not materialised, xenotransplantation could proceed on a larger scale.¹⁵ In the following discussion it is presumed that clinical trials of xenotransplantation are desirable (because of the potential benefits) but that the risks pointed out by Bach and others must be taken into consideration before starting clinical trials.

What restrictions should be imposed on early transplanted patients?

In discussions on clinical trials of xenotransplantation and on safeguarding the public, various forms of restrictions have been discussed. However, much more should be done in this area. That xenotrans-

planted patients should be monitored life-long, and should not give blood or donate organs are some of the not too severe restrictions which are often mentioned.¹⁶ But what about moving around freely in the population, what about sexual relationships, what about having children? And how long must these safeguards be kept in place?

In an influential report issued by the Nuffield Council it is stated that: "It would hardly be acceptable to isolate xenograft recipients suffering from an infectious disease, or to ask them to refrain from sexual intercourse or ... from having children".¹⁷ According to the Nuffield Council such restrictions would be ineffective as well as being ethically problematic. In a recent paper by Hughes criticising the Nuffield Council report for not taking its own risk assessment seriously enough, it is argued that: "... the conclusion to which we are led, if we take seriously both the interests of animals and the risk of disease transmission to humans, is that a moratorium should be imposed upon xenotransplantation procedures at least until possible avenues for increasing the supply of human organs have been exhausted and until a more reassuring judgment can be reached on the prospects for preventing and containing transmitted infections".¹⁸

In my opinion, we could indeed ask transplanted patients to consent to exactly what the Nuffield Council deemed unethical—namely, as part of their informed consent *before* any trials begin. To impose the restrictions afterwards is ethically problematic. And we must do our utmost to make the restrictions effective by backing them up with legal sanctions. Attempts to increase the number of human organs for transplantation should also be made. The scarcity of human organs will, however, probably remain, and one can envisage a widening of indications for transplantation if more organs become available. Even if most countries were as effective as Spain in harvesting cadaveric organs, there would still not be enough.

Given that stringent safeguards are introduced, a cautious start to the clinical trials of xenotransplantation is consistent with a cautious approach with regard to the risk of viral infections.

The difficulty of controlling and regulating is further aggravated by the freedom of physicians to use innovative measures in order to save lives, or more generally to restore the health of the patient. A new surgical technique can, for example, be used to try to save the life of a patient. Usually the physician does not have to submit the new procedure to an ethics committee for consideration—nor may there be time for such a consultation. The use of new experimental procedures goes on all the time and many of the early xenotransplantations took place in this way.¹⁹ The regulation of clinical research by the Helsinki declaration allows for experimental measures to be tried in the clinic without prior consultation with an ethics committee. This clinical freedom must be withdrawn for xenotransplantation procedures—otherwise regulation will be ineffective.

In this paper the risk of a spread of a human pathogen induced by PERV infection is assumed to be non-negligible, which means that therefore the early clinical trials must be performed under a strict safety regime. What conditions should be fulfilled by patients recruited to such early clinical trials? I will discuss this, starting with consideration of the Helsinki declaration.

The ethical framework for clinical research on humans

Originally adopted in 1964 the Helsinki declaration has been amended many times, but can still be considered as the basis for the ethical code for medical research on humans.²⁰ Most institutional review boards or other ethical committees in the area of medical research operate according to the principles of the declaration. Some of the most relevant points are briefly elucidated below.

One important point is that *all clinical trials should be entirely voluntary; the participants should be fully informed and consent freely*. The voluntary character of the trials is stressed by the clause that research subjects *must be able to exit from the research at any time*—no reason need be given—and the exit should not in any way affect the quality of the medical treatment they receive. Imposing strict legally binding safeguards on patients in order to protect the public from xenotransplantation-induced viral infections might conflict with the exit clause. One might, however, allow the research subjects to exit from the scientific part of the trial follow up (for example to study rejection processes) while making participation obligatory in the follow up related to protection against infections spreading to the public.²¹

Another point is that... *in any medical study, every patient ... should be assured of the best proven diagnostic and therapeutic method*. This puts, for example, stringent conditions on the design and execution of human medical research designed as randomised controlled studies. Such randomised clinical trials are consistent with the Helsinki principles, *if one does not know which of the alternatives in the trial is the better one*. As soon as there is a known (significant) difference between the alternatives, the trial should be terminated and all patients referred to the best possible treatment.

Although clear in theory, the application of the clause of best possible treatment is often difficult in practice. First of all, it is often a problem of statistical interpretation and evaluation of experimental data to find out if there is a significant difference in outcomes. Secondly, the earlier the trial is stopped (the smaller the difference detected) the less scientific information is obtained. There are further problems when trials are done in less developed countries.²²

The Helsinki declaration stresses that the interests of the research subject should be the first consideration for the medical researcher responsible for the trial. It is stated that an independent committee should investigate and judge the experimental protocol before the trial starts. It is clearly

stated that under *no circumstances* should the interests of society overrule considerations for the health of the research subject. In the xenotransplantation case, an implication of the Helsinki principles is that the potential beneficial use of future xenotransplantation for large patient groups should not overrule the risks to, and interests of, the actual patient recruited into a trial. In my opinion, free and voluntary informed consent is a necessary but not sufficient condition for inclusion in a clinical study. Such a point of view may be deemed to be paternalistic and therefore unacceptable.²³

On the other hand, while there is a generally recognised right for patients not to participate, there is no right of inclusion. Deliberations on how many to recruit to a study should be based on the need to obtain statistical significance and power, not on how many patients might potentially benefit from being included in the study.

The Helsinki declaration is strongly worded and in many ways restrictive. It has, however, a general positive view of medical research, although its general focus on the individual benefits for and risks to the participants make it adverse to more utilitarian arguments for certain types of research. It is not enough that a particular trial is good for society. The Helsinki declaration is, of course, not given by God and is open to change (for example the exit clause in xenotransplantation trials may be changed). I will discuss what the Helsinki principles imply for the early clinical trials of xenotransplantation.

First, the case of life-saving xenotransplantations will be discussed. The typical case would be a patient who needs an organ (or a cell transplantation) in the very near future. Secondly, the case of life-quality enhancing xenotransplantations will be discussed. The patient will not die in the foreseeable future without a new organ or a cell transplantation, but life quality may be increased. A typical case might be transplantation of some cells.

Life-saving xenotransplantations

Assume the safeguards and regulations are in place and clinical trials are about to start. Who should be included in these early studies? It should be in the interests of the research subject to participate. This means that there should be no clearly better alternative than xenotransplantation for that particular patient. Presumably, an allotransplantation will at the very start be better than receiving a xenograft—simply because the one technique has been successfully developed over a long period and the other is just starting. For each individual patient, to obtain an allograft is thus better than a xenograft in the early phase of the trials. The consent of the patient is a necessary but not sufficient condition for inclusion; it is the responsibility of the medical researcher to consider whether it is in the interests of the patient to receive a xenograft. Furthermore, I assume that at this early stage, if an allotransplantation is possible, most patients would prefer it. I certainly would.

Therefore, as a general rule *only patients who for some reason cannot obtain a human organ should in this early phase be considered—as there indeed exists an alternative*.²⁴ It is not entirely clear, however, what one may mean by an “alternative”. Below are four criteria for inclusion in clinical trials of xenotransplantation corresponding to differing interpretations of “alternative”. The first is what might broadly be called “medical”.

i) The patient cannot wait.

Typically, transplantation must take place at once and there are no human organs available at such short notice. Another group may be patients who have already been transplanted, perhaps more than once, and have become sensitised to human organs.

The second criteria might be labelled “political”.

ii) There are some rules which lay down that certain categories of patients will not receive allografts.

A typical case would be that some responsible body has adopted a principle, such as age, for example, as a criterion for exclusion in regard to human allotransplantation. Such rules excluding certain patients from allotransplantations must be part of the general health system—and not introduced in order to be able to start clinical trials of xenotransplantation.

If a country does not permit allotransplantation from cadaveric donors, patients in such a country will, in one interpretation, fall into category ii. (Organs obtainable from living donors, ie kidneys, would be an exception). Lack of financial resources on the part of the individual patient may be regarded as falling into this category too, if there has been a political decision that patients must pay for allotransplantation—and xenografts in trials are free. If such patients could be included in the early trials, many could be recruited among the poor in the Third World. But not all the patients that could be recruited should be recruited, and it would be an ugly situation if early xenotransplantation trials were carried out only with poor research subjects.²⁵ A criterion based on age is different; we all get older.

Apart from these medical and “political” criteria, it seems difficult to avoid introducing a third criterion of a more psychological kind.

iii) The patient cannot bear to wait for an organ for more than, say six months (or some other time to be fixed by “political” decisions).

There may even be a possible religious or moral criterion.

iv) The patient has religious or moral reasons against receiving human organs and would actually prefer animal organs.

There are various problems linked with the above conditions. The drawback of i) is that all the patients recruited to the xenotransplantation trials will be very ill. This means also that the chance of a successful xenotransplantation is also not too high. According to the Helsinki principles it would be wrong to include healthier patients because they are better off waiting for a human organ.

All patients participating in clinical trials of xenotransplantation should give informed consent.

One might wonder whether patients under pressure (being critically ill) can give informed consent. It is a common assumption when applying the Helsinki principles, that certain groups should never be included. Prisoners, for example, are often thought to be unable to give free consent. Their situation is so bad, the reasoning goes, that participating in medical research and leaving the prison environment for a hospital is “an offer they can’t refuse”. However, critically ill patients offered the choice between a dangerous but potentially life-saving treatment and doing nothing (and then dying) can also be said to having been given “an offer they can’t refuse”. Nevertheless, in the clinical setting we believe that free choices can be made by these very ill patients, who in many countries have a legal right to refuse even life-saving treatment. Hence, it is reasonable to think that in the same way category i) patients may be able to give informed consent.

Suicide risk

The drawback of ii) is that it is not so easy to draw the line in an acceptable way between those who should receive a human organ and those who should not. The problem with iii) is of course that it is more difficult to settle in an “objective” way. How strong should the inability to wait be? Should there be a clear suicide risk? Besides, the psychological reactions of patients depend a great deal on the quality of care and how they are treated while waiting. Applying this criterion might give rise to a conflict of interest. The chances of recruiting healthier patients for the trial (than those recruited under i) is increased if not too many resources are spent on giving this psychological help.

The moral and religious criteria pose problems. What is special about such convictions compared with, for example, an altruistic wish to help research? (This is not sufficient to include patients.) Perhaps the difference is that altruistic patients might accept human organs, while patients in category iv) will refuse. As all transplantation must take place with the consent of the patients, patients in this group cannot be given human organs. It is not clear to me if there actually are people with such convictions. If there are, such persons might be recruited into the early trials.

There are thus problems in connection with the criteria. In the early phase, however, it is not possible to go for something less restrictive—because every participant should have the best possible treatment. As pointed out earlier, informed consent is a necessary but not sufficient condition. Restrictions such as the four conditions above must be applied in order to safeguard the interests of the participants in the early trials.

Even if the above criteria seem necessary according to the Helsinki declaration, there are not enough human organs for everyone who needs a transplantation. Even if xenotransplantation is carried out only as a trial, everyone who participates in the trial—if successful—shortens the queue for human organs.²⁶ Altogether, more lives might be saved and new knowledge gained. The collective of

patients and society at large might be said to have an interest that some patients opt for xenotransplantation even in this early phase. True, but irrelevant according to the Helsinki principles. The interests of society should under no circumstances overrule the considerations of the health of the research subject. *The conclusion must be that only those patients who cannot receive a human organ should be included in the early phase* for dangerous but potentially life-saving xenotransplantation trials.

Whether or not it is in the interests of the patient to participate depends also on the burden of long term treatment with immunosuppressive drugs and also on what restrictions are imposed on the patient to safeguard the public. The more severe the restrictions, the less attractive is the xenograft compared to allograft. The age of the patient is also relevant; it will, in the early phase, be a heavier burden to receive a xenograft at a younger than at an older age.

Life-quality enhancing xenotransplantations

A typical case is a xenotransplantation involving cells, cell islets or tissue from animals carried out for pain relief, to produce insulin or to enhance the brain function for patients with Parkinson's disease. (Some cell transplantations might of course be life-saving; they fall under the discussion in the previous section.)

There are arguments that cell and islet transplantation is less risky than organ transplantation with regard to the spread of infections.²⁷ This might be so, but a cautious approach would, in any case, impose stringent safeguards. One might also suspect that the public would be willing to accept higher risks to themselves in order to save lives than to enhance life quality. A strict control system is also important for public acceptance. It is well known that risk is not the primary factor for the public acceptance of medical applications. Moral acceptability and trust in the control mechanism are more important.²⁸ The regulations for safeguarding the public should be designed primarily to minimise the risks to the public, not to avoid problems for transplanted patients.

As in the life-saving case the important question for each particular patient is: can it be in the patient's own interest to participate in such a study? This depends on risks and available alternatives. One should also look at long term risks. For example, will receiving pig cells lower the possibility of a successful future allotransplantation, if such should be necessary?

As in the organ case, the way the regulation and monitoring is organised will be very important; severe restriction might make the otherwise good life (after xenotransplantation) a life of low life quality. The restrictions imposed are relevant to the question if it would be in the interest of patients to participate. Therefore, it should be stated in advance what restrictions and monitoring will be applied—before any informed consent can be given. Otherwise, what are they consenting to?

Does it matter what disease is targeted? Generally, the more severe the disease and the fewer alternative treatments available, the stronger the case will be. In a similar discussion on what diseases to target with somatic gene therapy, diabetes has been ruled out as not being severe enough and because there are alternatives.²⁹

A case can be made that older patients are more suitable than younger ones to be included in life-quality enhancing trials in the early phase. The same holds for patients with painful and severe diseases. The reason is that if you are old, or in severe pain and suffering, you have less to lose. If the problem of informed consent can be solved, older and sicker patients are more suitable as research subjects than younger and healthier patients, in the early phase.

Given that safeguards are in place, patients at risk of dying by suicide—if they cannot stand living with the disease or with the conventional treatment—can be recruited to life-quality enhancing xenotransplantation trials in the early phase. Another possible category is old and severely sick patients with illnesses where no alternative treatments are available.

Concluding remarks

Legally binding regulations should be imposed on xenotransplantation. *This means that the opt-out clause in the Helsinki declaration cannot be fully applied.* Patients in life-threatening situations (whether for medical, political, psychological or moral/religious reasons), who cannot obtain a human organ, may be recruited to clinical life-saving xenotransplantation trials. Another possible category might be old and severely ill patients who may be asked to participate in life-quality enhancing xenotransplantation trials. Furthermore, the safeguard regime and the restrictions must be in force before trials begin—otherwise patients in the study will not know what they are consenting to.

In the public discussion of the risks of xenotransplantation for the public, important questions should be: are there any alternatives? Can the supply of human organs be increased? Can artificial organs be created, or will it be possible to create organs from one's own cells? The new technology developing around the use of human embryonic stem cells might lead to the development of tissue and perhaps organs. Technical alternatives to xenotransplantation may tip the scale in the public debate, and rightly so. In respect of new technologies, it is easier to envisage embryonic stem cell technological alternatives to xenotransplantation with cells and islet cells than to organs. In general, we should go more slowly on xenotransplantation with cells and islet cells (which are life-quality enhancing) than with life-saving xenotransplantations.

Will the public accept that the risk is worth taking and that the safeguards are adequate? My guess is that part of the answer depends on whether those involved with xenotransplantation take a responsible approach and do not simply ignore the risks. If

the public do not trust those involved in xenotransplantation, any system of regulation might seem insufficient and it may seem more promising to wait for alternative methods.

Acknowledgement

Crants from the research program BIO-CT97-2242 of the European Commission and from the Swedish Medical Research Council (K99-73X-13153-01A) have supported work on this paper.

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News and notes

Wisdom in Healthcare

The XVth international congress of the European Society for Philosophy of Medicine and Healthcare will be held from August 16-18 2001, in Lisbon, Portugal. The theme is Wisdom in Healthcare.

Some of the topics covered will be: Kairos in clinical decision making; philosophy and clinical epidemiology; care ethics; the wise healthcare professional, and the wise patient.

Abstracts should be received by **1st January 2001**.

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