



Australian Government

National Health and Medical Research Council

Animal-to-human transplantation research:

A guide for the community

Public consultation on xenotransplantation 2003/04

XENOTRANSPLANTATION WORKING PARTY

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Paper-based publications

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About this community guide

In 2001, the National Health and Medical Research Council (NHMRC) established the Xenotransplantation Working Party to provide advice on the scientific, ethical and technical issues relating to xenotransplantation research, produce guidelines for the assessment of animal-to-human transplantation trial proposals, and consult widely with the community about these issues.

In July 2002, the Xenotransplantation Working Party released a **Discussion Paper** titled: *Draft Guidelines and Discussion Paper on Xenotransplantation*. The primary role of the Discussion Paper was to provide background material to promote an informed community discussion on this issue. The paper also contained draft guidelines for the conduct of animal-to-human transplantation trials in Australia, if they were to go ahead.

The NHMRC placed advertisements in the major newspapers in all capital cities in Australia and on its website, inviting the community to comment on the Discussion Paper from August to October 2002. Ninety-seven written submissions were received from individuals and organisations within Australia and overseas. During the public consultation period, the working party also held public meetings in Sydney, Melbourne and Perth, and targeted meetings in Perth and Adelaide. These meetings attracted a total of 116 participants.

Thus, the public consultation promoted a high level of community engagement and provided considerable information to the NHMRC about community views on animal-to-human transplantation. However, the submissions received indicated considerable concern in the community that the issues of animal welfare and the potential to introduce new diseases from animals to humans had not been adequately addressed. A third issue of concern was how xenotransplantation research would be regulated in Australia. Finally, some respondents felt that much of the information provided was in a format that did not facilitate community understanding of the complex issues involved.

The NHMRC therefore agreed that the working party should respond to the issues raised and conduct a second round of consultation. As part of the second consultation, the NHMRC recommended that an additional document — a community guide to animal-to-human transplantation (xenotransplantation) — should be provided to facilitate public understanding of the issues. The NHMRC also agreed that the Xenotransplantation Working Party should be expanded to include additional members with expertise in animal welfare, infectious disease control and the regulation of clinical trials. An animal issues subcommittee was also established to assist the working party with issues of animal ethics, animal welfare and regulating the use of animals in xenotransplantation research.

This community guide to xenotransplantation, *Animal-to-Human Transplantation: A Guide for the Community*, has been developed to provide background information on what xenotransplantation is, why it is being considered now, and what the main issues are over which the community is being consulted. It is essential to understand that this community guide is NOT the consultation document. Rather, it is designed to complement and introduce the reader to a second document prepared by the Xenotransplantation Working Party, the **Response Paper** (*Animal-to-Human Transplantation Research: How Should Australia Proceed?*). The Response Paper incorporates the working party's response to submissions received

during the first round of public consultation and invites further public input to the matters being inquired into by the NHMRC. It also includes revised draft guidelines which, if approved, would be used to oversight xenotransplantation research should such research be authorised in Australia.

Readers of this community guide who wish to engage in the public debate are encouraged to obtain the Response Paper, consider the issues and to make a written submission to the NHMRC on the issues raised and, in particular, on the proposed guidelines for the conduct of xenotransplantation research in Australia.

To maximise the opportunity for public comment on the Response Paper, the Xenotransplantation Working Party will be conducting public meetings in all capital cities early in 2004. The meetings will provide information about xenotransplantation and the draft guidelines and enable members of the public to directly question, and put their views to, members of the working party. The public meetings will be advertised in all major newspapers and on the NHMRC website (see below).

The Response Paper and additional copies of this community guide can be obtained from the address given below. Both documents are also available on the NHMRC website.

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Contents

About this community guide	ii
Abbreviations	v
1 What is xenotransplantation?	1
2 What is xenotransplantation research?	3
3 Why is animal-to-human transplantation being considered?	3
4 Is animal-to-human transplantation ethical?	5
5 How well does animal-to-human transplantation work?	6
6 What are the risks?	8
7 How can the welfare of animals be protected?	10
8 How would animal-to-human transplantation trials be managed?	13
9 What are the alternatives?	15
10 How would resources be allocated?	17
11 How is animal-to-human transplantation research currently regulated?	17
12 The way forward	20
13 How you can participate in this public consultation	21
14 Further information	22
Glossary	23

Abbreviations

AEC	Animal Ethics Committee
GM	genetically modified
GTRAP	Gene and Related Therapies Research Advisory Panel (NHMRC)
HREC	Human Research Ethics Committee
NHMRC	National Health and Medical Research Council
NHP	nonhuman primate
PERV	porcine endogenous retrovirus
TGA	Therapeutic Goods Administration

1 What is xenotransplantation?

Many people know of someone who has received an organ transplant. The donor is usually a person who has died as a result of brain damage or an accident, but it may also be a living donor who has donated, for example, a kidney or some bone marrow. This type of transplant, where the donor and the recipient are both the same species (in this case, human), is called '**allotransplantation**'.¹

In recent years, another type of transplant technology has hit the headlines — '**xenotransplantation**'. In human medicine, xenotransplantation means using nonhuman animal cells, tissues or organs to treat humans. It is not a new idea — animal organ and tissue transplants have been tried a number of times over the centuries, but with little success. Now, however, researchers are working on this technology again. Section 3 of this guide explains why.

Allotransplantation: transplantation of a tissue or organ from one individual to another of the same species (for example, from human to human)

Xenotransplantation: transplantation of organs, tissue or cells from one species to another (for example, from pigs to humans)

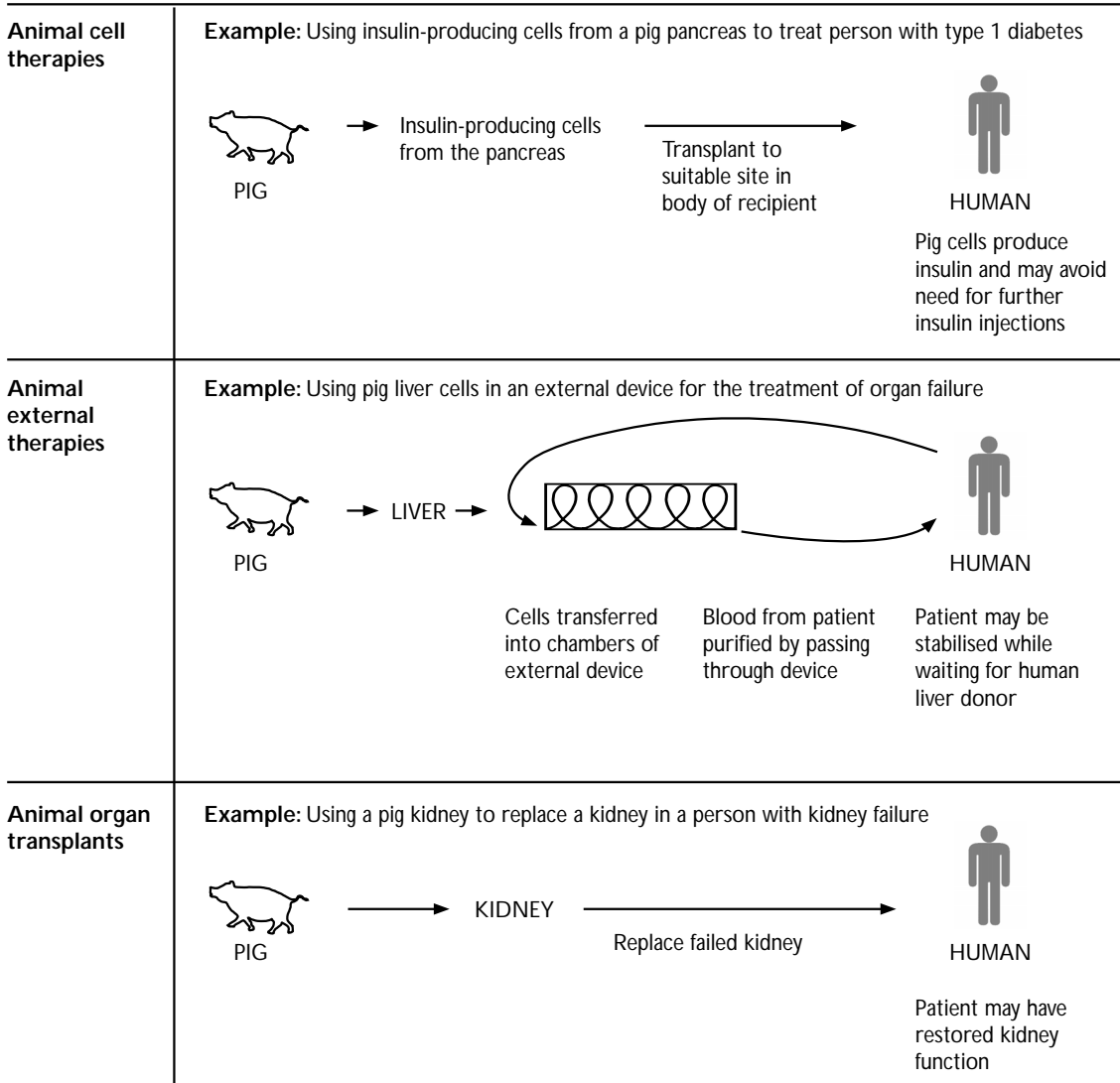
When we hear about transplantation, we usually think of organ transplants such as hearts or kidneys. However, transplants can also be tissues, such as skin or bone marrow, or clusters of specialised cells, such as brain cells or **pancreatic islet cells** (which produce insulin). In this guide, these transplants are called **cell therapies**.

Transplants can also involve different types of procedures. Most involve putting a living organ or tissue into a patient to replace a diseased or failing organ or tissue. Less well known are **external therapies**, which occur outside the body of the patient. An example is when blood from a patient with liver failure is passed through a machine containing animal liver cells to remove toxic substances (a procedure similar to kidney dialysis). Another external therapy involves growing human skin in the laboratory over a layer of animal cells and later using the skin as a graft to treat burns.

Figure 1 shows the different types of procedures that are defined as 'xenotransplantation'.

¹ There is a glossary at the end of this guide to provide more information about technical and other key terms used. The first time words that are described in the glossary are mentioned in the guide they are printed in bold (like this: **allotransplantation**).

**FIGURE 1: WHAT IS XENOTRANSPLANTATION?
(animal-to-human transplantation)**



For simplicity in this guide, we have used the term ‘animal-to-human transplantation’ wherever possible to refer to the use of xenotransplantation procedures for humans.

IMPORTANT POINT: Some devices derived from animals, such as pig heart valves, have been used to treat humans for many years. These devices, although derived from animal material, are inert and sterilised, unlike xenotransplants which are living tissues.

2 What is xenotransplantation research?

Researchers are working out the science of xenotransplantation step by step. They start with laboratory studies on cells and tissues to work out the underlying science. Then they conduct studies on small animals (such as mice, rats or rabbits) to test possible procedures. The same approach is used in other medical research, such as cancer research or the development of new drugs. If these early studies are successful, further thorough research is needed to develop procedures that can be used to treat humans. This research, which is the focus of this guide, includes:

Animal-to-animal studies — in which the source and recipient animals are as similar as possible to the proposed human treatment (for example, from pig to baboon). These **preclinical studies** are needed to make sure a procedure can be conducted safely and effectively on animals before it is tried on humans.

Animal-to-human trials — in which animal cells, tissues or organs are used for human treatments in closely monitored **clinical trials**. These trials, which are most likely to involve pig-to-human transplants, would be attempted only if animal-to-animal studies show a high likelihood of benefit to humans.

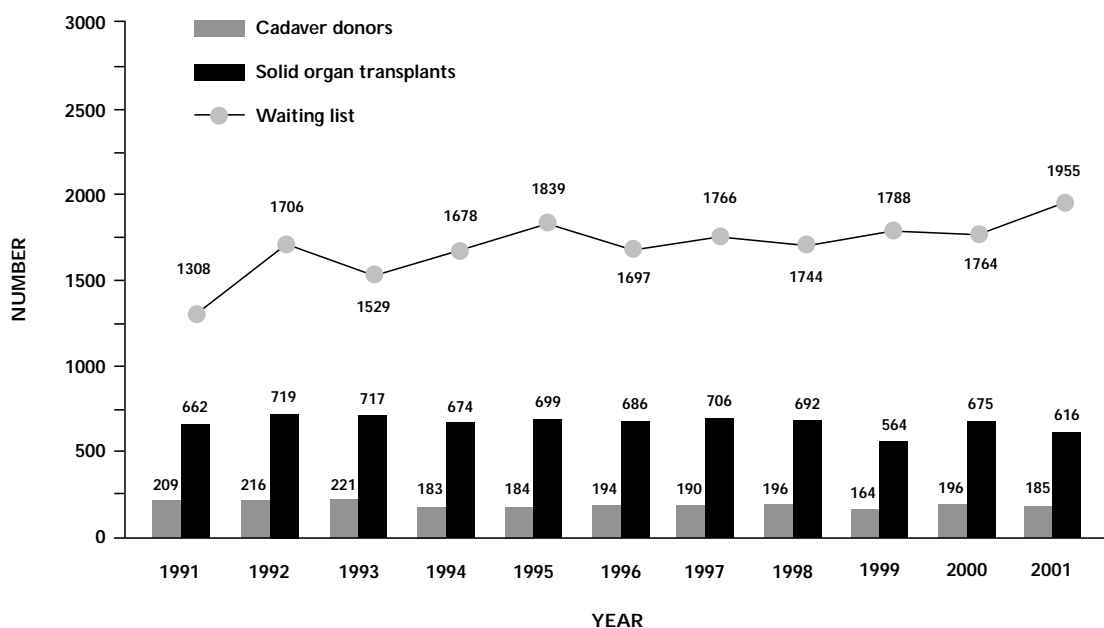
Clinical trials can be either **therapeutic** (in which participating patients are expected to benefit from their involvement in the study) or **nontherapeutic** (in which the study is designed to obtain further knowledge but may not be of direct benefit to the participant).

Because of the potential risks involved, only research with some prospect of therapeutic benefit is considered to be acceptable for clinical trials of animal-to-human transplantation. As with other medical technologies, the process of testing new therapeutic procedures through clinical trials can take many years and involve several phases.

3 Why is animal-to-human transplantation being considered?

Human-to-human transplantation has become a successful way of treating various human diseases and conditions (such as heart disease or kidney failure). However, human organ and tissue transplantation usually depends on donations from people who have died, most often as the result of brain damage (such as a tumour or stroke) or accidents. Over the past twenty years, transplants have become more frequent and successful. The number and scope of transplant procedures has also increased to include a broader range of organ, tissue and cellular transplants (such as transplants of insulin-producing pancreatic islet cells for treatment of diabetes). However, the number of donors has not risen to the same extent and Australia, like the rest of the world, has a severe shortage of donors. This is not a minor shortfall that can be easily overcome by greater effort or funding; it is extreme and it is increasing. Many people die while on a waiting list for a suitable transplant. Figure 2 shows the number of organ donations compared to the number of people waiting for donations in Australia from 1991–2001.

FIGURE 2: Number of organ donations and number of people on waiting lists, Australia 1991–2002



Source: Australian and New Zealand Organ Donor Registry, Annual Report 2002
<http://www.anzdata.org.au/ANZOD/ANZODReport/2002/2002.pdf>

The costs to society of these shortages can be measured in the deaths and illness of patients; in emotional, social and economic costs to their families; and in direct and indirect economic costs to the wider community. So medical researchers face two challenges. The first is to keep people alive while they wait for a suitable organ or tissue donation. The second is to find suitable alternatives to human donations for repairing or replacing damaged or diseased organs and tissues. Animal external therapies, such as liver perfusion, may help to overcome the first challenge, while transplants of animal organs, tissues or cells may offer a solution to the second — but only if several major obstacles, including rapid **immune rejection** and structural or functional incompatibility of the animal transplant, can be overcome.

With the rapid development of genetic technology over the past decade, some scientists believe that it might be possible to overcome these problems by genetically modifying the source animals to make their organs and tissues more compatible with humans.

Hence, the shortage of human organs, combined with developments in **genetic technology** has stimulated increased interest in animal-to-human transplantation. However, the use of **animal transplantation products** as human therapies raises ethical, social and scientific issues. These need to be considered by the Australian community before animal-to-human clinical trials, are allowed to go ahead. The key issues identified by the NHMRC are shown in Box 1 and discussed further in the remainder of this guide.

Box 1 Key issues for animal-to-human transplantation research

- Is it ethically acceptable to use live animal cells, tissues and organs as human therapies?
- How well does animal-to-human transplantation work?
- What are the risks?
- How can the welfare of animals be protected in both animal-to-animal studies and animal-to-human trials?
- How would animal-to-human transplantation trials be managed?
- What are the alternatives?
- How would resources be allocated?
- How would animal-to-human transplantation research be regulated?

4 Is animal-to-human transplantation ethical?

Animal-to-human transplantation raises very serious ethical issues, such as respect for the integrity of humans and whether it is morally wrong to use animals for the benefit of humans in this way (including whether it is acceptable to genetically modify animals).

People have differing views on these issues. This is influenced by their cultural and religious background, their personal or family members' medical conditions, their understanding of the range of technologies involved, and their opinion about the right of humans to kill animals for human use (for example for food) or to save human life (such as in medical therapies).

Most people accept the careful use of animals for the benefit of humans (such as in medical research), provided that the potential benefits of a research project, and the likelihood of the research achieving those benefits, outweigh any likely adverse effects on the animals (which should, in any case, be minimised). Judaism, Christianity and Islam all support the use of animal transplants or, at least, do not actively oppose it when human life is at stake. Buddhists may be opposed to animal-to-human transplantation because they believe that all living things should be treated equally. Hindus oppose all forms of transplantation since the body must remain whole to pass into the next life. However, members of both of these religious groups may exercise a personal choice to accept an animal transplant.

Overall, there does not appear to be any major ethical reason why the medical community should not at least consider animal-to-human transplantation therapies as a possible option for human therapy, as long as the research benefits society as a whole, respects the welfare of the animals used and allows for informed personal choice on the part of the recipient. Such research should be scientifically sound and supported by evidence that the likely benefits for humans justify the use of animals and outweigh any risks from the procedures.

5 How well does animal-to-human transplantation work?

Research on animal-to-human transplantation is still developing. The focus is to find out whether it can work and, if so, whether it is safe for use in humans. Because of the problems of rejection and other structural and functional factors, animal organ transplants will be the hardest procedures to perfect and may never be successful. Rather, researchers predict that, in the short-to-medium term, animal cell therapies (such as brain or pancreatic islet cells) or animal external therapies (such as devices using animal liver cells, or skin grafts) are more likely to be successful. This is because cell transplants and external procedures cause less immune rejection than organ transplants and present fewer structural and functional problems. These kinds of procedures are already being tested in limited clinical trials overseas. It is therefore these procedures, rather than organ transplants, which are likely to be the subject of the initial research proposals considered in Australia.

The following summary briefly describes the current state of research on each of the three types of animal transplantation procedures described in Section 1.

Potential for animal-to-human transplantation trials in Australia

The first proposals for clinical trials of animal-to-human transplantation in Australia would probably be for animal cell therapies (such as brain cells or pancreatic islet cells) or animal external therapies (such as external liver cell devices or skin grafts).

Animal organ transplants are not expected to be trialled in humans in the immediate future because the major problems of rejection and proper functioning of animal organs in humans need much more research. However, genetic modification of the source animals is leading to significant advances in this field.

Animal external therapies

The use of external machines containing animal liver cells to treat acute liver failure has been tested in many animal-to-animal studies with some promising results. The Food and Drug Administration in the United States and the relevant authorities in Europe have therefore allowed clinical trials of pig liver dialysis procedures. Although not conclusive, these animal-to-human trials have shown some success with 'buying time' for patients with liver failure who are waiting for a suitable liver transplant from a human donor. Importantly, the use of pig liver cells in this way has not caused any significant adverse effects. Some bigger trials are now planned overseas to obtain better information about the effectiveness of the procedure.

There have also been encouraging results from both animal studies and clinical trials of techniques to grow human skin on feeder layers of animal cells, then using the skin to repair burns.

Animal cell therapies

Animal cell therapies involve transplantation of isolated animal cells or cell clusters. They have the potential to treat diseases, such as type 1 diabetes, Parkinson's disease, and Huntington's disease. They may also be able to repair damaged tissues or organs, thus avoiding the need for more invasive surgery.

Research on animal cell therapies is at an early stage. Some success has been achieved in animal-to-animal studies, with good survival of the transplanted cells and minimal side effects. Based on these results, agencies in the United States and Europe have approved a number of animal-to-human trials of animal cell therapies. Some of these have already been carried out; others are either planned or are in progress.

So far, these clinical trials have included very few patients and the results obtained do not clearly show that animal cell therapies are effective. However, in many cases the cells survived well in the recipient and did not cause unwanted side effects. Further animal-to-animal research is now being carried out to discover how to promote the function of the cells as well as their survival.

Animal organ transplants

There are major obstacles to the transplantation of whole organs between species. This was shown by a succession of failed attempts from the 1960s to the early 1990s. For animal organ transplants to be successful, researchers need to prevent the transplant being rejected by the recipient's immune response (because it recognises the transplant as 'foreign' and attempts to destroy it) and also ensure that the organ functions properly. This presents huge challenges.

In recent years, researchers have been using genetic technology to genetically modify pigs in order to overcome the most severe forms of immune rejection. As a result, the survival times of animal-to-animal organ transplants have increased from minutes or hours, to days or weeks. Researchers think that these times may continue to improve as the science is better understood, new modifications are made to the donor animals and improved immunosuppressant drugs are developed and tested. However, although animal-to-animal studies are occurring in Australia, as elsewhere, there is clearly a long way to go before such transplants can be tested in humans.

What are genetically modified animals?

All living organisms have **genetic material** in each of their cells. This material is a 'code', which is organised into units called **genes**. The code determines what the organism is, and how it looks and functions. The genetic material divides and is passed to each new cell when the organism grows and from parents to offspring at reproduction. Over the past 20 years, scientists have developed methods to alter the genetic material of plants and animals either by inserting new genes from another organism or by preventing existing genes from working (switching them off). These methods can be used to change characteristics of plants or animals, such as size or colour, as well as more subtle chemical and biological properties. Animals that have had their genetic material altered in this way are called 'genetically modified animals'.

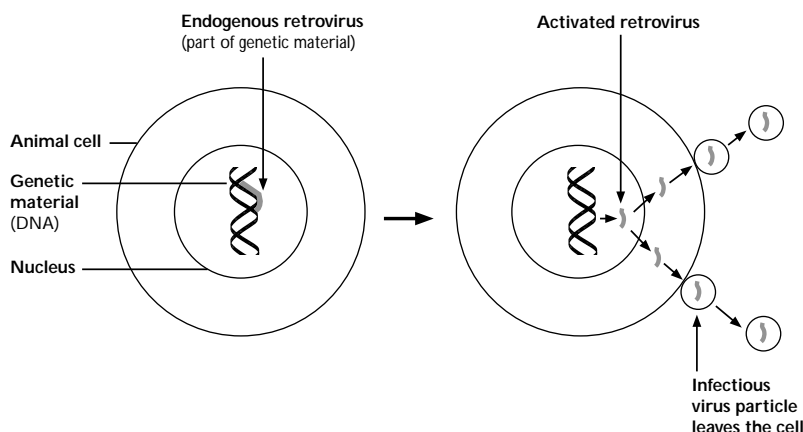
6 What are the risks?

The main risk for a person receiving animal transplant therapy is that the transplant might not function properly. However, there is also a risk that one of the wide range of viral, bacterial and other infections known to occur in the source animals, will infect the transplant recipient causing disease. The same problem occurs for human-to-human transplantation and transplant recipients have contracted infectious diseases from donor organs and tissues. Unfortunately, for both human-to-human and animal-to-human transplantation, the potential for an infection to occur is increased by the drug treatment that transplant patients receive to suppress the immune system and help prevent rejection of the transplant. However, researchers believe that the risk of infection by known animal diseases would be minimised in the same way as for human infections; that is, by rigorous screening of source animals and appropriate treatment of transplant recipients if an infection occurs.

While known animal infections may not pose a serious problem, animal-to-human transplantation does carry another potential risk that has more serious implications for both the individual patient and the wider community. This is the risk that a previously unknown disease, or a new form of a known disease, might emerge and infect recipients of animal transplants and subsequently spread to **close contacts** and the general public, causing a serious new epidemic.

A group of viruses called **endogenous retroviruses** are of particular concern. Instead of actively causing infections like other **retroviruses**, the endogenous viruses remain dormant in their host — embedded in the genetic material — not causing any obvious signs of disease. However, they may be activated occasionally and it is possible that they could then infect other animals, including different species. Little is known about what might make endogenous retroviruses become active but, if an animal transplantation product contains endogenous virus, there is the potential for it to activate at any time in the future and infect the transplant recipient (see Figure 3). Such an infection could spread to close contacts of the recipient and, in the worst case, to the general population.

FIGURE 3: Possible activation of an endogenous retrovirus



Most pigs have a retrovirus called **porcine endogenous retrovirus** (or 'PERV'). Recently, researchers have reported that when they mixed pig cells with human cells in the laboratory, some human cells became infected with PERV. This raises the possibility that the recipient of a pig transplant may be infected with PERV or with another, currently unknown, infectious disease agent.

Researchers consider that the risk of a new infectious disease emerging as a result of animal-to-human transplantation is very low. To date, more than 200 human patients have received pig transplant therapies and none have become infected with PERV or other new infectious agents. However, such an event cannot be completely ruled out and the consequences, were it to happen, could be serious. Human immunodeficiency virus (HIV: the virus that causes AIDS) is also a retrovirus, but is different to PERV because it is not an endogenous virus.

Such risks must therefore be assessed and weighed against the potential benefits of animal-to-human transplantation. It is impossible to generalise the level of risk associated with animal-to-human transplantation research (which must be assessed over the long term). The precise risk will vary from one procedure to another, depending on a range of factors including those described here:

- The amount of direct contact between animal and human tissues. This may be zero for some external procedures, such as liver perfusion devices, where the animal liver cells are contained within the device and separate from the patient's blood by a membrane. It may also be minimal in some cell therapies where the cells are contained in an organic capsule, such as collagen. However, in the case of organ transplants, direct contact would be considerable.
- The length of time that the animal and human tissues are in contact. This may be very short for external therapies, and long term for cell and organ transplants.
- Detailed information about any retroviruses or other infectious agents that the source animal carries.

Infection risks from research into animal-to-human transplantation

Transplant specialists have considerable expertise in managing infections in human-to-human transplant recipients. Most known animal diseases could be avoided in the same way as for human infections — by rigorous screening of source animals, use of preventive medicines and appropriate treatment of transplant recipients if an infection occurs.

The potential for a previously unknown infection to emerge is a serious concern for animal-to-human transplantation trials. Thus, very careful risk assessment would be required for each proposal before animal-to-human transplantation trials were allowed to proceed.

International cooperation and consistency

Infectious diseases can cross international boundaries. Any animal-to-human transplantation research carried out anywhere in the world could have implications worldwide. This means that whether animal-to-human transplantation trials are carried out in Australia or not, we need guidelines to manage people who have received an animal transplant in another country and who wish to come to Australia either to visit or to live. Of course, anyone who has previously received an animal transplant will need to be excluded from donating any of their organs or tissues in the future. This rule will need to apply in all countries, including those that operate a presumed consent system for organ donation (which is described in Section 9 of this guide).

The international community response to new emerging diseases has improved significantly in recent years. For example, the clinical, epidemiological, laboratory and infection control responses to the recent outbreak of severe acute respiratory syndrome (SARS), which were coordinated by the World Health Organization and government agencies, were effective in controlling the outbreak.

7 How can the welfare of animals be protected?

In Australia, research involving animals must comply with the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (referred to in this guide as the Code of Practice). The Code of Practice sets out the responsibilities of researchers and institutions for the care and use of animals for scientific purposes, with emphasis on the following principles:

- The research must be justified. That is, the benefits to humans of the information likely to be gained, must be weighed against the potential effects on the welfare of the animals.
- Researchers must treat animals with respect and consider their welfare as an essential factor in experiments.
- Animals must be used only when it is essential to do so and in the smallest numbers possible.
- Research procedures must minimise the impact on the animals.

Under the Code of Practice, which is enforced under State and Territory legislation, before any research using animals can proceed, the procedures must be approved and overseen by an institutional animal ethics committee. These committees examine the justification for the research by weighing up the benefits to humans of the proposed research, and the 'costs' in terms of the impact on the welfare of the experimental animals involved.

A summary of the major animal welfare considerations for xenotransplantation research is shown in Box 2.

Box 2 Animal welfare considerations for using animals in xenotransplantation research

- Housing and husbandry (including family grouping, social factors, environmental enrichment and diet) should maximise the health and social wellbeing of the animals.
- Transport arrangements should be sensitive to the needs and welfare of the animals.
- Pre- and post-surgery care, and the use of pain-killers, anaesthetics and immunosuppression, should all be carefully monitored by trained personnel and appropriate for the animals and the procedures undertaken.
- The time held in laboratories and the number of experimental and surgical procedures carried out on an individual animal should be minimised.
- The species of animal used should be appropriate to the research and chosen to minimise the impact on animal welfare.

Animals likely to be used in xenotransplantation

Researchers, research sponsors and the wider community generally agree that **nonhuman primates** (such as baboons and other monkeys) are not a suitable source for any of the proposed animal therapies (external therapies, cell therapies or organ transplants) because of the risk of infections to the recipient and the wider community.

At present, pigs are considered to be the most likely and appropriate nonhuman source of organs and tissues. The anatomy and functioning of pigs is very similar to those of humans. Pigs are domesticated animals that are easy to breed, and, importantly, pigs are suitable for genetic modification (see below). Researchers are also considering the use of other species (such as cattle, fish and mice) for cellular transplants.

Animal-to-animal transplantation studies would use a variety of animal species in the early stages of the research (such as mice, rats and rabbits). If these studies show promising results, researchers will need to trial the procedure in an animal study that is as much like the future clinical use of the therapy as possible. This will usually involve the use of nonhuman primates — specifically baboons — as transplant recipients.

Use of nonhuman primates

The use of nonhuman primates in medical research raises serious ethical issues. Nonhuman primates are highly intelligent animals with complex behavioural and social needs that are difficult to meet in a medical research environment. However, baboons are considered the most suitable species for animal-to-animal studies (such as pig to baboon) to obtain important information on the effectiveness of a procedure before it can be tested in an animal-to-human trial. Guidelines for the use of nonhuman primates in medical research are provided in the *NHMRC Policy on the Care and Use of Non-Human Primates for Scientific Purposes* (referred to in this guide as the NHP Policy).

The Code of Practice and the NHP Policy demand high standards of care and housing for nonhuman primates, with emphasis on the general health and physical and social needs of the animals, as well as high standards of care during experimental procedures by qualified personnel (see Box 2). They also sets out restrictions on the importation of primates for use in Australia, and the use of wild-caught primates.

Use of pigs

The use of pigs as the source animals for animal-to-animal transplants would also need to comply with the Code of Practice. The animals would be specially bred and separately housed. There would also need to be strict hygiene precautions to keep the source animals free from infections that might be transmitted to recipients of the xenotransplants (nonhuman primates or humans).

Genetic modification of animals

Researchers predict that immune rejection of animal-to-human transplants may be avoided by genetically modifying the source animals, as well as by treating the human recipient with drugs to suppress their immune response (immunosuppressant drugs). Genetic modification of source animals involves inserting some human genes into the animals to make their cells, tissues and organs behave more like human-to-human transplants.

This raises some difficult ethical issues about the rights and welfare of the animals, such as whether the insertion of human genes may make the animal in some way 'human', or whether inserted genes cause unexpected side effects in the animals. These issues need to be considered case by case to ensure that the proposed modification does not alter the animal in any other significant way. The aim is to make sure that the animals retain the essential characteristics of their species. To assist researchers with these issues, the NHMRC **Animal Welfare Committee** has drafted a new NHMRC policy document on the care and use of genetically modified animals. This new policy has been released for public comment (draft **GM Policy**; September 2003).

Policy for use of animals in xenotransplantation research

As well as the guidelines already provided by the NHP Policy and the draft GM Policy, the Animal Welfare Committee has decided to prepare a document specifically on the care and use of animals in xenotransplantation research.

Export and import of animals

The Australian Quarantine and Inspection Service oversees the import or export of animal tissue to or from Australia. Animals used to supply xenotransplantation products would need to be healthy and reared under high standards of animal welfare. The Animal Welfare Committee would seek assurance that any animals used to supply animal transplantation products meet these requirements, whether in Australia or overseas. Genetically modified animals that are imported into or exported from Australia would need to be raised in compliance with the relevant codes of practice.

8 How would animal-to-human transplantation trials be managed?

Animal-to-human clinical trial protocols would need to include some special arrangements, beyond those that apply to most other clinical trials (these are described in Section 11 of this guide).

Selection of participants

The careful selection of **participants** would be a very important aspect of any animal-to-human transplantation trials. The wellbeing of the patient would always be the first consideration. Not everyone who may wish to participate in such a trial would be able to do so for a variety of reasons. For example, they would need to be willing to comply with long-term postoperative treatment, which would be vital to reduce infection risks (see Section 6 of this guide) but might not be acceptable to some people. Thus, participants may need additional psychological assessment to ensure their suitability for the proposed trial.

In the early stages of animal-to-human transplantation research, trial proposals would involve very few patients, possibly only one. It has been agreed that any such trials should be therapeutic trials (see Section 2 of this guide), so the participants would need to have a realistic chance of benefiting from the procedure and have no other treatment options that offer a greater benefit.

For example, animal brain cell treatment for Parkinson's disease could be offered to patients if animal-to-animal studies had shown that the disease could be successfully treated this way. But the trial would not be offered if any other options for treatment had been shown to have a greater chance of success than animal cell therapy, such as existing drug therapy or human cell therapy (such as human stem cell therapy described in Section 9 of this guide).

Information sharing and consent arrangements

Once prospective trial participants have been identified, researchers would need to provide them with all the information that they need to make an informed decision about whether to participate. Section 11 of the National Statement states that this information must be provided by a person who is independent of the research and in a way that does not put any pressure on the person to participate. These guidelines would be very important for animal-to-human transplantation trials, because the patients involved may be very sick and vulnerable to coercion. The same considerations apply to other types of trials where the therapy involved is for a very serious or terminal condition.

Researchers would have to provide information for prospective participants about the infection risks associated with the trial and the need for long-term **monitoring** and follow-up. It would be very important for trial participants to understand the importance of continuing with such monitoring — even if the procedure itself is not successful — and to accept that they have a responsibility to comply with such arrangements in return for the opportunity to take part in the trial.

Because of the infection risks, it would also be necessary to discuss the trial with the family and other close contacts and carers of the trial participant and to inform them of any potential infection risks they face as a result of the trial. Close contacts would also need to understand very clearly the implications of the trial and to accept their responsibility to comply with any necessary monitoring arrangements.

After all the information about the trial had been provided and discussed with prospective participants, they would need to sign a form to consent to the transplant procedure itself and to any long-term monitoring arrangements, including storage of tissue samples and inclusion of their own details in a central register for future reference. Close contacts would also need to sign and return information sheets to indicate that they had read and understood the requirements.

Monitoring and follow-up

The amount of monitoring and follow-up needed for participants and close contacts would depend on the procedure used and the potential risks of infection (which are explained in Section 6 of this guide). Trial participants would need to be monitored on a long-term basis to see how they respond to the therapy, so it would not be difficult to include an additional check for emerging infections. However, even if the transplant itself were unsuccessful, it may be necessary for participants and their close contacts to continue to be checked for infectious diseases. This means that, as for all other clinical trials, participants would be able to withdraw their consent for further treatment at any time in the trial but they would not be able to withdraw from the monitoring and follow-up associated with infectious diseases. They would also not be able to donate their organs, tissues or cells at any time during their life or after death (this issue is also discussed in Section 6 of this guide under 'International cooperation and consistency').

Tissue samples from all procedures would need to be stored in a central **tissue bank** for future reference. Details of all trial participants and close contacts would also need to be entered in a central register to ensure that they could be traced and followed-up in future. This information would also need to be available to other countries so that trial participants and contacts could be traced, even if they were to move or travel abroad.

9 What are the alternatives?

Increasing the number of human donors

It has been suggested that animal-to-human transplantation would not be needed if the number of human donors could be increased. Unfortunately, most people do not indicate during their lifetime that they wish to donate their organs and tissues after death and different countries have different legislation to deal with this situation. In some countries, such as Australia and the United States, only people who have indicated their intention to donate before they die are considered to have consented (this is called an 'opt-in' approach). However, as long as the person has not registered a specific objection, the law allows close relatives to give consent for the organs to be donated.

Other countries have an 'opt out' system of consent, in which it is presumed that people are willing to donate their organs unless they clearly indicate before they die that they do not wish to be donors (presumed consent). The extent to which relatives can influence the donation in this case varies from country to country; for example, in Austria and Belgium, relatives are not consulted, but in Spain they may be.

The number of organs and tissues available for transplantation has increased in the countries that have adopted the presumed consent approach, but even this has not been enough to overcome the shortage of organs and tissues. Organ donation agencies and transplant medical professionals in Australia do not think that the presumed consent approach would work here. One reason is our multicultural population. Another is the federal system of government, which makes uniform regulation difficult.

Payment for organs has also been suggested as a way to increase the availability of human tissues and organs. But this approach is ethically very difficult and has not, so far, been considered acceptable in Australia. Increased support for emergency care professionals in their work with relatives of accident or sudden death victims could help to increase the number of donations, but would be unlikely to overcome the shortfall.

Living donor programs — in which living donors, often relatives, donate an organ (such as a lung or kidney), part of an organ (such as half the liver), or tissue (such as bone marrow) — are becoming more common. But there are limitations. Although the donation of a single kidney or some bone marrow is now accepted practice, the donation of half an adult liver is ethically controversial because such major surgery carries significant risks to donors, and there have been some reported deaths overseas. Because of this danger, this procedure has not been used in Australia. Donation of a smaller portion of adult liver to a child has much less risk for the donor, however, and such procedures have been carried out in Australia.

Human donations versus animal-to-human transplantation

Continued efforts are needed to increase the number of human donations to transplantation programs. However, it is very unlikely that such efforts will overcome the extreme shortfall of human donors, especially as more new therapies are developed.

Alternative therapies

At the same time as animal-to-human transplantation research is progressing, researchers are exploring other new therapies to overcome the shortage of donated organs and tissues and treat an increasing range of diseases and conditions that have not been treated before.

One such area of work is on human stem cells. Stem cells are early, unspecialised cells that can, under certain conditions, be induced to mature into specialised cell types (such as heart, liver, brain and pancreas). It is hoped that these cells will have the potential to repair human organs and to treat a similar range of diseases to those proposed for animal cell therapies. However, human stem cell technology raises a number of ethical issues of its own, and its development will require the use of animals in preclinical studies that are similar to those required for xenotransplantation research (including nonhuman primates). Also, some stem cell techniques cannot be regarded as an 'alternative' to xenotransplantation because the stem cell lines are grown on a layer of animal cells, so they come within the definition of animal external therapies.

A second area of research is into the use of mechanical or artificial organs, either for short-term 'bridging' procedures for people waiting for an organ to become available or for longer-term replacement or repair. The development of artificial devices may provide solutions to some conditions and diseases that currently require transplants, but not all.

Like xenotransplantation, research in both these areas is in the early stages and it is not clear whether they will be more or less successful than animal therapies across the wide range of diseases and conditions involved. Only further research will determine the best form of therapy for each condition.

Preventive measures

It has often been suggested that preventive programs and healthy lifestyle education on topics such as exercise and good nutrition could help to reduce the need for transplants. However, many conditions treated by transplantation, such as kidney failure, are not related to lifestyle. They can occur in young, otherwise healthy, people because of an infection or other factor. Similarly, type 1 diabetes and Parkinson's disease — both active areas of research on animal cell therapies — are not related to lifestyle. For example, type 1 diabetes is usually diagnosed in children and young adults and its cause is unknown; the cause of Parkinson's disease is also unknown.

Animal-to-human transplantation versus alternative approaches

Organ and tissue donations are required to overcome a large range of diseases and conditions. Xenotransplantation is one of a number of approaches that might be used because of the current shortage of human donations. Until it becomes clearer where the most benefit lies for particular diseases and conditions, an integrated approach involving a range of strategies may be required.

10 How would resources be allocated?

At this early stage in the development of animal-to-human transplantation, it is not possible to predict all the costs that may be involved for the treatment and continuing supervision of recipients of animal therapies. Ideally, in the longer term, the costs of ongoing treatment and care would be matched by the savings made in enabling recipients to lead healthy and productive lives.

In the meantime, it is important to ensure that animal-to-human transplantation research does not divert funds away from the other approaches to tissue and organ shortage described in Section 9 of this guide, including research into alternatives such as human stem cell therapies and artificial organs. For publicly funded research, funding bodies would continue to assess these options and ensure that funds are distributed amongst the various alternatives according to their potential for success. For privately funded research, the commercial interests of companies should ensure that the effort and funding focuses on the most promising procedures.

During the research phase, participation in a clinical trial would be free for the patient, as the costs would be borne by the research sponsors — often biotechnology companies. However, if clinical trials were to show that animal transplantation therapies are successful, this would lead to an increase in demand for such therapies, which would have implications for health care funding and resource allocation. Such issues concerning other medical procedures and technologies are dealt with through the Australian Government Department of Health and Ageing by the Medical Services Advisory Committee, the Pharmaceutical Benefits Advisory Committee and other programs designed to ensure the best and fairest allocation of health care resources. Many procedures are also funded through national and state/territory funding of specialist units in public hospitals.

11 How is animal-to-human transplantation research currently regulated?

Animal-to-human transplantation research in Australia (including preclinical animal-to-animal studies) is currently regulated in the same way as other human and animal medical research. This means that research proposals must be considered under arrangements administered by the NHMRC through three committees: the Australian Health Ethics Committee, the Animal Welfare Committee and the Research Committee.

Commonwealth laws regarding therapeutic goods and gene technology, and state and territory laws regarding animal welfare and public health, also apply.

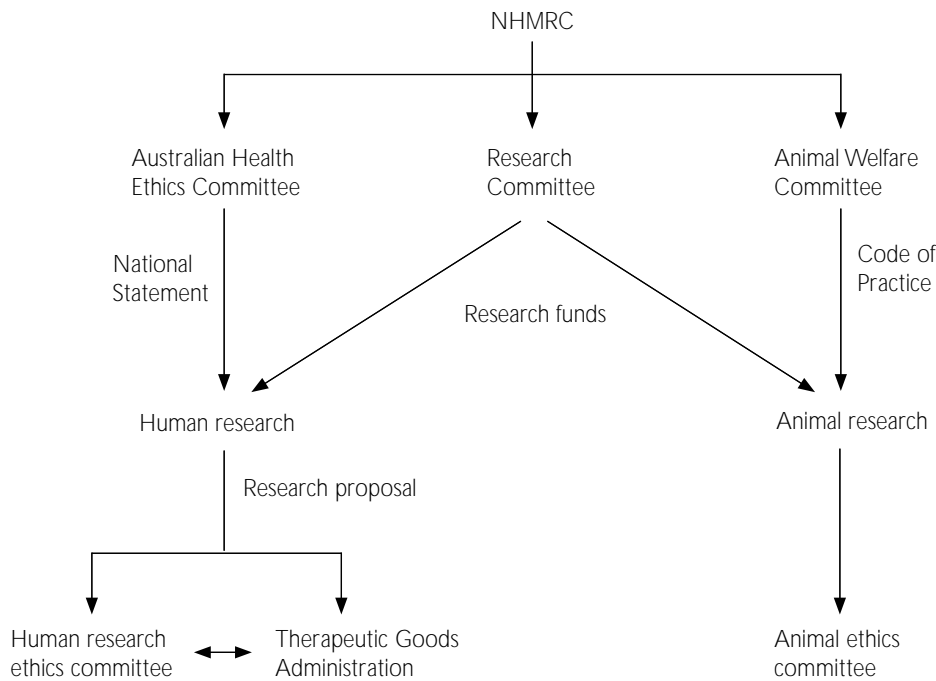
National oversight of animal research

The NHMRC Animal Welfare Committee is responsible for NHMRC-funded animal research and also oversees the Code of Practice (Section 7 of this guide gives more information about this code). Under the code, which is enforced through animal welfare legislation in the states and territories, all proposals involving the use of animals in research and teaching must be approved and monitored by an institutional animal ethics committee (AEC) (see Figure 4).

National oversight of research involving humans

The NHMRC Australian Health Ethics Committee is responsible for developing guideline for the conduct of medical research involving humans, and for advising the NHMRC on ethical issues related to health. In particular it has responsibility for developing and administering the *National Statement on Ethical Conduct in Research Involving Humans* (published by NHMRC in 1999). Under this statement, all proposals involving human research must be approved and monitored by an institutional human research ethics committee (HREC) (see Figure 4).

FIGURE 4: NHMRC oversight of medical research



Regulation of therapeutic goods

All medicines and devices (therapeutic goods) for marketing and routine use are registered or licensed under the Australian *Therapeutic Goods Act 1989* and its subsequent amendments, which is administered by the Therapeutic Goods Administration (TGA). This legislation allows the supply of unregistered therapeutic goods for experimental studies and clinical trials under the supervision of the TGA, NHMRC and the institutional HREC.

Clinical trial proposals for new drug treatments or other relatively straightforward therapies can be submitted directly to the HREC at the proposed institution for the research. However, trial proposals for more complex therapies, where the HREC may not have sufficient expertise to assess the safety and efficacy of the therapeutic product involved, are submitted first to the TGA, which undertakes an assessment of the trial protocol. In some cases, the HREC or TGA seeks expert advice from another committee or agency. In the case of emerging gene therapy and xenotransplantation technologies, the Gene and Related Therapies Research Advisory Panel (GTRAP) has been specifically set up by the NHMRC Research Committee to provide scientific advice on these procedures. However, GTRAP does not currently have any legislated powers to formally approve or prevent trials.

Regulation of genetically modified animals

The genetic modification of animals is regulated under the *Australian Gene Technology Act 2000* and Gene Technology Regulations 2001. These are administered by the Office of the Gene Technology Regulator. Research involving genetically modified organisms must be approved and licensed, based on risk assessment and community consultation. However, products derived or produced from a **genetically modified organism** are defined as genetically modified products and are regulated by the agencies involved in their use (eg the Therapeutic Goods Administration for medical products), with advice from the Gene Technology Regulator. Therefore the following arrangements would apply for animal-to-human transplantation research:

- A genetically modified pig is a genetically modified organism and its creation must be overseen by an **institutional bioethics committee** and licensed by the Gene Technology Regulator.
- Transplantation products (cells, tissues or organs) produced from a genetically modified pig would be genetically modified products. Their use would be assessed and monitored by animal ethics committees for animal-to-animal studies and regulated by the TGA for animal-to-human trials. Some products may require further assessment by the Gene Technology Regulator.
- Transplantation products from pigs that have not been genetically modified would not fall within the scope of the Gene Technology Act. Their use would nevertheless be assessed and monitored by animal ethics committees for animal-to-animal studies and regulated by the TGA for animal-to-human trials.

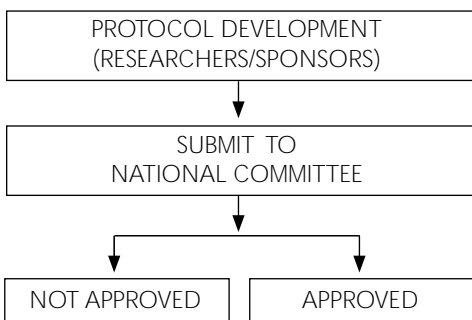
Other legislation

Other legislation that affects xenotransplantation research includes state and territory animal welfare and public health legislation and the Australian *Quarantine Act 1908*, which controls the import and export of animal or human tissues and products.

12 The way forward

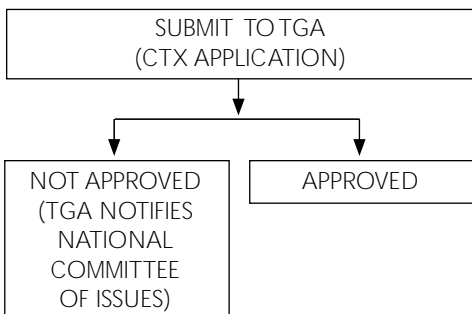
The NHMRC Xenotransplantation Working Party has considered the issues involved for animal-to-human transplantation research in Australia. They have also considered developments in the regulatory processes overseas and the consequences for Australia of either banning animal-to-human transplantation research or of not preparing any guidelines to deal with this issue.

As a result of these considerations, the Xenotransplantation Working Party has proposed that well planned and closely monitored animal-to-human transplantation clinical trials should be permitted in Australia under a strict regulatory system. The working party has therefore proposed a three-step system for assessing research applications for animal-to-human transplantation trials.



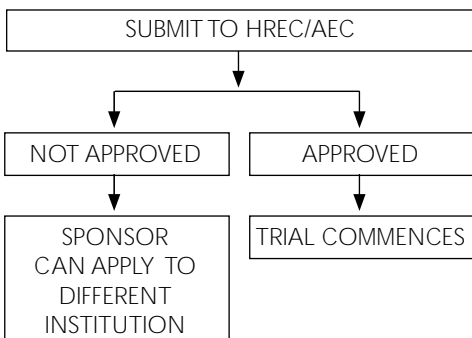
Step 1

Each research application for an animal-to-human transplantation trial would be assessed by a national xenotransplantation committee (based on an expanded GTRAP as described in Section 11 of this guide). This committee would assess the proposed trial protocol against NHMRC guidelines for the ethical conduct of animal-to-human transplantation trials (information about draft NHMRC guidelines is given below).



Step 2

Trial proposals that are approved by the national committee would be referred to the TGA for further assessment, particularly regarding the quality of the proposed animal transplantation product.



Step 3

If the TGA grants approval, the trials would be assessed by the HREC and AEC at the local institution where it is planned to hold the trial. If these committees grant permission, the trial would be able to begin.

Draft NHMRC guidelines

The Xenotransplantation Working Party has developed draft guidelines to underpin the assessment at Step 1, based on the following key issues:

- the overall benefit of the research (serving the common good)
- animal welfare
- effectiveness of the therapy
- safety
- trial protocols for participant selection, information sharing and consent
- monitoring and follow-up of participants and contacts.

These issues have been discussed in the previous sections of this guide. The draft guidelines are included with the Response Paper that has been released for public comment with this community guide (see Section 13). The Xenotransplantation Working Party would welcome comments on the draft guidelines from the community.

National overview of animal studies

Many respondents to the first round of public consultation about xenotransplantation commented that institutional AECs review proposals only for their own host institution and that there are currently no national arrangements to overview animal studies. The Xenotransplantation Working Party has therefore recommended that researchers should be required to submit information about animal-to-animal studies to a central register. Information from this register would be made available to the national committee and local HRECs and AECs to help guide decisions on the use of animals in further animal-to-animal studies.

13 How you can participate in this public consultation

You can participate in this public consultation on xenotransplantation in two ways:

- Attend public meetings and make your comments known to the Xenotransplantation Working Party. Information about dates and venues will be advertised in all major newspapers and provided on the NHMRC website (<http://www.nhmrc.gov.au>)
- Obtain a copy of the NHMRC Response Paper (see details below) and make a written submission on the Xenotransplantation Working Party's revised guidelines.

14 Further information

Second public consultation document (Response Paper)

Animal-to-Human Transplantation Research: How Should Australia Proceed? Response to the 2002 public consultation on Draft Guidelines and Discussion Paper on Xenotransplantation, Xenotransplantation Working Party, National Health and Medical Research Council, 2003. The Response Paper is available in PDF format on the NHMRC website <http://www.nhmrc.gov.au>. It is also available in hard copy from:

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NHMRC website: <http://www.nhmrc.gov.au>

Other NHMRC codes

NHMRC codes for research involving humans and animals are available from the NHMRC website as follows: *National Statement on Ethical Conduct in Research Involving Humans*, NHMRC, 1999. <http://www.nhmrc.gov.au/publications/humans/contents.htm>

Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, 6th Edition, NHMRC 1997. <http://www.nhmrc.gov.au/research/awc/code.htm>. NOTE: The 7th edition is currently in preparation. See: <http://www.nhmrc.gov.au/issues/animcode.htm>

Policy on the Care and Use of Non-Human Primates for Scientific Purposes, NHMRC 2003. <http://www.nhmrc.gov.au/research/awc/nonhsyn.htm>

Glossary

Words shown in bold (like this: **xenotransplantation**) are further defined elsewhere in the glossary.

allograft transplantation: transplantation of living tissue, organs or cells between individuals of the same species (for example, from human to human).

animal ethics committee: a local committee of professional and community representatives at a research institution who examine proposals for research involving animals at that institution to ensure they comply with the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (see also **Code of Practice**).

animal-to-animal studies: **xenotransplantation** research studies in which organs, cells or tissues are transferred from one animal species (such as pigs) to another (such as baboons) (see also **preclinical study**).

animal-to-human transplantation trials: **xenotransplantation** research in which organs, cells or tissues are transferred from an animal species (such as pigs) to a human (see also **clinical trials**).

animal transplantation product: a live cell, tissue or organ from an animal that is used in a **xenotransplantation** procedure.

cell therapies: transplants involving the use of living tissues, such as skin or bone marrow, or clusters of specialised cells, such as brain cells or insulin-producing **pancreatic islet cells**.

clinical trial: a research study that tests how well new medical treatments or other interventions work in people (see also **animal-to-human trials**).

close contacts: family members and other close associates of an animal-to-human transplant recipient. The precise definition would vary according to the type of procedure and other factors and would be included in the clinical trial **protocol**.

Code of Practice: Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (6th edition was published by the NHMRC in 1997; draft 7th edition was released for public comment in September 2003).

Discussion Paper: refers to the Xenotransplantation Working Party's first public consultation document — *Draft Guidelines and Discussion Paper on Xenotransplantation — Public Consultation 2002*, National Health and Medical Research Council, 2002.

endogenous retrovirus: a **retrovirus** that is incorporated in the **genetic material** in every cell in the body of its host, and is passed down from generation to generation. Normally, an endogenous retrovirus does not cause any obvious signs of disease.

external therapies: therapies that occur outside the patient's body, such as when blood from a patient with liver failure is passed through a machine containing live animal liver cells, to remove toxic substances (a procedure similar to kidney dialysis).

gene: a section of **genetic material** that codes for a specific characteristic of the organism.

genetic material: a molecular structure in living organisms that contains all the information about the structure and function of the organism (commonly a molecule called deoxyribonucleic acid, or DNA).

genetically modified animal: see **genetically modified organism**.

genetically modified organism (GMO): any live organism that has inherited characteristics produced by altering the **genetic material** of its 'parent' organism (Section 5 of this guide includes a more detailed description of this procedure).

genetically modified (GM) products: GM products are derived from GMOs but are not viable, capable of reproduction, or capable of transferring genetic material to other organisms.

genetic technology: term used to describe the methods used by scientists to modify the **genetic material** of living organisms.

GM Policy: Draft NHMRC guidelines for the creation, breeding, care and use of genetically modified animals (released for public comment in September 2003).

human research ethics committee: a local committee of professional and community representatives established at a research institution or health care facility where human research is conducted, who advise the institution on ethical approval of research protocols at that institution and ensure that the research complies with the **National Statement**.

immune rejection: immunological response by a person's body when it refuses to accept substances or organisms that it recognises as foreign; 'rejection of the transplanted liver' (see also **immune response**).

immune response: the body's mechanism for distinguishing 'self' from 'other' and eliminating invading microorganisms or other foreign material from the body. In transplantation, the immune response can lead to rejection of the transplanted organ, tissue or cells.

immunosuppressant drugs: drugs that suppress the natural immune response to foreign material. These drugs are usually given to transplant patients to help prevent rejection of the transplant.

monitoring [of transplant recipients and contacts]: regular testing for infectious disease status (including blood and other testing for any signs that an infection is either present or has occurred).

National Statement: *National Statement on Ethical Conduct in Research Involving Humans* (published by the NHMRC in 1999).

NHP Code: *Policy on the Care and Use of Non-Human Primates for Scientific Purposes* (published by the NHMRC in 2003).

nonhuman primate: mammals of the primate order apart from human beings (for example, apes, baboons, monkeys).

nontherapeutic research: a **clinical trial** in which the study is designed to obtain further knowledge but may not be of direct benefit to the participant.

organ transplants: transplants involving the use of whole living organs such as hearts or kidneys.

pancreatic islet cells: cells from the 'islets of Langerhans', which are specialised areas within the pancreas that produce insulin (see also **type 1 diabetes**).

participant: see *research participant*.

preclinical study: a study carried out using animals or laboratory methods to test the effectiveness or safety of a procedure before clinical trials are carried out on human patients (See also **animal-to-animal studies**).

protocol: a document that provides the outline or plan for a research project. It includes the background, rationale and objectives of a research project and describes its design, methods, organisation and the conditions under which it is to be performed and managed.

rejection: see **immune rejection**

research participant: a person who takes part in a clinical trial and about whom a researcher obtains information.

Response Paper: refers to the Xenotransplantation Working Party's second public consultation document — *Animal-to-Human Transplantation Research: How Should Australia Proceed?* Response to the 2002 public consultation on *Draft Guidelines and Discussion Paper on Xenotransplantation*, National Health and Medical Research Council, 2003 (see Section 14 of this guide for information on how to obtain a copy of this paper).

retrovirus: a family viruses defined by their particular genetic structure. The family includes the lentiviruses (such as human immunodeficiency virus/HIV), oncoviruses (such as human T-cell leukaemia virus) and endogenous retroviruses (which exist as sequences embedded in the genome of its host).

therapeutic research: **clinical trials** in which participating patients are expected to benefit from their involvement in the study.

tissue bank: a storage facility for samples of tissues used in transplantation procedures. Samples of tissue from every animal-to-human transplantation procedure (and some animal-to-animal procedures) would be stored for future reference in the event of an emerging infectious disease or other adverse event.

type 1 diabetes: the form of diabetes that starts in childhood or adolescence. The disease is also called insulin-dependent diabetes because sufferers they have little or no ability to produce insulin and are therefore dependent on insulin injections for survival (see also **pancreatic islet cells**).

xenotransplantation: transplantation of living tissue — organs, tissue or cells — from one species to another (eg from pigs to humans). Xenotransplantation procedures include animal **organ transplantation**, animal **cell therapies** and animal **external therapies**.

The National Health and Medical Research Council

The National Health and Medical Research Council (NHMRC) is a statutory authority within the portfolio of Australian Government Minister for Health and Ageing, established by the National Health and Medical Research Council Act 1992. The NHMRC advises the Australian community and the Australian Government, State and Territory governments on standards of individual and public health, and supports research to improve those standards.

The NHMRC advises the Australian Government on the funding of medical and public health research and training in Australia and supports many of the medical advances made by Australians.

The NHMRC also develops guidelines and standards for the ethical conduct of health and medical research.

The Council comprises nominees of the Australian Government, State and Territory health authorities, professional and scientific colleges and associations, unions, universities, business. Consumer groups, welfare organisations, conservation groups and the Aboriginal and Torres Strait Islander Commission.

The Council meets four times a year to consider and make decisions on reports prepared by Committees and working parties following wide consultation on the issues under consideration.

A regular publishing program ensures that Council's recommendations are widely available to governments, the community, scientific, industrial and education groups.

The Council publishes extensively in the following area:

- * Aged care
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- * Environmental health
- * Ethics - human
- * Health promotion
- * Men's health
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- * Sport/injury
- * Workforce
- * NHMRC - National Health and Medical Research Council
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- * Infection control
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- * Public health
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