Animal-to-human transplantation research: How should Australia proceed?

Response to the 2002 public consultation on Draft Guidelines and Discussion Paper on Xenotransplantation

Public consultation 2003–04

Xenotransplantation Working Party
National Health and Medical Research Council
The strategic intent of the NHMRC is to provide leadership and work with other relevant organisations to improve the health of all Australians by:

- fostering and supporting a high-quality and internationally recognised research base;
- providing evidence-based advice;
- applying research evidence to health issues, thus translating research into better health practice and outcomes; and
- promoting informed debate on health and medical research, health ethics and related issues.

NHMRC web address: http://www.nhmrc.gov.au
INVITATION TO MAKE A SUBMISSION

RESPONSE PAPER AND DRAFT GUIDELINES FOR CLINICAL XENOTRANSPLANTATION RESEARCH

You are invited under paragraph 13(1)(b) of the National Health and Medical Research Council Act 1992 to make a submission to the NHMRC about the draft guidelines for clinical xenotransplantation research detailed in the attached document, Animal-to-Human Transplantation Research: How Should Australia Proceed? (Response to the 2002 public consultation on Draft Guidelines and Discussion Paper on Xenotransplantation). This document, and the Draft Guidelines and Discussion Paper on Xenotransplantation (Public consultation 2002) on which it is based, are referred to as the Response Paper and the Discussion Paper, respectively in the remainder of this document.

The Response Paper was prepared by the NHMRC Xenotransplantation Working Party and has been approved for release for public consultation by the Australian Health Ethics Committee and the Research Committee. It was written in response to the issues raised about the Discussion Paper, which was the subject of the first round of public consultation in 2002, and to inform a second round of consultation.

The Xenotransplantation Working Party is proposing nine guidelines for the conduct of clinical xenotransplantation research in the following areas: animal welfare; efficacy; safety; patient selection; information giving; consent; monitoring and surveillance; data and tissue storage; and management of public health risks. These guidelines are included at the end of Section 12 of this Response Paper (see page 155). The whole of Section 12 (The way forward for Australia), including the draft guidelines, is printed on coloured paper for ease of reference. General responses, in addition to comment on the nine guidelines, would be welcome.

In the Discussion Paper, the working party proposed three models for the regulation of clinical xenotransplantation research in Australia. In this Response Paper, the working party has developed one of these options as its preferred model and seeks further comment from the public.

In addition to the Response Paper, the working party has produced a community guide to xenotransplantation (Animal-to-Human Transplantation: A Guide for the Community). The community guide complements the Response Paper by providing background information on xenotransplantation for the second round of community and stakeholder consultation. It is available on the NHMRC website (http://www.nhmrc.gov.au) or by contacting the Project Officer at the address below.

Your submission should include your name and address, or a telephone number at which we can contact you, and can be forwarded in writing, by e-mail or on audiotape to:
To assist you in preparing your submission, a copy of the NHMRC document *Public Consultation – Procedures for Making Submissions* is included as an attachment to this document (Animal-to-Human Transplantation Research: How Should Australia Proceed?)

**The closing date for submissions is Friday 12 March 2004.** Additional copies of the document are available from the NHMRC at the above address. The document is also available in PDF format on the NHMRC website at: [http://www.nhmrc.gov.au](http://www.nhmrc.gov.au).

In making your submission, please note that unless a submission is marked confidential, it will be made available to any organisation or person on request. If you want your submission, or any part of it, to be treated as confidential, please indicate this clearly. A request for access to a submission marked ‘confidential’ will be determined in accordance with the *Freedom of Information Act 1982* (Cwlth).

The NHMRC may include in its final report on this project a list of submissions received in response to this Response Paper, and may also refer to those submissions or reproduce portions of them in the text of the report and in other NHMRC publications. If you do not want your submission or any part of it to be used in any of these ways, please indicate this clearly.

You are also invited to attend public meetings to be held in all capital cities during February 2004 at which members of the Xenotransplantation Working Party will provide a short presentation on the guidelines and seek comments about them. Dates and venues for these meetings will be advertised in the local press and will also be available on the NHMRC website or by contacting the Project Officer at the above address.

I look forward to receiving your comments.

Yours sincerely

[Signature]

Dr John Sparrow

Chair
Xenotransplantation Working Party
National Health and Medical Research Council
20 November 2003
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1 Background

What is xenotransplantation?

1.1 Many people know of someone who has received an organ transplant. The donor is usually a person who has died as a result of a sudden brain injury or an accident, but it may also be a living donor (often a relative) who has donated, for example, a kidney or some bone marrow. This type of transplant, where the donor and the recipient are the same species (in this case, human), is called an ‘allotransplant’.

1.2 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 (animal-to-human transplantation). This 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.

1.3 When we hear the term ‘transplantation’ we usually think of organ transplants such as hearts or kidneys. However, transplants can also involve the use of tissues, such as skin or bone marrow, or clusters of specialised cells, such as brain cells or cells from the pancreas. In this guide, these transplants are called cell therapies.

1.4 ‘Transplantation’ also covers different types of procedures. The best known are those that involve transplanting living material into the 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 of an external therapy is 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). Another so-called external therapy involves growing human skin in the laboratory on a layer of animal cells and later using the skin as a graft to treat burns.

1.5 Thus, overall, animal-to-human transplantation research involves three types of transplantation therapy:

- animal external therapies (AETs)
- animal cell therapies (ACTs)
- animal organ transplants (AOTs).

1.6 As these three types of animal-to-human transplantation therapy involve different scientific and ethical considerations, they are discussed separately wherever possible in this Response Paper.

1.7 Researchers are working out the science of animal-to-human transplantation 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, including:
• **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 the animal-to-animal studies show successful outcomes.

1.8 Clinical trials may either be 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).

1.9 Because of the potential risks involved, only research that has some prospect of therapeutic benefit is considered to be acceptable for clinical trials of animal-to-human transplantation. That is, there would need to be a reasonable prospect that the patient would benefit from the procedure. As with other medical technologies, the process of testing new therapeutic procedures through clinical trials can take many years and involve several phases.

1.10 Further details about different types of animal-to-human transplantation and the research involved to develop them are given in Section 3 of this Response Paper.

### About this Response Paper

1.11 In early 2001, the National Health and Medical Research Council (NHMRC) established a Working Party on Xenotransplantation (XWP) to investigate whether research into animal-to-human transplantation should be allowed in Australia.

1.12 In July 2002, the XWP released a discussion paper titled: *Draft Guidelines and Discussion Paper on Xenotransplantation* (NHMRC 2002; referred to in this report as the Discussion Paper). The primary role of the Discussion Paper was to provide sufficient background material to promote informed community discussion on this issue. The Discussion Paper also contained draft guidelines to guide the conduct of xenotransplantation research in Australia.

1.13 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 (see paragraphs 2.1–2.3).

1.14 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.
1.15 The NHMRC acknowledged that the concerns raised showed that there is a strong community feeling against animal-to-human transplantation, at least amongst those groups that responded to the consultation. However, not all interest groups were represented among the respondents. In particular, there were very few submissions from potential transplant recipients or medical professional groups that may be involved in treating such patients (see paragraphs 2.8–2.9 for a more detailed breakdown of the responses received).

1.16 It was also clear that many respondents only considered whole organ animal-to-human transplants, rather than the broader range of treatment options involving animal products that are actually included in the definition of xenotransplantation (see paragraphs 3.1–3.4 for a detailed definition of these procedures).

1.17 The NHMRC therefore agreed that the working party should respond to the issues raised and conduct a second round of consultation in which these issues were highlighted in relation to all the types of animal-to-human transplantation procedures covered by the definition of xenotransplantation. This paper (Animal-to-Human Transplantation: How Should Australia Proceed?), which is referred to in the remainder of this document as the Response Paper, has therefore been prepared in order to respond to the issues raised in the first round of public consultation and to provide further information to inform a second round of public consultation.

1.18 The NHMRC also agreed that to facilitate the further investigation of the issues raised, in the light of the different types of animal-to-human transplantation procedures involved, 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. A list of members of the expanded XWP and the Animal Issues Subcommittee is shown in Appendix A.

1.19 Finally, some respondents felt that much of the information provided in the Discussion Paper was in a format that did not facilitate community understanding of the complex issues involved. To assist the community understanding of animal-to-human transplantation research, and to promote further informed debate, the XWP has also produced a plain English community guide to xenotransplantation (Animal-to-Human Transplantation: A Guide for the Community).

1.20 The community guide complements this Response Paper by providing background information on animal-to-human transplantation for the second round of community and stakeholder consultation. In addition to defining xenotransplantation and explaining what animal-to-human transplantation research involves, it discusses the reasons why such research is being considered in Australia, and considers the issues of ethics, risk and animal welfare. The community guide is available on the NHMRC website (http://www.nhmrc.gov.au) or by contacting the Project Officer as follows:

Project Officer – Xenotransplantation
Health Ethics Section
NHMRC (MDP100)
GPO Box 9848
CANBERRA ACT 2601
Telephone: (02) 6289 9545
Email: ahec.nhmrc@nhmrc.gov.au
Defining the scope of the investigation

1.21 The XWP’s terms of reference require consideration of the acceptability of proceeding with animal-to-human transplantation research. The XWP has not been asked to consider the regulation of animal-to-human transplantation clinical trials per se; in Australia, this is the responsibility of the Therapeutic Goods Administration.

1.22 The focus of the public consultation is on research rather than established clinical practice because the latter is still likely to be a long way in the future and because the same issues are likely to arise if any animal-to-human transplantation procedures become established practice. Further, the guidelines focus on aspects of animal-to-human transplantation research that are directly related to the provision of animal-to-human transplantation procedures as therapies to replace or augment diseased cells, tissues or organs in humans. Basic research not directly related to clinical practice provides essential background information for the preclinical and clinical applications, but is outside the scope of the current investigation.

Terms of reference (Xenotransplantation Working Party)

1.23 The terms of references of the Xenotransplantation Working Party (XWP) are to:

1. undertake a community education program on xenotransplantation;
2. undertake wide consultation to obtain community views on the acceptability of proceeding with clinical xenotransplantation research in Australia and on related issues;
3. produce guidelines covering the scientific, ethical and technical aspects of xenotransplantation research involving humans;
4. consider the issues that xenotransplantation raises in relation to the use of animals for this purpose;
5. undertake wide consultation on proposed guidelines and regulatory mechanisms for clinical xenotransplantation research; and
6. provide advice to Council (NHMRC) on the scientific, ethical and technical issues related to xenotransplantation research involving humans, including advice on how Australia should regulate xenotransplantation research.

Terms of reference (Animal Issues Subcommittee)

1.24 The NHMRC established the Animal Issues Subcommittee to report to the XWP on xenotransplantation to:

1. provide advice to the XWP on issues associated with animal ethics and welfare in the context of xenotransplantation research, including regulatory issues;
2. provide advice to the XWP on relevant issues raised in the public consultation activities; and
3. prepare input and provide comments on documents prepared by the XWP, which may include:
   – the second round consultation (response) document
   – the lay guide to xenotransplantation
the XWP’s advice to Council (NHMRC) on the scientific, ethical and technical issues related to xenotransplantation research involving humans, including advice on how Australia should proceed to regulate xenotransplantation research.

Development of the draft guidelines

1.25 The process to be used by the NHMRC for developing health-related guidelines and statutory obligations are set out in the *NHMRC Act 1992*. In practical terms, the process involves the following steps:

- preparation of draft guidelines for comment;
- publication in hard copy and on the internet of the draft guidelines and circulation to stakeholders;
- calls for public submissions through the Government Gazette, the internet and media advertisements requesting comments (including contact details for obtaining the draft guidelines and timeframe for receipt of comments);
- provision of other opportunities for public consultation as appropriate;
- consideration of submissions received;
- revision of the draft guidelines; and
- submission of finalised guidelines to the NHMRC.

Community and stakeholder consultation

1.26 The working party wishes to consult widely with the general public and all stakeholders on the issue of xenotransplantation. It therefore invites submissions on this Response Paper as well as on the revised draft guidelines which are contained in Section 12 of this document. Details of how to make a submission are provided on pages iii–iv and in the NHMRC procedures for making submissions, which are attached to the end of this document (page 191).

1.27 To maximise the opportunity for public comment, the working party will also be conducting public meetings in all capital cities in February 2004. In addition to providing information about animal-to-human transplantation and the draft guidelines, the meetings will enable members of the public to directly question, and put their views to, members of the XWP. Details of the public meetings will be made available in all major newspapers and on the NHMRC website (http://www.nhmrc.gov.au).

Structure of the Response Paper

1.28 Section 2 of this Response Paper gives an overview of the submissions received by the XWP during the first round of consultation and raises issues for further discussion throughout the document. To introduce the subject of animal-to-human transplantation to the general community, Section 3 defines the different types of procedures involved and discusses what animal-to-human transplantation research involves.

1.29 The subsequent sections deal with the issues raised in the *Draft Guidelines and Discussion Paper on Xenotransplantation* (Discussion Paper):

- an ethical overview of animal-to-human transplantation (Section 4);
animal welfare issues (Section 5);
alternatives to animal-to-human transplantation (Section 6);
resource issues (Section 7);
will animal-to-human transplantation work? (Section 8);
risks of infection (safety) (Section 9);
management of animal-to-human transplantation trials (Section 10); and
regulation of animal-to-human transplantation research (Section 11).

1.30 Each section starts with an overview of the relevant issues from the Discussion Paper and then responds to specific comments made in submissions to the XWP.

1.31 These sections are followed by Section 12 (The way forward for Australia), which summarises the overall conclusions of the XWP and its proposal for the way in which animal-to-human transplantation trial proposals could be handled in Australia (subject to community consultation). This summary is followed by revised draft guidelines for the conduct of animal-to-human transplantation research in Australia.

1.32 The revised draft guidelines included in this Response Paper here replace the draft guidelines published in the Discussion Paper (on which the public was invited to comment during the first round of consultation). Changes to the guidelines (compared to those included in the Discussion Paper) include the addition of new guidelines on animal welfare and patient selection. Public comment on these revised guidelines is now invited (see paragraphs 1.26–1.27).

IMPORTANT NOTE:
For ease of reference, Section 12 (including the draft guidelines; see paragraph 1.31) is printed on different coloured paper. Some readers may prefer to read Section 12, which also includes the overall conclusions of the Xenotransplantation Working Party, first before proceeding with the remainder of the document or cross refer to it section by section as they proceed with their reading.
2 Introduction

Submissions received in first round of public consultation

2.1 The NHMRC Xenotransplantation Working Party (XWP) received 97 written submissions on the Draft Guidelines and Discussion Paper (see Appendix B for full list). These came from individuals and organisations from both Australia and overseas. The submissions were of a high quality and many were very detailed. It was clear that respondents had considered the issues seriously and carefully.

2.2 Public meetings held in Perth, Melbourne and Sydney were attended by a total of 65 people and additional targeted meetings in Perth and Adelaide were attended by a total of 51 invited participants. The issues raised were recorded for consideration by the XWP alongside the written submissions.

2.3 The submissions and discussion at the public meetings raised many significant concerns and identified issues that were not fully covered by the Discussion Paper or were in need of further consideration and discussion.

Response to submissions

2.4 To facilitate further discussion and to address the concerns raised, the XWP decided to pursue a second round of public consultation. This Response Paper forms the basis for this second consultation and presents the issues raised by respondents to the Discussion Paper. It further discusses these issues and provides the response of the XWP. The information presented in this Response Paper is greatly revised from the Discussion Paper: new sections and extra information have been added to cover areas identified as weak or missing.

2.5 Each respondent to the Discussion Paper was contacted and asked if they would permit their submission to be quoted in a Response Paper. Submissions have been quoted to illustrate the concerns of, and additional information provided by, the respondents.

2.6 To select quotes for inclusion, the submissions were searched and responses to each topic highlighted (efficacy, safety, alternatives and so on). Quotes were then selected to represent the concerns expressed or new points raised, taking care to include quotes from all stakeholder groups (including individuals, professional groups, lay people, specialists, government, industry and animal welfare groups).

2.7 Permission was sought from respondents to quote from their submissions and where permission was obtained, quotes are identified by the name of the individual or group represented and the submission number given as ‘X’ and a number 1–98 (eg X010). A full list of submissions by number forms Appendix B. A few quotes where respondents did not give permission to be named in the document are included as ‘Respondent details confidential.’
Overall comments

2.8 The submissions included 13 from government agencies, 12 from animal welfare organisations, 5 from medical associations, 4 from religious organisations, 6 from other organisations, 3 from hospitals and universities, 4 from medical professionals, 3 from ethicists, 2 from transplant researchers and 1 from a consumer organisation. Other submissions (44) were from interested individuals. A more detailed breakdown of the respondents is shown in Appendix C.

2.9 There was only one submission from a consumer organisation and there were few submissions specifically from recipients of transplants, diabetics or other people who might have a direct interest in the benefits of xenotransplantation. The XWP is anxious to hear the views of these groups and seeks their input in this further round of consultation.

2.10 From the submissions received, it is clear that the community as represented has significant concerns about animal-to-human transplantation. Fifty-six respondents stated that they were opposed to animal-to-human transplantation trials proceeding; 10 stated that they were in favour. The remaining submissions did not directly state opposition or support but the text suggested that 10 were against animal-to-human transplantation, while 15 were supportive (see Table 2.1). Seven respondents were neither in favour of nor against animal-to-human transplantation.

Table 2.1 Respondents' views about whether animal-to-human transplantation trials should proceed

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<tr>
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<td>Yes</td>
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<tr>
<td>Submissions from individuals</td>
<td></td>
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<tr>
<td>— explicit statement</td>
<td>1</td>
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<tr>
<td>— views inferred from text</td>
<td>2</td>
</tr>
<tr>
<td>Submissions from organisations</td>
<td></td>
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<tr>
<td>— explicit statement</td>
<td>9</td>
</tr>
<tr>
<td>— views inferred from text</td>
<td>13</td>
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*From a total of 97 submissions. Not included in this total are 6 submissions that were not clearly for or against clinical xenotransplantation trials and one submission that was supportive of animal cell therapies but against animal organ transplants.

2.11 As might be expected for such a sensitive area of research, respondents held a wide range of views, both about xenotransplantation itself and about the Draft Guidelines and Discussion Paper:

The good of the community as a whole and the rights of animals must outweigh the good of the few who may possibly benefit from xenotransplantation.

*Lene Martens (Submission X007)*

... the draft guidelines are comprehensive and well written and ... present a thoughtful and balanced summary of the issues facing xenotransplantation ... Importantly, the discussion paper outlines a sound and compelling basis for xenotransplantation trials. *Transplantation Society of Australia and New Zealand* (Submission X053)

Arguments against animal-to-human transplantation

2.12 Respondents gave four major arguments against animal-to-human transplantation: the risk of infection for the transplant recipient and the entire community; the violation of animal
rights; that funds and other resources could be better directed elsewhere; and doubts about the likelihood of patients benefiting:

It is entirely unacceptable to … bring an animal into existence for the express purpose of ‘harvesting’ its body parts for organ transplants into humans … There is frightening potential for viruses to cross the species barrier … we believe the risks far outweigh the perceived benefits. Naomi and Michael Mairou (Submission X013)

I find it very difficult to see how this type of research would be able to proceed and yet comply with your proposed guidelines. Xenotransplants will be putting all in the community at risk, with no realistic hope that recipients will benefit. A/Professor Peter Collignon (Submission X063)

2.13 Other reasons given by respondents for not proceeding included:

• the risks exceed the benefits;
• it is not acceptable to genetically modify source animals, or the ethical implications of doing so have not been explored;
• community education and debate should precede any decisions in this area;
• results of animal-to-animal experimentation cannot be used to reliably infer results in humans;
• there are too many unknown factors to allow any confidence in the safety of the procedures;
• recipients may be ostracised by the community; and
• it is not clear who would be responsible if a new human disease arose and how it would be stopped.

Arguments in support of animal-to-human transplantation

2.14 Reasons given by respondents for supporting animal-to-human transplantation were: the potential benefit to patients; the shortage of human tissues for transplantation; and the rigorous and comprehensive guidelines proposed by the working party:

[Xenotransplantation] is a necessary step for Australia since there is a shortage of human tissue for transplantation. Professor Bernie Tuch, Diabetes Transplant Unit (Submission X016)

In general, xenotransplantation has the potential to improve human health and diminish human suffering. Salvation Army (Submission X035)

2.15 Often, submissions which supported xenotransplantation did so with caution:

GTEC agrees that, in principle, the procedure is justifiable. However, there are serious impediments to its implementation, particularly arising from concerns about risk. GTEC considered it would not be ethical to do what is unsafe. Gene Technology Ethics Committee (Submission X084)
Issues for further discussion

Ethical issues

2.16 Many respondents stated that they were ethically or morally opposed to animal-to-human transplantation, while others believed it was acceptable. These ethical views are discussed in Section 4 of this Response Paper. Ethical opposition was often on the grounds of cruelty to animals.

Animal welfare

2.17 In addition to overall concerns about cruelty to animals, specific problems relating to animal welfare were raised:

Special husbandry and housing conditions required for transgenic source animals is a major welfare concern. Adherence to strict levels of hygiene and disease control will reduce access to the outside environment and minimise human contact … The presence of a transgene may also affect the animal’s ability to perform normal behaviour. *Humane Charities Australia (Submission X033)*

The NHMRC report … does not make it clear that this research uses techniques that can cause animals substantial pain, suffering and distress, including highly invasive surgery and treatment with immunosuppressive drugs. *RSPCA UK (Submission X091)*

2.18 This issue is discussed in detail in Section 5 of this Response Paper.

Alternatives to xenotransplantation and resource allocation

2.19 Many respondents called for the alternatives to animal-to-human transplantation to be explored more seriously and raised issues about the allocation of resources:

It is inappropriate even in the context of this document to ‘put these alternatives to one side’ since they must be considered alongside xenotransplantation. Further allocation of funds to xenotransplantation may lead to a reduction in the availability of other therapies. *RSPCA Australia (Submission X050)*

2.20 These issues are discussed in detail in Sections 6 and 7 of this Response Paper.

Efficacy and safety

2.21 As outlined in paragraphs 2.12 to 2.15, many respondents, both those opposing and those supporting animal-to-human transplantation, were concerned about the risk of infection from transplanted material (safety) and questioned whether animal-to-human transplantation will work (efficacy). Section 8 of this Response Paper discusses responses concerning the efficacy of the techniques; Section 9 discusses responses about safety issues.
Management of clinical trials

2.22 Many respondents also expressed concern about how animal-to-human clinical trials would be conducted if they were permitted to go ahead — for example how protocols for consent both from trial participants and from their close contacts would be drawn up and what arrangements there would be for monitoring and follow-up. These issues are discussed further in Section 10 of this Response Paper.

Regulation

2.23 Respondents also commented on the means of regulating animal-to-human transplantation research and the models that were proposed in the Discussion Paper and Draft Guidelines. These issues are the subjects of Sections 10 and 11 of this Response Paper.

The role of guidelines

The relationship between guidelines and research

2.24 Many respondents to the consultation saw the release of draft guidelines with the Discussion Paper as an indication that the NHMRC had agreed to animal-to-human transplantation research. However, the XWP is anxious to clarify that this was not the case and, while the XWP considers that Australia needs to have clear guidelines to regulate animal-to-human transplantation research, it does not regard such research as inevitable.

2.25 Rather, the purpose of guidelines is to provide a cautious framework within which unsafe or unsuitable research would be effectively blocked, while potentially safe and beneficial research may be allowed to proceed under strictly monitored conditions.

2.26 In considering this issue, the XWP was mindful that proposals for research have already been, and will continue to be, submitted to human research ethics committees (HRECs) and animal ethics committees (AECs) in Australia for approval. These committees need clear guidelines on how to process such proposals and under what conditions the research may or may not be permitted.

Implications if Australia does not prepare guidelines

2.27 If Australia has no guidelines for animal-to-human transplantation research, proposals will inevitably be considered under existing arrangements for other types of clinical research. These arrangements were not developed with animal-to-human transplantation in mind; the XWP identified several legal loopholes in the arrangements that could allow animal-to-human transplantation trials to go ahead without due consideration of the special problems and requirements of the research. It cannot be stressed too strongly that without specific guidelines, appropriately backed by legislation, attempts to block unsuitable animal-to-human transplantation research proposals under current arrangements may be open to legal challenge.
What about having a complete ban?

2.28 Many respondents indicated that they would prefer a complete ban on animal-to-human transplantation research in Australia. This is an understandable response to an area of research that involves many challenging ethical, social and scientific issues. If backed by suitable legislation, a ban could certainly overcome the problem described in paragraph 2.27.

2.29 On the other hand, as described in paragraph 3.3, the technology described by the term ‘animal-to-human transplantation’ covers a range of procedures that have different potentials for success and do not all carry the same risks. A total ban may therefore prevent progress in a research field that has the potential to yield future benefits.

2.30 A total ban in countries such as Australia may also force research offshore. This may be detrimental to the participants involved and, if strict guidelines and monitoring are not in place in the host countries, the infectious disease risk to the whole world may be higher than for strictly monitored research in countries with rigorous guidelines.

2.31 Finally, as such research is currently occurring overseas, it is inevitable that some people in Australia will seek to travel overseas for treatment and then return to Australia. Similarly, people who have received animal-to-human transplants overseas may travel to Australia for either a short visit or a more permanent stay. Procedures are therefore needed to ensure that animal-to-human transplant recipients who enter the country are identified on arrival and that the necessary monitoring of such people occurs while they are in Australia. Procedures also need to be in place to deal with any infectious disease events that may occur. While guidelines could be prepared to deal with these issues alone (ie while banning animal-to-human transplantation within Australia), the XWP considers that such arrangements will be more effective within a broader framework of regulation of animal-to-human transplantation research in Australia.

Conclusion

2.32 The XWP shares the concerns expressed by respondents to the public consultation, including those about both the human and animal participants in the research and the potential infectious risks to society.

2.33 Therefore, the XWP considers that, if animal-to-human transplantation trials were to proceed in Australia, the development of careful and cautious guidelines would ensure that clinical trial proposals would be submitted to rigorous consideration. Under such guidelines, only proposals that are deemed safe, provide a real possibility of therapeutic success and have protocols that ensure the highest ethical standards for both the human and animal participants, should be allowed to proceed. Subsequent sections in this Response Paper discuss these issues in more detail, as well as alternatives to animal-to-human transplantation, resource issues and regulatory mechanisms.
3  What does xenotransplantation research involve?

**Overview of issues from Discussion Paper and Draft Guidelines**

The term ‘xenotransplantation’ means the transplant of cells, tissues and organs from one species of animal to another, such as from mouse to pig or pig to human. This consultation process is primarily concerned with animal-to-human xenotransplantation, which was defined in Chapter 2 of the Discussion Paper as:

*any procedure that involves transplantation, implantation or infusion into a human recipient of cells, tissues or organs from a nonhuman animal source. (Discussion Paper, Section 2.1.2)*

Organ transplantation (eg heart, kidney) is the most obvious example of animal-to-human transplantation, but the technology also includes tissue and cell transplants (eg pancreatic cells that produce insulin) and procedures that occur outside the body in which cells or fluids from the patient are cultured with or perfused through animal cells and then returned to the patient. These procedures were further defined in Section 2.1.2 of the Discussion Paper.

Respondents found the breadth of the procedures covered under the definition of xenotransplantation confusing. Hence, most of the comments received were directed towards organ transplants rather than the other procedures (cellular and external procedures). Further discussion and definition of the three types of xenotransplantation procedures are given in paragraphs 3.1–3.4 of this Response Paper.

A ‘xenotransplantation product’ was defined in the Discussion Paper (Section 2.1.3) as:

*... a live cell, tissue or organ that is used in xenotransplantation.*

The Discussion Paper noted that this definition did not include nonliving, inert (denatured and sterilised) tissues, such as pig heart valves. To ensure that the community agreed with this interpretation, the XWP posed the following question:

*Is it agreed that nonliving, inert (denatured and sterilised) animal tissues should be excluded from consideration as xenotransplants?*

Response to this question indicated support for the inclusion of only live tissues in the definition of xenotransplantation products. Further discussion is given in paragraphs 3.1–3.4.

Chapter 2 of the Discussion Paper also considered why we need to consider xenotransplantation, in terms of the burden of disease and demand for transplants. It described the scope of xenotransplantation research in terms of animal-to-animal preclinical studies and animal-to-human clinical trials. These issues are considered further in (paragraphs 3.9–3.10 and paragraphs 3.20–3.33, respectively) of this Response Paper.

Information on what is happening overseas was given in Chapter 10 of the Discussion Paper and is updated in paragraphs 3.34–3.51 below.
Definition of animal-to-human transplantation terms and procedures

**Types of procedures**

3.1 As noted in the overview above, the Xenotransplantation Working Party (XWP) defined animal-to-human transplantation to include any procedure that involves transplantation, implantation or infusion into a human recipient of cells, tissues or organs from a nonhuman animal source. This definition is based on the definition currently used by the United States Food and Drug Administration (US FDA 2001, 2003).

3.2 Respondents noted that grouping such diverse therapies together under the banner of ‘xenotransplantation’ is not very helpful. They thought it would be more helpful if the different types of animal-to-human transplantation (ie external procedures, cells, organs) were considered separately when discussing whether the proposed procedures will work, the risks involved and the clinical management required:

At the [public] meeting the ethical issue of xenotransplanting cells, tissues or organs was raised. They were all three lumped together. I disagree with this as I think there are fundamental differences. A few cells used as a tool in the course of therapeutic procedures is not in the same category as a whole organ.
Emeritus Professor David Allbrook (Submission X039)

… a key point was that the draft document did not draw adequate distinction between implantation of dissociated cells and whole organs, nor did it draw distinction between use of animal cells separated by semipermeable membranes from implantation of dissociated cells. All these scenarios carried quite different levels of risk and need to be clearly defined and categorised as separate risk levels in the necessary risk/benefit analysis. WA Stem Cell Consultative Group (Submission X087)

3.3 To address this issue, the XWP has developed new terminology for the three different types of animal-to-human transplantation procedures under consideration, as follows:

**Animal external therapies (AETs)**
- Procedures that occur outside the body, in which cells or fluids from the patient are perfused through or cultured with animal cells and returned to the patient. For example, blood from a patient with liver failure may be purified by passage through pig liver cells in an external device (Hepatassist machine) similar to a kidney dialysis machine.

**Animal cell therapies (ACTs)**
- Procedures in which cells from a nonhuman animal source are transplanted or implanted into a human patient to compensate for deficient functioning of the patient’s own cells. For example, pig pancreatic cells may produce insulin for people with diabetes. Transplanted cells can either be enclosed in a semipermeable capsule (encapsulated) or have no such capsule.

**Animal organ transplants (AOTs)**
- Procedures in which whole organs (eg a heart, kidney) or tissues (eg skin) from a nonhuman animal source are transplanted or implanted into a human patient to replace a diseased organ.
3.4 Further details and examples of these therapies are given in paragraphs 3.14–3.19. In the remainder of this Response Paper, the three different procedures are considered separately wherever possible. By providing information about the efficacy, levels of risk and clinical management associated with each type of procedure, the XWP hopes to gather further comment about community acceptability of these different therapies.

Xenotransplantation products

3.5 As noted in the overview above, ‘xenotransplantation products’ have been defined as any live animal cell, tissue or organ that is used in a xenotransplantation procedure.

3.6 Only a few submissions responded directly to the question concerning nonliving animal products (such as pig heart valves). All agreed that such products should not be classed as xenotransplantation products.

Status of animals

3.7 Some respondents pointed out that the animals that provide tissues or organs for xenotransplants should not be referred to as ‘donors’ because they do not consent to, or have any choice about, their involvement in the procedures.

… we refer to the use of source animals rather than donor animals throughout [our submission] … This is due to the fact that they are not providing consent and are therefore not donating their organs. Humane Charities Australia (Submission X033)

3.8 In this Response Paper, to better reflect the status of animals as passive participants in animal-to-human transplantation, the XWP has avoided the terms ‘donor’ and ‘donation’ when referring to animal-to-human transplantation. Rather, the animals used to obtain xenotransplantation products are referred to as ‘source animals’. Ethical issues relating to human and animal involvement in animal-to-human transplantation are discussed in Section 4 of this Response Paper. Animal welfare issues are discussed in Section 5.

Why consider animal-to-human transplantation?

3.9 Allotransplantation (transplantation between members of the same species, such as between humans) can be a very successful way of treating various diseases and conditions. However, human organ and tissue transplantation depends upon donations from people who have died as the result of brain damage (e.g. aneurysms, brain tumours) or accidents. Unfortunately, while transplants have become more frequent and successful, and the number and scope of the procedures have increased, the number of donors has not risen to the same extent. In Australia, as elsewhere in the world, there are not enough donors available. This is not just a minor shortfall that can be easily overcome by greater effort or funding; it is extreme and is increasing. Many people die while on a waiting list for a suitable transplant.

3.10 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. Research is proceeding to reduce or prevent diseases in the organs and tissues concerned, and to develop alternative therapies that do not require human donors; but this cannot be guaranteed to overcome the need for transplantation (see Section 6 of this Response Paper).
3.11 At the same time, increased medical knowledge about a range of previously incurable diseases has offered hope that transplant therapy involving cells and tissues, as well as whole organs, will provide improvements for a broader range of conditions than has previously been possible (such as Parkinson’s disease, some other neurological conditions and type 1 diabetes).

3.12 Finally, with the rapid development of genetic technology over the past decade, some scientists now feel that the major problems associated with animal transplants (such as rapid rejection of the transplant) may be overcome by genetic modification of the source animals to make them more compatible with humans.

3.13 All these factors have boosted interest in xenotransplantation. The different types of animal-to-human transplantation have different potential therapeutic uses and therefore different reasons for being pursued. Chapters 2 and 5 of the Discussion Paper discussed these uses, which are summarised briefly below for each type of procedure.

**Animal external therapies**

3.14 Current research into AETs focuses on two major areas of use. The first is to provide temporary organ function until a suitable organ donor is found. For example, there has been considerable research on methods to provide external perfusion of a patient’s blood through liver cells (a similar concept to kidney dialysis machines), thereby maintaining life until either the patient recovers from an acute case of liver failure or a suitable liver becomes available for transplant. The second is for people with very extensive burns who could benefit from grafts of human skin grown on a ‘feeder’ layer of animal (usually mouse) cells.

**Animal cell therapies**

3.15 Transplants of particular cells from animals may offer new therapies for a number of human diseases. In particular, researchers believe that ACTs show promise for the treatment of diabetes and degenerative diseases of the brain. Furthermore, encapsulation of the cellular transplant in a small ‘package’ made from a biological material such as collagen may avoid the need for immunosuppression (see paragraph 8.6).

3.16 Approximately 80,000 people in Australia (4 per 1000 population; 1 in 700 children) suffer type 1 (insulin-dependent) diabetes (ABS 1995). This form of diabetes is not preventable. Recently, human pancreatic islet cell allotransplantation (ie a form of human cell therapy) has become a successful and accepted treatment for type 1 diabetes. However, there is a shortage of human pancreatic islet cells for transplant, so the procedure is currently restricted to only a tiny fraction of diabetics who might benefit from it. If the technical issues can be overcome, pig pancreatic islet cell ACT has the potential for widespread clinical application.

3.17 It may be possible to overcome disabling degenerative diseases of the brain such as Huntington’s chorea and Parkinson’s disease by transplanting fetal pig neural cells into the brain. In Australia, Parkinson’s disease occurs in approximately 1 in 1000 adults (Selby and Herkes 1996) while Huntington’s disease occurs in approximately 4–10 people per 100,000 population (Harper 1991).
What does xenotransplantation research involve?

Animal organ transplants

3.18 More than 30,000 Australians have received transplants in the past 60 years. Despite efforts to increase the number of human organ donors, demand outstrips supply: many people on waiting lists die before an organ becomes available. The severity of the current organ shortage was detailed in Section 2.2.2 of the Discussion Paper.

3.19 Because of the shortage of human organs and tissues for transplantation, researchers are considering the use of animal products. For example, AOTs could be used to treat patients with organ failure (eg severe heart disease or kidney failure) or diseases such as cystic fibrosis.

Scope of xenotransplantation research

3.20 The term ‘xenotransplantation’ means the transplantation of cells, tissues or organs between any two different animal species (eg mice, rats, rabbits, pigs, nonhuman primates and humans). Although the main subject of this public discussion process is animal-to-human trials, it is also important to consider the animal-to-animal studies that are carried out to develop and test proposed procedures.

Preclinical studies

3.21 Before a procedure is considered for an animal-to-human transplantation trial, extensive research is needed in animal models. These preclinical animal-to-animal xenotransplantation studies include all stages of research, from preliminary studies with laboratory animals (such as rats and mice) to more advanced studies using nonhuman primates (such as baboons).

3.22 Preclinical xenotransplantation studies may also involve human-to-animal procedures. For example, research on the development and efficacy of human stem cell therapies may involve the transplantation of human stem cells into laboratory animals (including nonhuman primates in later stages of research). Such human-to-animal transplant studies will involve many of the same animal welfare issues as animal-to-animal studies and will require the same level of oversight (see Section 5 of this Response Paper).

Clinical trials

3.23 If animal-to-animal studies are successful for specific xenotransplantation procedures, researchers will seek to set up animal-to-human trials in which cells, tissues or organs are transplanted from animals to humans (eg pig-to-human) in a closely monitored clinical setting.

Therapeutic versus nontherapeutic trials

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

3.25 The Discussion Paper stressed that, because of the potential risks, an important prerequisite for an animal-to-human transplantation trial should be that the trial is
therapeutic in design. That is, the intent of the research should be to provide direct benefit to the participants and there must be a reasonable prospect that the patient will actually benefit from the procedure.

3.26 Respondents who commented on this aspect of the Discussion Paper agreed that animal-to-human transplantation trials should be therapeutic in design. One respondent stressed the importance of not repeating the mistake of the infamous ‘Baby Fae’ case:

In 1984, doctors at Loma Linda University in California transplanted a baboon heart into an infant born with serious heart defects. ‘Baby Fae’ died 20 days later. Afterward, an independent review panel determined that there were at least three other options — all more promising than a xenograft — available to treat her condition. (Respondent details confidential)

3.27 NHMRC guidelines would ensure that such trials would not be allowed in Australia without a full ethical review of the trial protocols, including participant selection, to ensure that such problems do not occur. Under the proposed procedures, for animal-to-human transplantation trials, this ethical review will occur at both a national and local (institutional) level (see Section 11).

3.28 As for other medical technologies, it may take many years to test xenotransplantation procedures through clinical trials. Clinical trials of new drugs are carried out in three phases (phase I, II and III), as described in Section 2.3.2 of the Discussion Paper. Under this terminology, phase 1 and early phase II (IIa) studies are concerned with the safety of the treatment rather than its effectiveness (that is, they are not designed to be therapeutic, although they may be so). The Gene and Related Therapies Research Advisory Panel (GTRAP) noted that, while the therapeutic design of studies was a worthy goal, it could present a difficulty for some early trials.

A comment in the discussion document implies that non-therapeutic trials of XTP [xenotransplantation] are unsafe and unethical and the measure for acceptability in XTP should be a therapeutic outcome. This is confusing as it would exclude phase I/IIa XTP studies which are essential to identify potential safety/toxicity, and do not necessarily have a measurable therapeutic outcome … A direct link between the acceptability of a XTP study and a therapeutic outcome is, therefore, difficult to follow. Gene and Related Therapies Research Advisory Panel (Submission X041)

3.29 The XWP agreed that, although valuable safety information would be gained from the first animal-to-human transplantation trials conducted for a given procedure, even the earliest trials (phase I/IIa) should enrol only patient volunteers and not healthy volunteers. In addition, although these early trials would be exploratory and a positive outcome for the patient could not be guaranteed, such trials would need to be based on strong scientific evidence (from animal-to-animal studies) of therapeutic benefit.

3.30 Paragraphs 8.58–8.68 of this Response Paper discuss the criteria that could be used to determine whether a proposed trial of xenotransplantation can be considered to be ‘therapeutic’. The criteria will be the subject of debate and consideration by the committee charged with assessing animal-to-human transplantation trial proposals and implementing NHMRC guidelines. In preparing draft guidelines, it is the intention of the XWP that the ‘bar’ for such considerations should be set very high.
**Single-patient use**

3.31 A distinction needs to be drawn between an early animal-to-human transplantation trial and a single-patient study or individual use. As described in Chapter 9 of the Discussion Paper, there are a number of schemes such as the Special Access Scheme operating under the *Therapeutic Goods Act 1989* that allow patients and doctors to have access to unregistered therapeutic products for individual use in special circumstances. These schemes were set up in response to consumer pressure for access to medications available overseas or in clinical trials but not yet registered in Australia. Under current arrangements there is therefore a danger that single-patient studies or individual use could be approved under such schemes. This issue was raised by GTRAP:

> An example of what is both unsafe and unethical would be a single patient study which is presently allowed under the TGA’s Special Access Scheme. In this circumstance, the treatment of a single patient will produce very little knowledge of any value. The current recommendation coming from the XTP working party that the TGA reviews the Special Access Scheme to exclude XTP is timely.

*Gene and Related Therapies Research Advisory Panel (Submission X041)*

3.32 The XWP has consulted the Therapeutic Goods Administration (TGA) about the Special Access Scheme and similar schemes for access to unregistered products outside a clinical trial. The TGA is currently considering changes to its legislation to ensure that these schemes are not available for high-risk biotechnology products, including xenotransplantation products (see Section 11 of this Response Paper).

**Clinical trials versus clinical practice**

3.33 This document focuses on providing an ethical framework and guidelines for the assessment of animal-to-human transplantation research proposals (clinical trials), rather than on regulating routine clinical practice. This is because research into animal-to-human transplantation is still at a very early stage, so animal therapies are not likely to become routine clinical practice in the foreseeable future. Before a procedure can become routine clinical practice, it would have to pass through several phases of clinical trials (see paragraphs 3.23–3.30) and would come under the TGA’s approval system.

**Overseas experience**

3.34 Chapter 10 of the Discussion Paper outlined the state of animal-to-human transplantation regulation in various countries as at July 2001. Since then, there have been changes in several countries. These changes are outlined below.

**United Kingdom**

3.35 The United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) has continued to provide a focal point for animal-to-human transplantation activity in the UK.¹ UKXIRA is the central agency through which applications to undertake animal-to-human transplantation trials are considered and which considers the underlying evidence about xenotransplantation developments in order to assess whether such clinical trials are

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¹ [http://www.doh.gov.uk/ukxira/index.htm](http://www.doh.gov.uk/ukxira/index.htm)
justified. The fourth annual report of UKXIRA (2000–01) indicated that in that year there had been no applications to undertake clinical trials and that no clinical trials of animal- to-human transplantation (within the current definition; see paragraph 3.37 below) were taking place in the UK.

3.36 An important issue is that, to date, UKXIRA has defined xenotransplantation differently from the United States Food and Drug Administration (FDA), which raises an important issue of whether certain types of procedures require the same ethical and medicoscientific review as others. The controversy revolves around external procedures (AETs). In the United Kingdom, AETs are defined narrowly to only include procedures that involve live cells, tissues or organs from a nonhuman animal source for ‘ex vivo perfusion’. In the United States, however, AETs are defined more broadly as procedures in which human body fluids, cells tissues or organs have ‘had ex vivo contact’ with live nonhuman cells, tissues or organs.

3.37 The UK definition therefore includes external perfusion but not other forms of external contact with animal cells, such as human skin cells grown on a feeder layer of mouse or pig cells. Treatments using this type of process are already in use and include the culturing and replacement of skin for burns victims and for other forms of plastic surgery. In 2002, UKXIRA commissioned a review of the risks of infection associated with skin culturing. UKXIRA has also recommended that the definition of xenotransplantation be amended in line with the United States version.

3.38 UKXIRA has no direct role in the regulation of animal-to-animal transplantation research, but the authority’s decisions have an impact on, and influence the use of, animals in research. Accordingly, UKXIRA and the United Kingdom Animals Procedures Committee (APC) have been developing a closer relationship. In 2001, a member of UKXIRA was coopted onto the APC primate subcommittee to review applications to undertake xenotransplantation research using primates. However, disclosure of actual animal-to-animal transplant research proposals to UKXIRA is not possible due to confidentiality constraints.

3.39 UKXIRA has prepared draft guidance notes on biosecurity considerations in relation to xenotransplantation (UKXIRA 1999) and worked with the UK Home Office to develop a code of practice for the housing and care of pigs intended for use as xenotransplant source animals (UK Home Office, no date).

3.40 Finally, UKXIRA is currently considering the feasibility of developing a national infection surveillance scheme.

United States

3.41 In April 2003, the FDA Center for Biologics Evaluation and Research issued finalised regulations covering the use of animal therapies in the United States (US FDA 2003).

3.42 A number of clinical trials of ACTs are in progress with FDA approval (see Section 8, Table 8.1 of this Response Paper).

2 http://www.doh.gov.uk/ukxira/biosecurity.htm
3 http://www.fda.gov/cber/gdlns/clinxeno.htm
Canada

3.43 Health Canada, through the Expert Advisory Committee on Xenograft Regulation, has funded the Canadian Public Health Association to form a Public Advisory Group on Xenotransplantation to consult with the public across Canada. The group’s final report concluded that Canadians felt that Canada should not proceed with animal-to-human transplantation at this time. Reasons included the lack of knowledge about disease transfer, the effectiveness of the techniques and a need to further explore alternatives (CPHA 2001).

3.44 Health Canada and the Canadian Standards Association have begun work on a formal standard for animal-to-human transplantation, but following the public consultation process the standard has been put on hold.4

3.45 Currently no animal-to-human transplantation trials are being conducted in Canada. However, preclinical testing and research into xenotransplantation that does not involve the use of human subjects is under way.

New Zealand


3.47 The Act does not call for a ban on animal-to-human transplantation. Instead, any procedure involving animal-to-human transplantation requires authorisation from the Minister of Health. Before authorising any procedure, the Minister must be satisfied that it does not pose an unacceptable risk to the health or safety of the public and that cultural, ethical and spiritual concerns have been addressed. These measures have recently been extended until 30 June 2005.

European Union

3.48 The Council of Europe Committee of Ministers has passed a recommendation on xenotransplantation (Council of Europe 2003). The recommendation states that member states should put in place legislation xenotransplantation that only allows authorisation of animal-to-human transplantation activity under a set of principles and guidelines set out in the recommendation. Central requirements for authorisation include:

- preclinical research has demonstrated it is highly probable that there is no risk, in particular of infection, to public health;
- a therapeutic benefit to the patient has been established; and
- the potential level of efficacy and safety justifies the intervention, having regard to the risks incurred.

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4 http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/bgtd/xeno_std_e.html
3.49 Some clinical trials are in progress in European Union member states (see Section 8, Table 8.1 of this Response Paper).

Other countries

3.50 When the New Zealand Government turned down an application for clinical trials of pancreatic islet cell AET for type 1 diabetes in children, the trial was set up instead in Mexico using pig islet cells prepared in New Zealand and transported to Mexico.

3.51 Transnational clinical trials raise important issues that reinforce the need for effective national and international regulation of animal-to-human transplantation trials, including effective monitoring and surveillance of transplant recipients (McKenzie et al 2002).

Conclusion

3.52 The XWP concluded that it is appropriate to define animal-to-human transplantation as:

... any procedure that involves transplantation, implantation or infusion into a human recipient of cells, tissues or organs from a nonhuman animal source.

However, the working party agreed that in further discussions of animal-to-human transplantation, careful distinction needs to be made between animal external therapies (AETs), animal cell therapies (ACTs) and animal organ transplants (AOTs).

3.53 Such procedures might be considered in order to meet differing needs. AETs offer a potentially successful bridging procedure for people with liver failure, and may save the lives of other patients, such as burns victims. ACTs offer hope for conditions for which there is no current treatment or for which current treatment is unsatisfactory. AOTs offer an alternative to human organ transplants for whole organ failure.

3.54 Research into animal-to-human transplantation is at a very early stage of development and therefore should not be confused with routine clinical practice. Clearly, for the foreseeable future, any treatment of a person with animal cells, tissues or organs will be research rather than clinical practice and will have to be approved by a national committee as well as by the human research ethics committee at the institution where it is proposed to take place. While the XWP understands that therapeutic benefit cannot be guaranteed in a very early clinical trial, under the proposed guidelines, animal-to-human transplantation research should be based on some prospect of therapeutic benefit (based on preclinical animal-to-animal studies).
4 Ethical overview of animal-to-human transplantation

Overview of issues from Discussion Paper and Draft Guidelines

Chapter 3 of the Discussion Paper proposed an overall framework for the ethical consideration of animal-to-human transplantation through consideration of the ends, the means, the consequences and the social significance of the procedure.

Section 3.2 of the Discussion Paper considered whether there are any inherent ethical objections to animal-to-human transplantation that might prevent any further consideration of the issue (that is, whether there are reasons why it should not be done at all, irrespective of the benefits or risks). In this context, two themes were identified: respect for human beings, and the welfare of animals. To prompt further discussion of these issues with the public, the XWP posed the question:

*Have any inherent ethical objections to using live animal cells, tissues or organs for xenotransplantation been adequately addressed?*

Some submissions agreed that the inherent ethical objections had been adequately addressed, but others did not think they had been, particularly in regard to the welfare and genetic modification of animals. Further discussion of these responses is given in paragraphs 4.17–4.45 of this Response Paper.

Several respondents also expressed religious views on animal-to-human transplantation; paragraphs 4.46–4.66 therefore provide a more detailed discussion of religious views.

Section 3.3 of the Discussion Paper considered the principles for the ethical conduct of animal-to-human transplantation research should it be allowed to proceed. These principles and the responses to them are discussed in paragraphs 4.67–4.77.

To determine if there were additional ethical issues relating to the conduct of animal-to-human transplantation that they had not considered, the XWP posed the following question:

*Are there other important ethical issues that need to be considered in this debate about xenotransplantation?*

Several respondents suggested that the scope of the ethical considerations needed to be extended to include animal-to-animal studies as well as animal-to-human trials. This issue has been considered by the Animal Issues Subcommittee (see paragraph 1.18) and is discussed further in Section 5 of this Response Paper.

Some respondents suggested that the ethical notion of ‘serving the common good’ had not been sufficiently defined and additional issues had not been covered, such as the place of animals in the ecosystem and other ecological issues. This is discussed further in paragraphs 4.69–4.75.

Section 3.4 of the Discussion Paper flagged some of the complex issues surrounding the social significance of using xenotransplantation products, such as justice and equity issues in resource allocation. Some respondents felt that this issue required further discussion. Resource allocation is therefore discussed in more detail in Section 7 of this Response Paper.
Should we pursue animal-to-human transplantation at all?

4.1 In considering the ethical issues inherent in animal-to-human transplantation, the Discussion Paper (page 25) stated that:

... an ethical discussion about animals as sources of transplantable organs and tissues (with the implication that, whatever the potential for human health, we perhaps ought not to do it) involves serious questions about what violates respect for the dignity of human beings and what violates the welfare of animals.

4.2 The Discussion Paper concluded that, based on these considerations, there was no in-principle objection to animal-to-human transplantation that would prevent any further consideration of the technology under ethical guidelines.

4.3 The submissions reflected the diverse range of views in the community. Some respondents agreed with the view stated in paragraph 4.2. However, a number of respondents held that animal-to-human transplantation ought not to be pursued as a medical therapy because of lack of respect for humans or for animals, or both.

4.4 For some people, such in-principle objections to animal-to-human transplantation were enough to settle the issue without further consideration of guidelines or trial protocols. These considerations are discussed further in the remainder of this section.

Respect for humans

4.5 Treating human beings with living products from animals is not morally acceptable to some people. Section 3.2.1 of the Discussion Paper considered three issues relating to proper respect for human beings:

- crossing the species barrier, which goes against a deep-seated taboo in human culture;
- potential loss of identity of the human recipient, including possible psychological problems and feelings that he or she is somehow less human; and
- the lack of a proper relationship between the giver and the receiver of the transplant.

4.6 The Discussion Paper argued that these concerns can be met so long as the animal transplant does not impair the essential psychological or genetic identity of the person receiving the transplant. Not all the submissions agreed, as indicated in the following discussion.

Crossing the species barrier

4.7 One of the key issues raised by animal-to-human transplantation concerns the mixing of human and animal tissues. It was clear from the submissions that many people are quite uneasy about the concept of inserting animal organs or tissues into a human being.

Add to it the fact that these Animal Parts would be going into human beings and the whole scenario sounds just like a B grade horror movie …

Carly Cooper (Submission X027)

4.8 However, it was also clear that, when considering this issue, many respondents were primarily thinking of animal whole organ transplants (such as pig heart-to-human). It was not so clear whether animal cell transplants or animal external therapies raised such
concerns. Public views specifically on animal external therapies and animal cell therapies will be sought in this round of consultation.

4.9 As indicated in the Discussion Paper (Section 2.4), the limited data available on public opinion indicate that people’s views are usually influenced by whether a person or loved one needs a transplant: people for whom an animal-to-human transplant is a potential therapy are more likely to support the technology. Unfortunately, few submissions were received from potential patients, past recipients of human organ transplants or groups representing such people. The views of these groups will therefore be sought in this round of consultation.

4.10 Several respondents said that religion was the reason for their concern about crossing the species barrier by putting animal tissues into human beings. However, this view was not substantiated by the submissions from representatives of a number of major religions (see paragraphs 4.46–4.66).

4.11 Genetic modification of source animals to include human genes was seen as another form of blurring the species boundaries between humans and animals. This issue is discussed further in paragraphs 4.27–4.33.

Identity of the human recipient

4.12 A transplant of living animal tissue may confuse the personal identity of the recipient or cause other psychological distress. Such problems are already known to occur for human organ transplant recipients, who are given support to alleviate any distress they may feel. The Discussion Paper noted that recipients of animal transplants would require similar support to overcome any psychological problems associated with the transplant.

4.13 Some respondents agreed that the psychological effect on the animal transplant recipient is one of the risks that both researchers and transplant recipients would need to take seriously into account.

This is a risk that must be delineated for the individual xenotransplant recipient, and must be considered as thoroughly as possible in advance of the transplant and managed appropriately if it does occur. International Xenotransplantation Association (Submission X077)

4.14 Overall, the submissions that commented on identity concerns in animal transplant recipients saw the issue as an important but not insurmountable ethical concern.

Relationship between the giver and the receiver

4.15 The Discussion Paper noted that the lack of a proper relationship between giver and receiver in animal-to-human transplantation was a potential problem for people who feel that, to respect all the parties involved, an organ transfer should involve the kind of communality between giver and receiver that is implied by the notion of ‘donation’. This is clearly not the case when animals are raised solely for the production of transplantation products.

4.16 The reality of animal-to-human transplantation is better reflected by avoiding the terms ‘donor’ and ‘donation’ and referring to the animals used to prepare xenotransplantation products as ‘source animals’ (see paragraphs 3.7–3.8).
Respect for animals

4.17 In considering whether there is anything inherently unethical or unacceptable about using animal organs, tissues and cells for transplantation to humans, Section 3.2.2 of the Discussion Paper addressed questions about respect for animals. It presented arguments for and against the proposition that killing animals in order to use their organs and tissues for human medical therapies is morally acceptable. This proposition was discussed in relation to three issues:

- speciesism;
- treating animals as human property; and
- genetic modification of animals.

4.18 The Discussion Paper concluded that inherent ethical objections based on these three issues could be satisfactorily answered, drawing on existing arrangements for the use of animals in medical research. However, not all the respondents agreed with this conclusion. The objections put forward and responses to them are discussed below.

**Speciesism**

4.19 There are several philosophical and ethical positions on the use of animals as a resource for humans, including:

- that there is moral equivalence between at least some higher animals (including nonhuman primates) and humans and that using such animals as resources for humans shows the prejudice of speciesism;
- that, although there is not moral equivalence as such, higher animals are, nevertheless, creatures of moral worth and should not be treated as means to human ends; and
- that there are morally significant differences between human beings and animals, and animals may therefore be used as resources for human benefit as long as ethical standards of care are met.

4.20 Some respondents believed that, although inherent ethical objections to using live animal cells, tissues or organs for xenotransplantation had been broadly recognised in the Discussion Paper, they had not been adequately addressed with respect to animals and their welfare:

> There are many important principles and ideas associated with the concept of speciesism that are key to the xenotransplantation debate and that deserve serious consideration. The report dismisses all of these arguments in a highly simplistic way. There is very little explanation or recognition of the intrinsic worth of animals as sentient individuals and this is a major concern. RSPCA UK (Submission X091)

4.21 Other respondents disputed the right to use nonhuman animals as tools for research and to farm them for ‘spare parts’:

> Generally speaking, humans regard their own lives as having greater value than non-human animals — presumably because of our supposed higher level of intelligence, communication skills and ability for reasoning. If however, another species were to emerge (hypothetically) that demonstrated a higher intelligence and social structure than that of humans, would we then concede acceptance and allow ourselves to be utilised for their benefit? Presumably we would not, yet because non-human animals are unable to defend their own rights we use them to our advantage, as if their right to life is of no significant value. Humane Charities Australia (Submission X033)
4.22 On the other hand, the Gene Technology Ethics Committee said that it had considered the principle of respecting intrinsic value while testing a framework designed for ethical reflection on gene technology. They applied the principle to animal-to-human transplantation and found that recognition of the intrinsic, or moral, value of the source animals in animal-to-human transplantation need not preclude their use in such procedures:

Thus the moral value of the source animal entity being used to provide organs or cells for transplantation is real and ought not to be ignored … This does not however prohibit their use in this way … Their own needs and situations — including their own level of consciousness — need to be taken into account but this need not prohibit their ‘use’ in an appropriate manner for xenotransplantation any more than their use for consumption. Gene Technology Ethics Committee (Submission X084 Attachment 1)

Animals treated as human property

4.23 Some people think it is morally wrong to use animals for any medical research at all and therefore that it would also be wrong to use them as source animals for human therapies. This view was reflected in a number of the submissions. However, the mainstream view in society is that it is acceptable to use animals for the benefit of humans. (See also paragraphs 4.46–4.66 for a discussion of the views of the major religions.) For example:

By some the principle is rejected as unethical behaviour … I do not subscribe to this view. I do think humans have a duty of care to animals … I think the present requirements for research proposals to be submitted to ethics committees are sufficient safeguard, always providing these are well constituted and do their work well! They should ask questions that force the researcher to clarify the reasoning for the use of animal tissues in the proposed work. Emeritus Professor David Allbrook (Submission X039)

4.24 Reflecting this view, the breeding and rearing of animals for medical research is permitted in Australia as long as the protocols used are humane to the animals and respect the essential characteristics and welfare of their species. To ensure that this requirement is met, all research involving animals must comply with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC 1997a), which is enforced under State/Territory animal welfare legislation.

4.25 However, animal welfare organisations highlighted the exceptional nature of animal-to-human transplantation in terms of the breeding, rearing and use of animals. They argued that these special factors pose ethical dilemmas for the community over and above the already complex issues of the use of animals in medical research and that these were not adequately addressed in the Discussion Paper.

4.26 The XWP agreed that the value and welfare of animals was not covered in sufficient detail in the Discussion Paper. A subcommittee with additional expertise in animal welfare and regulatory issues was therefore formed to consider the issues raised in the submissions in more detail (see paragraph 1.18). Section 5 of this Response Paper discusses these issues in detail.

Genetic modification of animals

4.27 Genetic modification of source animals is not an absolute prerequisite for all animal-to-human transplantation. However, researchers think that problems of immune rejection
and other functional mismatching between animal and human tissues can be best overcome by genetic modification of the source animals.

4.28 Genetic modification of source animals involves inserting some key human genes to help make animal transplants behave more like human transplants (see paragraphs 5.43–5.55). Many respondents expressed concern about such genetic modification of animals:

Procedures causing pain, suffering and distress such as hormone treatment and embryo transfer surgery are required, the process as a whole is inherently far more wasteful of animals’ lives than conventional breeding, and many people have legitimate concerns about artificially changing the integrity of a species.

RSPCA UK (Submission X091)

The discussion paper addresses this question [genetic modification] only as a matter of bio-safety and animal dignity. There is another question altogether as to whether from a human perspective it ought to be ethically permissible to alter an animal embryo by adding part of a human genome so as to produce human biological characteristics in the animal. Dr Nicholas Tonti-Filippini (X001)

4.29 Others thought that genetic modification of animals is acceptable and that concerns can be met as long as the protocols used are humane to animals and respect the essential characteristics and welfare of the species:

Genetic modifications of xenogeneic source animals are considered to be acceptable as long as they do not change the overall character of the animal species. It is noteworthy that genetically modified animals have been bred and utilized for many years in agriculture. International Xenotransplantation Association (Submission X077)

4.30 Others stressed the need for caution:

This has unknown potential for good or bad effects which may not become apparent for some years. The Preterm Foundation (Submission X081)

4.31 Clearly, these are very difficult issues to resolve and it would be beyond the scope of the XWP to attempt to do so at this time. The consensus reached by several overseas agencies that have reviewed this issue is that genetically modifying a pig with a few human genes does not significantly alter the essential characteristics of the pig.

4.32 However, the genetic modification of animals with human genes is clearly an emerging issue in the community and is attracting rigorous academic analysis by both secular and religious moral philosophers (see also paragraphs 4.46–4.66). The outcomes of the debate will direct future scientific research in a number of areas, including animal-to-human transplantation.

4.33 Some respondents thought that the Discussion Paper did not adequately address animal welfare issues concerning the breeding and care of genetically modified animals. These issues are discussed further in Section 5 of this Response Paper.

Use of primates

4.34 Whatever their view about the use of animals for the benefit of humans, most people share some concern about the use of nonhuman primates in medical research. It is accepted that such research should occur only under strictly controlled conditions and to provide essential evidence of significant benefit to humans. This principle is reflected in
the NHMRC Policy on the Care and Use of Non-human Primates for Scientific Purposes (NHP Policy; NHMRC 2003b).

4.35 The Discussion Paper stated that nonhuman primates should not be allowed to be used as source animals for xenotransplantation products in Australia. However, this decision was made on the grounds of safety rather than ethics: nonhuman primate-to-human transplants are considered too dangerous because of the potential for transfer of retroviruses or other infectious agents that could infect humans.

4.36 RSPCA Australia and RSPCA UK (Submissions X050 and X091) both stated that the Draft Guidelines and Discussion Paper should state more strongly that nonhuman primates may not be used as source animals for human xenotransplantation products on both safety and ethical grounds.

4.37 Specifically, the use of nonhuman primates as source animals would involve the need for housing and husbandry procedures to minimise pathogens (including biocontainment). These conditions are not considered ethically acceptable for nonhuman primates.

4.38 The XWP therefore considers that nonhuman primates should not be used as source animals for whole organ transplants or other procedures that involve biocontainment or rigorous husbandry conditions that would impose stress on the animals. However, the use of nonhuman primate cells (such as stem cells) obtained from animals that are not reared under these conditions cannot be ruled out if the welfare of the animals meets the standards set down by the NHP Policy (see paragraph 4.34.

4.39 Animal-to-animal transplantation studies also use nonhuman primates — most frequently baboons — as transplant recipients because these species provide researchers with the closest comparison to human recipients. This was reflected in the Draft Guidelines, which stated that proposals for animal-to-human trials should be substantiated by evidence from studies with nonhuman primates.

4.40 However, the Discussion Paper did not include a detailed discussion about the ethics of using nonhuman primates in preclinical research, which some respondents saw as a serious limitation:

> No mention is given to the ethical issues arising from the development of xenotransplantation, ie the use of primates and other animals in animal-to-animal transplants, the development and testing of immunosuppressive and other drugs for associated treatment, and the development of transgenic models of pigs as source animals. This use of animals, especially nonhuman primates, has implications in terms of the acceptability of xenotransplantation.
> *RSPCA Australia (Submission X050)*

4.41 The submissions highlighted that many people are concerned about the use of nonhuman primates in animal-to-animal transplantation studies on several ethical grounds, including welfare and the protection of endangered species:

> The rights of the xenograft source animals are another major consideration, and these have generated considerable controversy. For many members of society, these issues vary according to the species under consideration as a source animal. Non-human primates such as baboons have complex social behaviors, and there are many concerns, ethical as well as financial and practical, relating to the breeding of large numbers of these animals in captivity for use as source organ donors.
> *International Xenotransplantation Association (Submission X077)*
4.42 The great apes (gorillas, orang-outangs, chimpanzees and bonobos) are the nonhuman primates most closely related to humans in evolution. They are also endangered species and hence their use in any scientific research is very closely regulated. The NHP Policy includes a statement that great apes may only be used for scientific purposes if:

- resources, including staffing, are available to ensure the highest standards of care;
- the research benefits either the animal itself or the species; and
- the benefits of the scientific knowledge gained outweigh any harm to the animal itself.

4.43 Therefore, it is highly unlikely that great apes would be used either as source animals for transplants to humans or as recipients in animal-to-animal studies.

4.44 However, most studies with nonhuman primates use baboons, which are Old World monkeys and are common. In addition, the NHP Policy currently precludes the importation of nonhuman primates from wild populations and hence baboons used in medical research are supplied by breeding colonies maintained specifically for that purpose.

4.45 Section 5 of this Response Paper provides further detailed discussion about welfare issues associated with the use of nonhuman primates.

**Views of the major religions**

4.46 The religious and spiritual views of people in Australia, as elsewhere, are very diverse and complex. The attitudes of the three major monotheistic religions are discussed in paragraphs 4.47–4.65. 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.

**Attitudes of Christianity, Judaism and Islam**

4.47 Submissions were received from representatives of the Christian, Jewish and Islamic religions. There were no substantial comments representing the views of other religions. The International Xenotransplantation Association (IXA) submitted a report prepared by its Ethics Committee, which included an overview of the views of these three religions.

4.48 Five religious issues were identified:

- intervention in the order of creation;
- the acceptability of using animal organs to improve the chances of survival and wellbeing of humans;
- the impact of the xenotransplant on the identity of the human recipient;
- the acceptability of pig transplants to Jewish and Islamic people; and
- the ethics of mixing human and animal genetic material, as occurs when pigs are genetically modified with human genes to reduce rejection reactions.

Each of these issues is discussed below.
Intervention in the order of creation

4.49 Submissions from representatives of the three religions and the conclusion of the IXA Ethics Committee all agreed that animal-to-human transplantation does not contravene the order of creation for any of the three religions.

4.50 The view of the Catholic Church is described in a discussion paper entitled Prospects for Xenotransplantation: Scientific Aspects and Ethical Consideration published by the Pontifical Academy for Life in September 2001, which states:

For a theological reflection that will help to formulate an ethical assessment on the practice of xenotransplantation, we do well to consider what the intention of the creator was in bringing animals into existence. Since they are creatures, animals have their own specific value which man must recognise and respect. However, God placed them, together with the other nonhuman creatures, at the service of man, so that man could achieve his overall development also through them.

Furthermore:

Catholic theology does not have preclusions, on a religious or ritual basis, in using any animal [nonhuman primates or nonprimates] as a source of organs or tissues for transplantation to man.

However:

… there is the ethical requirement that in using animals, man must observe certain conditions: unnecessary animal suffering must be prevented; criteria of real necessity and reasonableness must be respected; genetic modifications that could significantly alter the biodiversity and balance of the species in the animal world must be avoided.

4.51 Another Christian viewpoint was provided by the Salvation Army in its submitted paper Xenotransplantation: A Salvation Army Perspective:

It would seem that there is no biblical prohibition against such an intervention although a number of questions regarding health issues remain.

Salvation Army (Submission X035)

4.52 Rabbi Dr Shimon Cowen, Director of the Institute for Judaism and Civilisation, Melbourne, provided an article he had written describing the laws of Noah (Noahide laws), which underpin the Jewish tradition. On the issue of the order of nature, he wrote:

The transcultural norm of the Noahide laws here teaches that the animal world is to be elevated materially and spiritually through its incorporation in the Divine service of human beings. … Thus Noahide law permits the consumption of animal flesh after slaughter. It would also permit the use of animal experimentation for the benefit of human beings. In all these cases, however, it teaches to minimize the suffering of animals.

In terms of xenotransplantation, he concluded:

I see no objection to xenotransplantation, where of course, all due precautions are taken, including the minimization of cruelty to animals.

_Rabbi Dr Shimon Cowen, Institute for Judaism and Civilisation (Submission X076)_

4.53 The submission by Dr Shabbir Ahmed (Imam, King Abdul Aziz Mosque), describing the Islamic viewpoint, was mainly concerned with the use of pigs for human transplantation products. Overall Islamic support for such procedures is indicated by the following statement in Dr Ahmed’s conclusions:

Hence, I hereby suggest to direct attention towards the research of some other animal compatible to human system other than pig to avoid uncertainty and controversy.

_Dr Shabbir Ahmed (Submission X098)_

**Using animal organs for the benefit of humans**

4.54 In regard to the acceptability of using animal organs to save lives and improve human wellbeing, the IXA Ethics Committee noted that:

... all three major religions justify the sacrifice of animals only if there are to be significant benefits to humans; the preservation of a human life would justify xenotransplantation. Nevertheless all three religions prohibit cruelty to animals, and insist on humane treatment and that suffering be minimized.

_International Xenotransplantation Association (Submission X077)_

4.55 The Salvation Army submission considered animal-to-human transplantation in terms of three characteristics of personhood — consciousness, responsibility and relatedness — and concluded:

... The use of animal tissue and organs does not threaten our ability for conscious human existence ... Humanity was given custody of all other creatures and the environment and xenotransplantation does not undermine such responsibility ... Human relationships are ended by death. Xenotransplantation may save lives, thereby allowing relatedness to continue and increasing the ability of humans to care for one another. _Salvation Army (Submission X035)_

**Impact on human identity**

4.56 The impact of animal-to-human transplantation on the identity of the human recipient was identified in the Discussion Paper as one of the ethical issues inherent in xenotransplantation, and is discussed earlier (paragraphs 4.12–4.14). It was also one of the religious issues flagged by the IXA Ethics Committee:

Another religious issue ... is whether the xenograft will affect the recipient’s personality or identity, and, more importantly, whether pig DNA will enter the human genome, particularly in germ cells, and thus be transferred to offspring ... Furthermore, allotransplantation is now acceptable to all three religions, with the allograft being viewed as purely a functional organ without affecting the recipient’s identity. _International Xenotransplantation Association (Submission X077)_

4.57 The Catholic Church does not consider that the use of pig tissues or organs would affect identity per se, but the report of the Pontifical Academy for Life noted that some organs and tissues have a stronger link with identity than others. In many cases this depends on the subjectivity of the individual and can only be assessed case by case. However, in some cases, such as for gonads and brain tissue, the association with personal identity is strongly linked to function, independent of any more symbolic or subjective considerations. The Academy suggests that transplantation of such organs or tissues is not morally acceptable.
4.58 The Salvation Army also finds no biblical objection to xenotransplantation on the grounds of loss of identity:

It is reasonable to see continuity between using animal products for human sustenance and using animal tissue, cells and organs for transplantation to humans. Xenotransplantation is not cross-breeding, which is prohibited in Levitical law (18:23). When animal organs or tissues are transplanted into a human person, the person remains human and does not become another species.

_Salvation Army (Submission X035)_

**Acceptability of pig transplant products to Jewish and Islamic people**

4.59 Several respondents raised the specific issue of the acceptability of pig transplant products to Jewish and Islamic peoples:

Since the Draft Guidelines state: ‘Currently, both researchers and ethicists consider pigs to be the most likely and appropriate source of organs and tissues for xenotransplantation’ (p.34), it is important that the NMHRC consider the implications for a number of religious communities, in particular those who follow the Islamic and Jewish faiths, for whom the pig is taboo.

_Federation of Ethnic Communities’ Councils of Australia (Submission X047)_

4.60 The IXA Ethics Committee addressed this concern in the following way:

However, using pig organs for transplantation is not regarded as eating pork, but as deriving a substantial benefit from pigs. Furthermore, both Judaic and Islamic laws allow for exceptions to dietary laws, particularly when it comes to saving a human life.

_International Xenotransplantation Association (Submission X077)_

4.61 This analysis appeared to be supported by Rabbi Dr Shimon Cowen, who did not exclude pigs from his conclusion that there was no objection under Noahide laws to xenotransplantation (see paragraph 4.52).

4.62 Dr Shabbir Ahmed (Imam, King Abdul Aziz Mosque) indicated that, in his opinion, pig-to-human transplantation may be permitted under Islamic law if the following conditions are met:

1. No alternative animal organ of category 1 [animals permitted to be eaten under Islamic law] [or organ] of a human being is available.
2. It is declared by the attending doctors that the patient is going to die if his organ is not transplanted at the moment.
3. There should be very strong chance of the life saving. If there is a probability but not certainty (at least 75 percent) its use is not valid.
4. It is associated like no physical, mental, psychological or moral degeneration would take place in future because of transplantation.

_Dr Shabbir Ahmed (Submission X098)_

However, he suggested that research should preferably be directed towards animals other than pigs, to avoid uncertainty and controversy.

**Introducing human genes into animals**

4.63 Dr Nicholas Tonti-Filippini provided a detailed discussion of the moral aspects of attempting to transform an animal embryo by introducing human DNA into its genome so that the developing embryo inherits some human biological characteristics. He identified this as one of several topics on which the Pontifical Academy has not provided any
analysis and therefore ‘offers no authoritative teaching’. In an attached paper written to address this issue, Dr Tonti-Filippini and his co-authors concluded:

It seems to us that when a scientist fragments the human genome and adds parts of it to an animal genome in the formation of a hybrid zygote, he or she has begun to confuse the identity of what is or is not human and what or who is or is not made in the image and likeness of God, and does or does not count as my neighbour.

Dr Nicholas Tonti-Filippini (Submission X0,1 Attachment 1)

4.64 The genetic modification of animals is discussed further in Section 5 of this Response Paper.

Sharing information

4.65 The differences in views among different religions indicate how important it is for prospective xenotransplantation participants to be provided with detailed information, in their own languages, about the procedures, including the source animals. They could then take their own religious views into account in making a decision about whether to proceed:

It is the obligation of the researcher to ensure that the individual is fully informed of the source animal of the organs and/or tissues for transplantation, as well as any risks involved in the research. This information must be provided in the language and format with which the individual is most proficient. Federation of Ethnic Communities’ Councils of Australia (Submission X047)

4.66 The provision of information to potential research participants is discussed in more detail in Section 10 of this Response Paper.

Ethical conduct of animal-to-human transplantation research

4.67 Section 3.3 of the Discussion Paper outlined a set of principles that could be followed for the conduct of animal-to-human transplantation trials. These principles broadly reflect the National Statement on Ethical Conduct in Research Involving Humans (NHMRC 1999) and the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC 1997a), as well as specific issues relating to animal-to-human transplantation, such as consent arrangements, monitoring and follow-up. The principles were used to guide the development of the Draft Guidelines and were included in the preamble to the guidelines (Draft Guidelines and Discussion Paper, page xxi) as follows:

- the research must serve the common good;
- the research must be scientifically sound;
- the research must be based on relevant efficacy data from preclinical studies;
- the research must be therapeutic in design;
- the benefits must justify any risks;
- the research should not expose the participants, their contacts or society to any unreasonable risks;

6 Nicholas Tonti-Filippini, John I Fleming, Gregory K Pike, Ray Campbell, Ethics and human-animal transgenesis, *Medicina e Morale* (forthcoming)
• the research must respect the dignity of participants;
• participants must give adequately informed and voluntary consent;
• arrangements for monitoring and follow-up must take account of the participant’s right to withdraw from the trial;
• the safety and rights of close contacts of the participants must be protected; and
• the research must respect the welfare of animals used in the trial and be conducted according to the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes*.

4.68 Most of these issues (efficacy, safety, consent, monitoring, animal welfare) are discussed in detail elsewhere in this Response Paper. However, some issues relate to a broader ethical perspective and these are discussed further below.

**Serving the common good**

4.69 The first principle noted above — ‘serving the common good’ — was discussed further in Section 2.4 of the Discussion Paper and was intended to provide an overarching paradigm for the other ethical issues that would form the basis of guidelines for research (efficacy, safety, research protocols and animal welfare). However, some respondents noted that the ‘common good’ was not defined in the Discussion Paper:

> ‘Common good’ is not clearly defined by the paper and it must be hoped that it does not refer to the satisfaction of scientific curiosity nor the possible health benefits to a few while the rest of humanity is put at enormous risk. There is also no ‘dignity’ or ‘common good’ in one species killing another to steal organs.
> *Lene Martens (Submission X007)*

4.70 The term ‘common good’ originated over 2000 years ago in Greek and Roman philosophy and in the early Christian church. More recently, the contemporary ethicist John Rawls defined the common good as ‘certain general conditions that are … equally to everyone’s advantage’. The Catholic religious tradition has a long history of struggling to define and promote the common good. In this tradition, common good is inseparable from the social wellbeing of the human community, from peace, and from respect for each person. When applied to health care, the common good refers to a delivery system that promotes the health of all members of a community.

4.71 By placing the other ethical issues relating to animal-to-human transplantation research under a ‘banner’ of serving the common good, the XWP intended that the committee that assesses research proposals should consider the effects of the research on society as a whole as well as the needs of the research participants and the researchers. Clearly this is a very important consideration for animal-to-human transplantation, as the technology carries potential health risks for the wider community that need to be balanced against possible benefits to individual transplant recipients.

4.72 The Gene Technology Ethics Committee (GTEC) suggested that there should be a specific guideline on ‘the common good’:

> There is no specific guideline on the ‘common good’. A guideline to the effect that ‘any proposed xenotransplantation trial should demonstrate that there are both public and individual benefits and that there are no suitable alternative procedures available’ should be included. *Gene Technology Ethics Committee (Submission X084)*
In the Draft Guidelines and Discussion Paper, the XWP did not provide a specific draft guideline for researchers concerning ‘serving the common good’. However, the ‘Advice regarding application of the proposed guidelines’, which was included with the Draft Guidelines, provided the following issues for the proposed national xenotransplantation committee to consider when assessing research applications:

- Are the ethical issues associated with this procedure acceptable to the general public?
- What are the public and individual benefits of this procedure?
- What are the public and individual risks of this procedure?
- Are there any alternative procedures available?
- Are the infectious risks associated with this procedure acceptable to the general public?

GTEC suggested that the scope of the Draft Guidelines and Discussion Paper needed to extend beyond a medical model.

… The ethical guidelines proposed by the Discussion Paper are strictly in accord with those already in place for medical research and the interpretation of the last of them (‘public health risks’) is likely to be similarly limited. However the model needs to be far more holistic – for example, the involvement of gene technology research requires the inclusion of ecological issues and social justice issues.

Gene Technology Ethics Committee (X084)

The XWP agrees that there should be more emphasis on whether there are any alternative procedures that would provide the same or more benefits with fewer risks, and has included additional wording to this effect to the draft guideline on efficacy. (Revised draft guidelines are included at the end of Section 12 of this Response Paper.)

Ethical conduct of animal-to-animal studies

The Draft Guidelines applied to the assessment of animal-to-human trials (for example, pig-to-human brain cell therapy) and did not address studies in which xenotransplantation procedures are tested in animal-to-animal studies (for example, pig-to-baboon kidney transplant) because ‘such studies are subject to existing NHMRC guidelines, State and Territory legislation and, in relevant situations, oversight by the Office of the Gene Technology Regulator’ (Discussion Paper, page xx). RSPCA Australia described this as its fundamental concern:

The RSPCA believes that current controls do not give adequate consideration to the welfare of animals involved in xenotransplantation studies, nor do they do justice to the seriousness of the ethical questions this research raises. RSPCA Australia believes that any guidelines developed for clinical studies should also apply to preclinical studies to help address this problem.

RSPCA Australia (Submission X050)

The XWP agrees that the lack of ethical consideration of animal-to-animal transplantation research was a shortcoming of the Discussion Paper and has formed a subcommittee to consider this issue more fully (see paragraph 1.18. Section 5 of this Response Paper presents the findings and recommendations of the subcommittee.)
The need for public debate

4.78 The submissions indicated wide agreement about the need for informed public debate as a basis for deciding the future of animal-to-human transplantation research. As indicated in Section 6.2 of the Discussion Paper, risk communication should not be seen as public education that occurs only after a decision has been made, but as an integral part of the decision process. However, the submissions indicated that there are concerns about the quality, accessibility, substance and amount of information available to facilitate this debate. The Consumers’ Health Forum advocated greater access to information for consumers:

It is likely in many cases that both the potential benefits and the hazards [of xenotransplantation] will be unclear [to the wider community]. Consumers are therefore seeking greater access to both the knowledge and basis upon which approval of xenotransplantation decisions might be made. Experience suggests that it can be difficult to reconcile the highly complex and evolving scientific knowledge required to properly assess safety issues, with the range of other considerations likely to be important for consumers. Consumers’ Health Forum (Submission X086)

4.79 Other respondents also called for further public debate:

… Given the potential major implications for the health of our community in the future if an infection did jump across species, then I think it is essential that this fundamental debate occurs first. An informed decision needs to be made by the general community, before processes are put into place that will allow this research to occur in people. A/Professor Peter Collignon (X063)

Because the risk is societal and not merely individual, the decision whether to undertake the procedure involves more than ensuring the ability of the surgeon and the transplant team, the capacity of the institution, and the willingness of the patient. Where the risks are collective, the public must not only be educated about the risk but must also be involved in decision-making. The first level of decision-making must therefore occur at the level of social policy. Dr Anthony Raizis (Submission X034)

… government-level approval of xenotransplantation procedures may be seen as an implicit form of social acceptance that the potential risks of xenotransplantation are outweighed by its potential benefits. For this reason, public input into the decision as to whether or not a country will proceed with xenotransplantation studies is of the utmost importance. International Xenotransplantation Association (Submission X077)

4.80 NSW Health suggested the need for further mechanisms to engage the general public in education and debate about the complex and important issues surrounding animal-to-human transplantation, because society at large is being put at potential risk:

… thus there is an obligation to ensure that the community understands the technology, the ethical considerations and the risks. Society must then be afforded the ability to participate in the debate and be able to have input into the decisions about, for example, the level of the risk, if any, it would be willing to accept. NSW Health (Submission X090)

4.81 Some respondents had attended one of the public meetings and wrote about the difficulties of debating such complex issues at such a meeting:
Based on the questions and comments I heard, I make the point that it is extremely difficult in one short meeting for people without a substantial education in modern biology to make an informed opinion in complex scientific issues such as these. There could be a case for a ‘citizens’ forum’. I recognise that the documents supplied were an attempt to meet this problem. Similar comments might apply also to the ethical issues raised. *Emeritus Professor David Allbrook (Submission X039)*

### 4.82 Other respondents saw the perceived inadequacy of public information and debate to date as a reason not to proceed with research into animal-to-human transplantation. Ratifiers for Democracy contended that, at this stage, neither the public nor its elected representatives know enough about animal-to-human transplantation for the recommenders to say it passes any ethical criteria, and that there has not been sufficient discussion about it in the media (Submission X040).

### 4.83 The general perception was that the level of public debate was not sufficient to allow an informed public decision to either pursue or reject animal-to-human transplantation. To address this issue, the XWP and NHMRC have decided to continue the public consultation in three ways:

- careful consideration of the submissions received after release of the Draft Guidelines and Discussion Paper in June 2002, and preparation of this Response Paper, which will be released for further public comment;
- preparation of a short, plain English guide to xenotransplantation (*Animal-to-Human Transplantation: A Guide for the Community*) to help members of the general public to understand the complex issues relating to the development of animal medical therapies based on living animal transplantation products; and
- further public meetings or forums to debate the issues raised in the Response Paper.

### Conclusion

#### 4.84 Throughout the development of the Discussion Paper and this Response Paper, the XWP has focused on two issues:

- Is animal-to-human transplantation ethical? That is, should medical therapies based on live animal products be considered at all?
- How should xenotransplantation research be conducted? That is, if we agree that it is acceptable to develop therapies based on live animal products, how should the research associated with its development be conducted?

#### 4.85 The first question has been answered in terms of secular and religious arguments about the value and dignity of humans and animals. The conclusion reached by the XWP is that, overall, society favours the use of animals for the needs of humanity. This conclusion does not mean to convey any disrespect to those that hold an opposing view; it is merely a reflection of the prevailing view, which has been substantiated by moral arguments from many different cultural perspectives.

#### 4.86 However, the views of people who disagree with the use of animals in medical research and, particularly, to provide parts of use by humans, should be seriously considered in the development of any research program. Measures should be taken to minimise animal welfare concerns.

#### 4.87 Even though the prevailing view of society is that it is acceptable to use animals for the needs of humanity, the public acceptability of animal transplants per se is not well known.
Many people who have commented negatively so far may have been thinking predominantly of organ transplants, which inevitably carry some disconcerting images to those thinking about this issue for the first time. To date, no responses have been received from potential transplant recipients or consumer groups; the XWP would welcome comments from these groups. The XWP would also welcome public comments on the acceptability of cellular or external transplants, as opposed to organ transplants (which are unlikely to become a medical reality for many years).

4.88 If animal-to-human transplantation is an acceptable medical therapy, the next question relates to how research to develop animal transplant therapies should be conducted. This research necessarily includes both animal-to-animal and animal-to-human transplantation research. The XWP has identified a number of basic principles that such research needs to meet (see paragraph 4.67). These principles provide the framework upon which guidelines for the ethical conduct of research can be based.

4.89 In response to the submissions received, the XWP agrees that more prominence needs to be given to animal welfare both in animal-to-animal studies and in animal-to-human transplantation trials. The procedures under investigation need to be weighed against other alternative therapies and the likelihood that the research will yield useful human therapies needs to be constantly assessed. That is, animal experiments should only be carried out to support significant, promising lines of investigation where there are no alternative therapies available that do not require the use of animals.

4.90 To provide a stronger emphasis on animal welfare in both animal-to-animal and animal-to-human transplantation research, and for overall simplicity, the principles outlined in paragraph 4.67 can be re-expressed as:

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

4.91 When applied to health care, the common good refers to a delivery system that promotes the health and wellbeing of all members of a community. Hence, the assessment of animal-to-human transplantation research proposals should consider the effects of the research on society as a whole, including those who oppose the use of animals in this way, and take account of social and ecological considerations as well as the needs of the research participants and the researchers.

4.92 This assessment would therefore need to include careful consideration of alternative therapies that may be available to treat the same disease or condition but without the public health risks associated with animal therapies.

4.93 The other principles shown in paragraph 4.89 are discussed in other sections of this Response Paper and reflected in the revised draft guidelines included at the end of Section 12.
5 Animal welfare

Overview of issues raised in Discussion Paper and Draft Guidelines

Chapter 3 of the Discussion Paper explored the overarching question of whether it is wrong to use animal parts to treat humans. That ethical issue is discussed further in Section 4 of this Response Paper. Chapter 8 of the Discussion Paper focused on animal-to-human transplantation trial protocols with respect to the protection of animal welfare. It briefly described the role of animal ethics committees, animal husbandry, genetic modification of animals, personnel involved in research, production and control of animal products, import/export of animals and the assessment of animal welfare issues. Chapter 9 briefly described the way in which animal research is currently regulated in Australia.

The focus of these discussions was on the animals that would be used in animal-to-human transplantation trials rather than on those used in animal-to-animal preclinical studies. This was because the terms of reference of the Xenotransplantation Working Party (XWP) were to review xenotransplantation research involving humans (see Discussion Paper Section 1.3.1). The Draft Guidelines did not include a guideline directly relating to animal welfare but Draft Guideline 1 (efficacy) stressed that preclinical (animal-to-animal) studies must be:

... conducted in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes

The XWP posed the following question:

Does this discussion adequately cover the key issues for animal welfare in xenotransplantation research?

Many respondents did not believe that the Discussion Paper adequately covered the key issues. Perceived omissions included:

- explicit detail about the experience of animals involved;
- information on the national management of animal-to-animal transplantation research and the role of institutional animal ethics committees;
- the welfare of both source and recipient animals (particularly nonhuman primates) in animal-to-animal studies, animal housing and transport arrangements; and
- specific guidelines on animal ethics and animal welfare issues.

Many animal welfare groups felt that, in order to ensure that animal-to-animal studies are justified, an across-institution overview is necessary, but this is not possible under current arrangements.

In response to these concerns, the XWP recommended to the NHMRC that a subcommittee should be formed, including representatives of animal welfare organisations, to consider issues relating to the use of animals in xenotransplantation research in greater detail. The NHMRC subsequently set up the Animal Issues Subcommittee to report to the XWP on these issues (see paragraph 1.18 and Appendix A).

Finally, Section 8.6 of the Discussion Paper considered the expertise that would be required to assess animal welfare issues relating to research protocols and stated that the relevant regulatory authority would need to include members with expertise in ethical, regulatory and legal issues, veterinary medicine, animal husbandry, and animal welfare concerns. The XWP posed the question:

Are there any other areas of expertise that may be needed by the regulatory authority responsible for xenotransplantation in order to address the issues addressed in this chapter [on animal welfare]?

Several respondents nominated additional areas of expertise that would be required to adequately consider animal welfare issues. This issue is discussed in paragraphs 5.117–5.121.
General considerations on the use of animals for medical purposes

5.1 Xenotransplantation research involves the use of animals to provide transplant material for animal-to-human trials and also to act as both source animals and experimental recipients in animal-to-animal studies.

5.2 Section 4 of this Response Paper discusses the principles of using animals, including nonhuman primates, in the context of the question: Is xenotransplantation ethically and socially acceptable? The conclusion reached by the Xenotransplantation Working Party (XWP) is that, although there are diverse views within the community that are difficult to resolve on an individual level, the majority view is that some use of animals in biomedical research is justified to safeguard and improve health, and to alleviate suffering of human beings and other animals.

5.3 However, because the use of animals in biomedical research will often compromise their welfare, decisions over whether to use animals must be fully considered. This is done by weighing up the potential benefits of a research project, and the likelihood of the research achieving those benefits, against the likely adverse effects to the animals.

5.4 It is generally considered that all vertebrate animals, as well as (to date) a number of invertebrate species, are capable of experiencing pain. It is also recognised that many such species — most notably the higher primates but to some extent other intelligent and sociable animals such as pigs — have highly developed mental processes and form complex social relationships. Animals that exhibit these characteristics can be expected to have an increased capacity to experience stress and suffering as a result of confinement, denial of normal social relationships and the imposition of invasive medical procedures.

5.5 When judging the acceptability of procedures involving animals in biomedical research, an ethical decision must be made about whether any pain and suffering caused to the animals can be justified by the potential benefit of the research involved to humans or other animals. If the use of animals is considered to be justified, then every effort must be made to minimise the overall pain and suffering involved, and to maximise the potential benefit of the research. This should be reflected in experimental design to ensure that the animals are cared for in a way that provides for their social and environmental needs and minimises pain and suffering.

5.6 These issues are reflected in the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC 1997a). This code, its supplementary policies, and their implementation by institutional animal ethics committees is discussed in paragraphs 5.8–5.28.

5.7 The remainder of this section provides a description of the procedures that animals undergo for xenotransplantation research, the animal welfare concerns raised by these procedures and the approaches that could be used to protect the animals, and a proposed framework for national oversight of the use of animals in xenotransplantation research.
Regulation of animal research

Australian Code of Practice for the Care and Use of Animals for Scientific Purposes
(Code of Practice)

5.8 Research involving animals in Australia must comply with the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (NHMRC 1997a; referred to here as the Code of Practice), and its supplementary policies. Legislative administration of the code is a State/Territory responsibility under individual State/Territory legislation.

5.9 The Code of Practice is currently being revised by the NHMRC Animal Welfare Committee which appointed a Code Liaison Group comprising members from the NHMRC, CSIRO, Australian Research Council, Australian Vice-Chancellors’ Committee, representatives of State and Territory governments and animal welfare organisations. The group has also considered submissions from the public in the review process and the first draft of the revised code was released for public consultation in March 2003. Submissions were considered and a revised draft was released for further comment in August 2003 (NHMRC 2003a).

5.10 Under the Code of Practice, all proposals involving the use of animals for scientific purposes must be approved and monitored by an institutional animal ethics committee (AEC). However, there is no provision for national oversight of animal research. The limitations of these arrangements were highlighted by several respondents. For example:

… there is insufficient detail provided to assist AECs, but more importantly, there is a mistaken impression that the NH&MRC AWC can monitor the animal-to-animal transplant work across Australia. A new system with legal power and adequate resources will be required while this type of research continues, and for the welfare of source animals if indeed animal-to-human transplants occur.

*Animals Australia (Submission X079)*

5.11 Several respondents claimed that the primary purpose of the Code of Practice and its relationship to the role of AECs had been misrepresented in the Discussion Paper:

… despite the frequent mention of the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes*, the purpose and principles included in this Code are not reflected in [the Discussion Paper]. For example, the frequent use of the phrase ‘respect animal welfare’ does not adequately encompass the responsibilities of those who are involved in the use of animals for scientific purposes as described in the Code. *Bureau of Animal Welfare, Department of Natural Resources and Environment, Victoria (Submission X073)*

5.12 The central goals of the Code of Practice are described in the introduction to the revised draft code, as shown in the box below.
Purpose of the Code

The purpose of the code is to ensure the ethical and humane use and care of animals for scientific purposes, as defined in this Code.

The Code emphasises the responsibilities of investigators, teachers and institutions using animals to:

- ensure that the use of animals is justified, taking into consideration the scientific or educational benefits and the potential effects on the welfare of the animals;
- ensure that the welfare of animals is always considered;
- promote the development and use of techniques which replace animal use in scientific and teaching activities;
- minimise the number of animals used in projects; and
- avoid pain or distress of each animal used in scientific and teaching activities.

The Code establishes Animal Ethics Committees (AECs) to determine whether the case for animal use is justified and to ensure adherence to the principles of Replacement, Reduction and Refinement (the 3Rs). AECs apply a set of principles, outlined in this Code, governing the ethical conduct of people whose work involves the use of animals for scientific purposes.

Source: NHMRC 2003a

5.13 The principles of ‘replacement, reduction and refinement’ are further defined as:

- the replacement of animals with other methods;
- the reduction in the number of animals used; and
- the refinement of techniques used to reduce the impact on animals.

5.14 Regulatory arrangements for the oversight of animal xenotransplantation research must therefore take account of these principles. A new paragraph relating to xenotransplantation has also been added to the latest draft of the revised code as follows:

Skilled and specialised attention is required in the care of animals following organ or tissue transplantation. Animals must be assessed frequently for signs of pain, distress, infection and tissue rejection and treated immediately where signs occur. Special attention should be given to the management of immunosuppression. Where animals are allowed to recover from anaesthesia, the use of death as an end-point must be avoided. (NHMRC 2003a)

5.15 A new section on genetic modification of animals has also been included in the revised draft code, which states that all work involving genetic modification of animals must be conducted in accordance with the requirements of the Office of the Gene Technology Regulator and the relevant biosafety committee at the host institution (see paragraphs 11.22–11.23 and Table 11.1 of this Response Paper). Such studies must also be approved by an AEC and must comply with a number of other requirements to safeguard the welfare of the animals.

Supplementary policy documents

5.16 The Animal Welfare Committee has also recently prepared a supplementary policy document: Policy on the Care and Use of Nonhuman Primates for Scientific Purposes,
which was endorsed and released in June 2003 (referred to here as the NHP Policy; NHMRC 2003b).

5.17 A further policy document is also being prepared on the creation, breeding, care and use of genetically modified animals (referred to here as the GM Policy; NHMRC 2003c).

5.18 In addition, the Animal Welfare Committee has decided to develop a new policy document with specific guidance for the care and use of animals in xenotransplantation research. Drafting of this policy document is expected to begin in the near future.

5.19 Together, these three supplementary policy documents will provide comprehensive guidance for researchers using animals in xenotransplantation research.

**Animal ethics committees**

5.20 The primary responsibility of AECs is to ensure, on behalf of the institution, that all care and use of animals is conducted in compliance with the Code of Practice. Chapters 8 and 9 and Appendix 4 of the Discussion Paper described the role of AECs, decision making, membership and the importance of representation from animal welfare organisations in the system that approves research on animals.

5.21 Several respondents noted that the work of AECs is often hampered by isolation and confidentiality issues and that the committees are therefore not able to learn from previous experience or identify overall trends:

… AECs work in isolation from each other, and no central register of animal-to-animal xenotransplantation work is available under this system. AECs do not communicate with each other, nor are the nature of the proposals they see in the public domain. *Gene Technology Ethics Committee (X084)*

… strict confidentiality restrictions between committees means that no single AEC can know of similar work being done elsewhere, leading to duplication, the use of outdated techniques, and a likelihood of more animals being used than the absolute minimum. There is a desperate need for research of this kind to be examined by a well-resourced and sufficiently constituted national committee (in addition to the institutional arrangements). *Animals Australia (Submission X079)*

By assessing proposals on a case-by-case basis, the overview of general trends is lost and the overarching moral questions are obscured … *Bernice Bovenkerk (Submission X052)*

5.22 Other respondents stressed the need to assess the efficacy of animal-to-human transplantation procedures across both preclinical (animal-to-animal) and clinical (animal-to-human) studies:

Xenotransplantation research must pass through many developmental stages before reaching a proposal for clinical trials. These stages will involve many animals, may take place over a number of separate institutions and may be examined by a number of separate institutional Animal Ethics Committees (AECs). At present there is no means of monitoring the development of xenotransplantation through animal-to-animal studies, since there is no requirement for these studies to be reported outside the AEC. *RSPCA Australia (Submission X050)*
The draft guidelines and regulatory structure draw an artificial distinction between animal-to-animal studies and animal-to-human studies. The proposed regulatory system must be able to examine and discuss the full range of ethical and scientific issues arising from xenotransplantation research. Animal welfare concerns arise with both pre-clinical and clinical research, and these concerns are the same whether the source animal’s tissue is transplanted to a human or another animal. The regulatory authority will require information on animal-to-animal studies to inform its decisions on when it is appropriate to progress to clinical studies. The same researchers will be involved and there is likely to be considerable overlap between the two study types, especially since they will be using the same source animals. It is also likely that animal-to-animal studies will be carried out in parallel to animal-to-human transplants as the science progresses.

Gene Technology Ethics Committee (Submission X084)

5.23 It was clear from the above submissions that the current system of institutional AECs does not provide a mechanism for the national oversight of animal-based research. In response to this very important issue, several submissions advocated the establishment of a specialist body:

Adequate regulation requires the immediate establishment of a specialist body to gather information on current projects, and to monitor, oversee and direct further research in this area. There is a misplaced optimism here that the current system is adequate for current animal-to-animal xenotransplant studies.

Animals Australia (Submission X079)

5.24 The issue of national oversight of animal research is discussed further in paragraphs 5.110–5.116.

Functioning of AECs

5.25 AECs must include at least four categories of membership as specified in the Code of Practice. The categories include: (A) a veterinarian; (B) a researcher; (C) an independent member with animal welfare experience; and (D) an independent lay member. Several submissions suggested that category C members are placed in a difficult position because many of them are opposed to the use of animals in research. These concerns may also apply to category D members:

… lay members of committees tend to be intimidated by a high level of technical talk. I have been a member of animal ethics committees and have experienced that it is very hard to insist that something is too morally objectionable to allow, because of the dynamics around the table. Bernice Bovenkerk (Submission X052)

5.26 A properly functioning AEC should work to ensure that all views are taken into account before reaching a decision through a process of consensus. However, the current review of the Code of Practice has recognised that further guidance is required in the code to emphasise these points. To address this, the draft revised code includes guidance on:

- declaration of conflict of interest;
- use of lay language; and
- clarification of the process of reaching a consensus.

5.27 In addition, the new draft of the Code of Practice contains a recommendation that institutions undertake an external triennial review to enable the institution to assess the functioning of the AEC and compliance with the code.
5.28 For xenotransplantation research, the oversight provided by a national committee and NHMRC guidelines for the care and use of animals in xenotransplantation research should also help to alleviate these problems.

Procedures that animals undergo for xenotransplantation research

5.29 Several respondents felt that to inform public debate about the use of animals in xenotransplantation research, more explicit details are needed about what such research actually involves for animals. For example:

It is absolutely essential that the potential harms to animals of xenotransplantation research and its consequences for the individual animals involved are described in detail so that people are fully aware of these when they are called upon to make decisions about whether xenotransplantation should go ahead.

RSPCA UK (Submission X091)

5.30 To address this issue, this section presents a brief factual summary of the procedures that animals undergo when they are used in xenotransplantation research, including a general description of the broad range of studies that involve animals, genetic modification of animals, removing organs and tissues for use as transplantation products, and raising animals that are free of specific infections. Some other areas of animal research that are related to, but not specific to, xenotransplantation studies, such as the effects of immunosuppressive drugs (eg susceptibility of animals to infection), are not described in detail here.

Use of animals in preclinical studies (animal-to-animal studies)

5.31 In the early stages of research to develop xenotransplantation therapies for the treatment of human diseases and conditions, studies are carried out on small animals (mice, rats, rabbits etc). These studies test theories and methods related to the technology being developed and the disease or condition to be treated. This may involve a range of procedures (hormone or drug treatments, surgery, injections and so on) similar to those carried out for the development of other medical technologies.

5.32 Later, as the underlying mechanisms are better understood, studies are designed to more closely replicate the proposed human therapy (ie transplant of an organ or cells between different species of animals, or extraction of animal cells or tissues for use in an external therapy). Initially, such studies involve various different species of animals, such as mice, rats, rabbits, dogs and pigs.

5.33 Finally, a stage is reached in the development of the technologies when it is considered necessary to test the procedures in animals that are as closely related to humans as possible; in other words, in nonhuman primates. This stage is needed in order to assess whether the procedure is likely to work in humans before an application for a clinical trial is made.

5.34 Further details of the types of studies that may be involved for each category of xenotransplantation procedure are given below. These types of studies are not unique to xenotransplantation research. The development of human organ transplantation in the 1960s and 1970s involved a similar range of animal studies as those described here for the development of animal organ transplantation. Current research on the use of human cells or tissues in human external therapies or human cell therapies also involves the same
range of animal studies as for animal external therapies (AETs) and animal cell therapies (ACTs). Such research is also likely to include studies in nonhuman primates in order to allow researchers to assess the potential efficacy of the procedures before progressing to human clinical trials.

**Animal external therapies**

5.35 AETs cover a large range of procedures where cells, tissue or fluids from one animal are removed and interacted with cells or tissue from another animal. The two procedures that have attracted most attention are external liver perfusion and skin grafts (see paragraph 3.14).

5.36 Liver perfusion involves anaesthetising the source animal (see paragraph 5.59), removing the liver and disaggregating the cells for use in the liver perfusion device. After this procedure, the source animal is humanely killed. The recipient animal may be given surgical or drug treatment to induce liver failure. Blood from the recipient animal is circulated through tubes to the liver perfusion device and back to the animal. Blood tests are then carried out on the recipient animal to assess liver function (ie to see if the external device is compensating for the recipient animal’s own liver). After the study is complete, the recipient animal would be humanely killed.

5.37 Studies of skin grafting involve the use of cultured animal cell lines as feeder layers. These cell lines are grown continuously in the laboratory and therefore whole animals are not used in these studies.

**Animal cell therapies**

5.38 In ACTs, various procedures may be involved in the extraction of cells from a source animal. For example, bone marrow can be extracted from an anaesthetised animal, or a tissue, such as pancreas or brain, may be removed surgically (see paragraph 5.56). In some cases, fetal or embryonic cells are required, which may involve killing a pregnant female animal and removing the fetuses or embryos for extraction of the cells required. Stem cells may also be obtained from embryos that have been produced by in vitro fertilisation of an oocyte (egg) by a sperm.

5.39 The recipient animal may have a disease or condition induced by the use of surgery or drugs (eg diabetes, Parkinson’s disease) before receiving the cellular transplant. The animal is then tested for improvement in the induced disease state or condition.

**Animal organ transplants**

5.40 The use of animals in organ transplant experiments (animal-to-animal) is the cause of most concern amongst animal welfare groups. The surgery involved is highly invasive and the transplanted organs are usually rejected very quickly, causing the animals to become extremely sick necessitating humane killing.

5.41 Two types of organ transplant experiments are carried out in animals. The first type is to test whether the transplanted organ will be rejected, rather than its ability to function normally. This involves transplanting the organ (eg heart or kidney) at a different site to that of the recipient animal’s own organ, which remains functioning as usual. As the transplanted organ is not performing its normal function, its rejection is tolerated by the animal. Careful monitoring is necessary to reduce the suffering and distress of the animal.
5.42 The other type of experiment involves removing the recipient animal’s own organ and replacing it with the transplanted organ. This tests the ability of the transplanted organ to function in the recipient animal, as well as whether it is rejected. In this case, rejection of the transplanted organ is not tolerated by the animal and, once again, careful monitoring is required to ensure that the animal is humanely killed with a minimum of pain and distress.

Genetic modification of animals

5.43 Genetic modification of animals is not a new technique. Thousands of different genetic modifications have been made to mice and other animals to test how genes function, develop new medical therapies and acquire new knowledge about biological issues. More recently, genetically modified farm animals have also been produced with a variety of introduced human and other animal genes to allow the production of therapeutic products or for improved food production.

5.44 In the case of the modification of animals for use in animal-to-human transplantation therapies, human genes are either inserted so that the animal tissues are more compatible with human tissues and are less likely to be rejected, or the animal’s genes are inactivated (‘knocked out’) to reduce the potential for immune rejection of the animal tissues by humans.

Gene insertions

5.45 Insertion of human genes into pigs can be achieved by a number of different methods. One method involves insertion of the required gene into a fertilised egg. This involves treating mature female pigs with hormones that induce the production of many eggs (similar to fertility treatment in women). The sows are then mated and the fertilised eggs are removed. Alternatively, eggs may be obtained from the ovaries of sows killed at an abattoir (ie no hormonal treatment of live sows to allow retrieval of eggs is required in this case).

5.46 The eggs are maintained in a nutrient solution in the laboratory and a human gene is introduced into each egg using a fine glass needle guided by a microscope, an electric current, or a nonpathogenic virus to transmit the gene into the cell. The transferred gene is called a transgene. The treated fertilised eggs are implanted into a surrogate mother (which may need to be treated with hormones to accept the implant).

5.47 When the offspring are born, they are tested to find out which ones carry the transgene. Many offspring have to be tested in this way, because the transgene only incorporates fully into a small proportion of the eggs treated. At this stage, the modified offspring (which are called ‘founders’) only have one copy of the transgene. That is, it is only incorporated into one chromosome of the pair of chromosomes that carry the gene site (heterozygous). This means that the required characteristic may be dormant and would be quickly lost if the animals were bred with unmodified animals.

5.48 By selective breeding of pigs that carry one copy of the gene, however, animals can be produced that carry the gene on each copy of the chromosome pair involved (homozygous) and therefore display the required characteristic. Continued interbreeding maintains a pure breeding line of the genetically modified animals.
5.49 Because the transgene does not always incorporate, the process of transgene insertion, selection of heterozygous offspring and interbreeding involves the use of many animals to produce one genetically modified breeding line.

5.50 Apart from the procedures involved in the genetic modification process, the insertion of a transgene may affect the animals in a number of ways. Humane Charities Australia and Animals Australia both identified behavioural and other problems in genetically modified animals:

The presence of a transgene may also affect the animal’s ability to perform normal behaviour. Beltsville pigs for example (genetically modified to express additional growth hormones), experienced such extreme welfare problems that normal behaviour was impossible for them. They suffered from lethargy, lameness, lack of coordination, thickened skin, gastric ulcers, severe synovitis, degenerative joint disease, pericarditis and endocarditis, cardiomegaly, paraketosis, nephritis and pneumonia. Humane Charities Australia (Submission X033)

5.51 However, the XWP noted that, in the case of the Beltsville pigs, the most likely cause of the problem was the additional growth hormone, rather than the genetic modification per se. Nevertheless, the XWP recognised that adverse effects may occur, for example, because the transgene damages the genetic material of the host egg when it is inserted (see paragraph 5.46). Such an adverse effect may show up immediately at birth or at any stage in the lifespan of the animal or its offspring. The welfare and genetic stability of genetically modified animals and their offspring therefore needs to be carefully monitored across a number of generations, at least until detailed information regarding the phenotype (physical attributes) of the animals and any adverse side effects of the genetic manipulation have been documented. Such monitoring is therefore a requirement of the Code of Practice and GM Policy.

5.52 Another method that is used to produce animals with an additional gene is cloning. For pigs, this may involve obtaining eggs from pigs killed at an abattoir (i.e. no hormonal treatment of live sows and subsequent retrieval of eggs is required in this case) or hormonal treatment of sows to induce multiple ovulations and subsequent collection of eggs as described in paragraph 5.45. In the laboratory, the nuclei are removed from the eggs and replaced with nuclei from cultured pig cells that already have the required genetic modification. Once the eggs with implanted nuclei start to develop as embryos, they are implanted into sows for gestation.

5.53 In this case, because the transgene is initially inserted into cells that are growing in the laboratory, in some cases these cells can be tested and only nuclei from those that are known to have incorporated the transgene used to produce cloned embryos. This reduces the number of animals required and may also reduce the potential for long-term side effects due to random incorporation of the transgene. Also, because the laboratory-grown cells are permanently growing cell cultures, this method further reduces the use of live animals. Cell cultures are maintained by placing some of the cells in culture dishes with a special growth-promoting solution that allows the cells to divide. When the dish is full of cells, they are washed off and split between several new dishes with fresh solution, and so on indefinitely. Cell culture has been promoted by animal welfare groups as a better alternative to using whole live animals for medical research.

5.54 When the cloned offspring are born they are tested and further cross-bred, as described in paragraphs 5.47–5.48.
Gene silencing

5.55 Turning off genes (silencing or ‘knocking out’ specific genes) is usually achieved using cloning, with a similar approach to that described for adding genes (paragraph 5.52). In this case the required gene is first turned off in the cultured cells using targeted biotechnology methods and the nuclei from these cells are inserted into eggs obtained from the oварies of female pigs killed at abattoirs or laboratories, as described in paragraphs 5.52–5.54.

Removal of organs and tissues

5.56 Two approaches can be used for the removal of organs and tissues from an adult source animal; each has different animal welfare implications:

- killing the animal and removal of one or a number of organs and tissues after death; and
- removing the required organ or tissue while the animal is alive under a range of anaesthetic procedures (and possible recovery of the animal).

5.57 In addition, some of the cellular therapies (ACTs) being developed involve the use of fetal cells. This involves removing fetuses from pregnant animals either by killing the animals or by caesarean section.

5.58 When animals are killed without anaesthesia, requirements for humane killing set out in the Code of Practice must be followed. The code also states that, where practical, tissues from animals being used should be shared among investigators so as to maximise use of the animal. In the case of slaughter of agricultural animals, organs may be byproducts that can be retrieved for use in animal-to-animal studies, thus avoiding the slaughter of additional animals specifically for research.

5.59 To maintain optimum function, for some studies, organs and tissues may need to be removed from live animals under anaesthetic. Because the removal of some organs and tissues would not necessarily cause the death of the animal, it would be possible to use the same source animal more than once.

5.60 However, the repeated use of the same animal under anaesthetic raises specific animal welfare issues. The Code of Practice states that animals may not be used in more than one study without the express approval of the AEC. The AEC must take account of the pain or distress and the long-term effects of the previous and proposed subsequent procedures, the total time involved and the need for full recovery by the animal between procedures.

Production of animals that are free from specific infectious organisms

5.61 Animals (usually pigs) raised to provide organs or tissues for animal-to-human transplantation will need to be bred in conditions that are, as far as possible, free from infectious organisms and in good health. However, specific procedures will limit their freedom and impose invasive interventions upon them.

5.62 Some procedures for breeding animals free from specific infectious organisms involve delivery by caesarean section, after which the animals are reared in incubators that isolate the animals and reduce the chance of infection. An alternative, and less severe, practice is
to rear the animals in small groups, using rigorous testing of a ‘sentinel’ animal as an indicator of the infectious status of the whole group. In either case, the environment needs to be kept relatively sterile and be easy to clean because of the susceptibility of animals to infection. Human contact also needs to be minimised.

5.63 Monitoring of animals raised to be free of specific infection involves regular blood tests and tissue biopsy, which, in turn, require restraint (physical or drug induced), regular transfer to operating areas, anaesthesia etc.

Animal welfare consequences of xenotransplantation research

5.64 The Discussion Paper referred to animal welfare issues in the context of the Code of Practice. However, respondents were concerned that it did not address specific issues relating to the use and welfare of animals for xenotransplantation research. For example:

Many of these techniques [involved in the breeding and rearing of source animals] will have significant adverse effects on the welfare of the animals involved and should not be glossed over in a few sentences. Details of each of these techniques and their welfare consequences should be provided. A statement should be added on the need to ensure that any adverse effects arising from the production of qualified-pathogen-free animals are minimised. RSPCA Australia (Submission X050)

5.65 Some respondents commented that, although the Discussion Paper deferred to the Code of Practice for the standards to be followed for research involving animals, the code itself does not provide specific instructions on what constitutes a high standard of welfare. For example:

The report also mentions ‘highest standards of welfare’ with respect to animals, but does not define what these are. It refers to the NHMRC Code of Practice yet this contains no explicit instructions even for the minimum requirements to provide for the animals’ basic needs. RSPCA UK (Submission X091)

5.66 Many of the animal welfare issues raised are not specific to xenotransplantation research (eg pen sizes, raising of pathogen-free animals, use of surgical and drug treatments and so on) and are not discussed further here. These issues are considered and dealt with by AECs on a case-by-case basis as part of the proposal assessment process. The Code of Practice is not prescriptive in terms of setting specific housing and husbandry standards; however, the ways in which animals are housed, cared for, and used in scientific procedures are all integral to the assessment of a proposal by the AEC.

5.67 It is clear from the descriptions in paragraphs 5.29–5.63 that some issues require careful consideration and regulation to avoid unnecessary suffering by the animals. The main issues for consideration are:

- use of nonhuman primates;
- production of pigs; and
- genetic modification of animals.

5.68 These issues are discussed in further detail in paragraph 5.69–5.109.
Use of nonhuman primates

5.69 The overall ethical concerns regarding the use of nonhuman primates in animal-to-animal studies are addressed in Section 4 of this Response Paper.

5.70 Paragraphs 5.29–5.68 describe the procedures involved for animals that are used in animal-to-human transplantation studies. These uses raise the following animal welfare issues for the use of nonhuman primates:

- numbers bred and used;
- capture from wild and importation/transport;
- housing, confinement and husbandry; and
- impact of procedures on primates (including monitoring of studies and defining endpoints).

5.71 Each of these issues is discussed below, followed by the overall response of the XWP.

Numbers of nonhuman primates bred and used

5.72 There are no legal restrictions on the use of nonhuman primates for scientific purposes in Australia. As with any animal use, researchers are required to justify their choice of species, and AECs will only approve the use of nonhuman primates where no other species is considered appropriate. Laboratory primate breeding is under NHMRC supervision and further detailed guidelines for the use of primates are provided by the NHP Policy (NHMRC 2003b).

5.73 Baboons are currently considered to be the most appropriate nonhuman primate species for use in whole organ animal-to-animal xenotransplantation studies. The Discussion Paper indicated that the number of baboons currently available in Australia may not be adequate for the volume of proposed animal-to-animal research and that an expanded breeding program has been put in place. This raised concerns amongst respondents that a large number of baboons would be used for this research, possibly without due attention paid to the need for such studies or to the welfare of the animals.

5.74 Some respondents argued that nonhuman primate studies should not be permitted in Australia at the present time, citing lack of scientific justification and the suffering endured by animals, particularly higher primates, involved in xenotransplantation research:

…it is disheartening that the NHMRC calls for more gruesome pig-to-primate experiments to be conducted in Australia. Hundreds of these experiments have already been conducted around the world with dubious outcomes. Researchers admit that nonhuman primates are poor models for humans, and that pig-to-primate experiments yield limited, if any, useful information that is relevant to the safety or efficacy of xenotransplantation in humans. Numerous factors involved include: complex species differences between nonhuman primates and human beings, the invasive nature of the experimental protocols themselves which impair the collection of meaningful data, and the fact that these studies cannot assess risk. As such, pig-to-primate experiments should not be conducted in Australia, contracted out by the government, or condoned by the NHMRC.

Campaign for Responsible Transplantation (Submission X067)
Importation

5.75 The Discussion Paper implied that, because of the small supply of baboons available for preclinical studies in Australia and their long gestation period (and hence slow production through the breeding program), some animals might need to be imported. Several respondents were concerned about the welfare issues involved in transportation:

… During long distance air travel many animals have suffered and died from heat, cold, hunger, thirst and the stress of being confined in small crates … Removal of offspring can cause distress to both parent and offspring as well as the rest of the colony due to their advanced social structure. Young primates form a close bond with their mothers and would suffer from extreme deprivation if reared in isolation.

Humane Charities Australia (Submission X033)

The transport of any large animal places tremendous stress on that animal and this is particularly so for nonhuman primates, especially if it also involves disruption of their social groups. The use of primates in animal-to-animal studies should be limited to as few animals as possible and only those that have been captive-bred within Australia at an NHMRC-funded breeding and holding colony.

RSPCA Australia (Submission X050)

5.76 However, the NHP Policy only allows the importation of nonhuman primates under special circumstances. Permission must be sought from the Australian Quarantine and Inspection Service (AQIS) and Environment Australia, as well as approval from the relevant AEC. The NHMRC Animal Welfare Committee must also be notified of any intended importation. The NHP Policy does not allow importation of wild-caught nonhuman primates.

5.77 Arrangements for air travel must comply with the Live Animals Regulations of the International Air Transport Association (IATA 1999).

Housing, confinement and husbandry

5.78 Some respondents noted that the Discussion Paper lacked detail on how nonhuman primates (primarily baboons) would be cared for:

The section leaves many questions unanswered — no information is provided here on the specific requirements for housing and husbandry imposed by xenotransplantation studies (ie level of biocontainment and associated restrictions on enrichment, socialisation, rearing practices etc), or how many baboons it is anticipated will be required for these studies, or the age at which they are suitable for transplant work.

RSPCA Australia (Submission X050)

5.79 All research involving the use of nonhuman primates from NHMRC colonies is covered by the NHP Policy. It is up to individual AECs to approve the specific standards of housing and care at individual institutions. In the case of the supply of baboons from the NHMRC colony, approval is required from both the institutional AEC where the work is to be carried out and from the AEC of the colony itself, before a study can commence. Although it is difficult to predict the numbers of animals that will be required in the future, current breeding programs are generally regarded as sufficient to supply demand in the present research environment.

Impact of procedures

5.80 The impact that procedures involved in xenotransplantation research would have on primates was also the cause of considerable concern for several respondents:
Page 59 of the discussion paper suggests that baboons are ‘very difficult to work with and usually require an anaesthetic for even simple examinations or blood sampling’. This reaction indicates that the procedures are stressful and traumatic to the animals. They would also suffer the consequences of being dosed with immunosuppressive drugs leaving them vulnerable to infection, or suffer the slower build up of rejection of the transplant organ over days or weeks. *Animals Australia (Submission X079)*

The animal welfare aspect of this issue is also of grave concern. How many animals will be sacrificed and experimented upon before they ‘get it right’? What physical and psychological suffering will these animals endure? How will their welfare be monitored and policed? *(Respondent details confidential)*

5.81 RSPCA UK stressed the importance of communication and collaboration issues in reducing unnecessary animal suffering. Some respondents also referred specifically to the problems that can arise when primates have received additional organ transplants at other body sites (see paragraphs 5.41–5.42):

In xenotransplantation pre-clinical research, nonhuman primates, such as baboons and cynomolgus monkeys, have had organs from pigs and other primates grafted into their necks and stomachs. None have survived longer than days or weeks; many have died from infections and/or poisoning from the toxicity of immunosuppressive drugs. CRT believes that such suffering is unjustifiable and should not be condoned by the NHMRC. *Campaign for Responsible Transplantation (Submission X067)*

5.82 In this regard, several submissions referred to xenotransplantation research on primates carried out in the United Kingdom on behalf of a biotechnology company. The research involved the transplantation of pig hearts, kidneys, pancreatic islets and/or bone into baboons or cynomolgus macaques. All the research was licensed by the Home Office under the United Kingdom *Animals (Scientific Procedures) Act 1986*. RSPCA UK investigated the research after complaints were received and prepared a report, which sets out their concerns in detail. In summary, the report raised important issues about the regulation of animal studies in terms of:

- how the predicted harms and benefits of a study should be assessed;
- the need for clear experimental end-points, monitoring of animals and measures to reduce suffering;
- the animal husbandry training requirements for staff; and
- the need for both an ongoing and retrospective review of such studies, with clear roles and relationships between the various regulatory bodies and an established system of reporting.

5.83 According to RSPCA Australia, the United Kingdom report:

… raises a number of issues regarding the use of nonhuman primates that are very relevant to the Australian situation. It provides an insight into some of the problems that could well occur in Australia in the absence of adequate controls over this research. *RSPCA Australia (X050)*
XWP response (use of nonhuman primates)

5.84 The XWP considers that to develop animal transplantation therapies, some studies will be required using nonhuman primates as the transplant recipients. This is because, although these species are not a perfect model for animal-to-human transplantation, such studies give the best indication of the predicted efficacy of a proposed procedure in humans. Therefore, without evidence of efficacy obtained from nonhuman primate studies, it would not be ethical to proceed to animal-to-human transplantation trials.

5.85 However, the XWP also agrees that the use of nonhuman primates in xenotransplantation research raises significant animal welfare considerations. After consideration of these issues, the committee concluded that, although the Code of Practice and NHP Policy provide the overall framework within which such studies should be allowed in Australia, more specific guidelines are required to guide the use of animals in xenotransplantation research.

5.86 To address this issue, the Animal Welfare Committee has decided to develop a new supplementary policy for the use of animals in xenotransplantation research (see paragraph 5.18). This new policy will provide specific guidance for the use of nonhuman primates in animal-to-animal studies.

5.87 As the result of a recommendation from its Animal Issues Subcommittee, the XWP also proposes that there should be some national oversight of animal-to-animal xenotransplantation research (see paragraph 5.110–5.116).

Use of pigs as source animals

5.88 As indicated in the Discussion Paper, researchers currently believe that pigs would be the most common source animals for animal-to-human transplantation therapies. Many respondents criticised Section 8.4.2 of the Discussion Paper on the care of pigs for not providing enough detail on the welfare issues arising from the use of pigs as source animals. For example, RSPCA Australia stated:

Procedures causing harm to the source animals and breeding stock include: egg removal and replacement in pregnant sows, hysterectomy and hysterotomy (which means that the piglets never have contact with their mother and may also include killing the sow), early weaning/separation of piglets from sow, repeated blood and tissue sampling, sequential use of tissue from individual animals and restrictions on the behavioural and physiological needs of pigs due to level of biocontainment (including lack of environmental enrichment and appropriate socialisation). Many of these techniques will have significant adverse effects on the welfare of the animals involved and should not be glossed over in a few sentences. Details of each of these techniques and their welfare consequences should be provided.

*RSPCA Australia (Submission X050)*

5.89 The procedures used to raise pigs as source animals are described in paragraph 5.61–5.63. The welfare issues raised by these procedures are:

- impact of procedures (surgical/pharmaceutical/reproductive interventions);
- housing and husbandry (specific requirements for freedom from pathogens etc); and
- behavioural/ethological issues across the lifespan (eg mother–offspring bond, socialisation in groups).
Impact of procedures

5.90 The impact of procedures for pigs is not specifically different from impacts on other animals (pain, stress etc) and is therefore covered by the provisions of the Code of Practice (see paragraphs 5.8–5.19).

5.91 The impact of genetic modification procedures raises animal welfare issues. These are covered in detail in paragraph 5.99–5.109.

5.92 As for all animal research, the number of pigs used in xenotransplantation research must be justified and the minimum number used to achieve scientifically valid results. This principle applies for all transplantation research studies using pigs as source animals, whether animal-to-animal or animal-to-human. The Code of Practice also encourages the sharing of tissues and organs amongst researchers when an animal is killed, to ensure that additional animals are not killed unnecessarily.

Housing and husbandry

5.93 Housing and husbandry requirements for pigs to be used as source animals for xenotransplantation research were also a cause for concern among respondents:

Special husbandry and housing conditions required for transgenic source animals is a major welfare concern. Adherence to strict levels of hygiene and disease control will reduce access to the outside environment and minimise human contact. Will the pathogen-free housing mean that pigs will not have access to nesting and rooting materials — important requirements for their environmental enrichment? Pigs will be born by caesarean section with their mothers being killed and the piglets will therefore never have the opportunity to suckle and bond with their parent.

Humane Charities Australia (Submission X033)

5.94 RSPCA Australia (Submission X050) indicated that a checklist along the lines of that proposed in the ‘Advice regarding application of the proposed guidelines’ section of the Discussion Paper (pages xxv–xxx) would be helpful and that consideration should also be given to developing guidelines on the housing and care of pigs intended for use as xenotransplant source animals similar to those already produced in the United Kingdom (UK Home Office, no date). Animals Australia made the following specific suggestion:

Detailed guidelines, similar to the NH&MRC guidelines relating to non-human primates, and including guidance on the usual techniques of genetic modification and bio-containment housing, will be necessary to assist AECs.

Animals Australia (Submission X079)

Behavioural/ethological issues

5.95 Submissions raised concerns over the behavioural restrictions imposed by the breeding and raising of pigs in biocontainment facilities. These concerns included: the separation of piglets from their mother at birth, or soon after birth, and consequent early weaning; restrictions on the provision of enrichment materials to allow pigs to express exploratory and foraging behaviours; lack of appropriate socialisation; and restriction of movement. RSPCA Australia suggested:

A statement should be added on the need to ensure that any adverse effects arising from the production of qualified-pathogen-free animals are minimised.

RSPCA Australia (Submission X050)
**XWP response (use of pigs)**

5.96 The XWP agrees that the use of pigs in xenotransplantation research raises significant animal welfare considerations, including a range of issues specifically related to the animals’ genetic modification and use as source animals for animal-to-human transplantation research. After consideration of these issues, the working party concluded that, although the revised Code of Practice (NHMRC 2003a) and the new NHMRC policy on the creation, breeding, care and use of genetically modified animals (NHMRC 2003c) provide an overall framework within which such studies should be allowed in Australia, more specific guidelines will be required to guide the use of animals in xenotransplantation.

5.97 The XWP has therefore proposed that the NHMRC develop a new supplementary policy for the use of animals in xenotransplantation research (see paragraph 5.18). This new policy will provide specific guidance for the use of pigs as source animals both in animal-to-animal studies and in animal-to-human trials.

5.98 The XWP has also proposed a new system for national oversight of animal-to-animal xenotransplantation research (see paragraphs 5.110–5.116). This will ensure that a register of animal studies is maintained and that animal-to-animal xenotransplantation studies are restricted to those that are scientifically justified and essential for the development of human therapy.

**Genetic modification of animals**

5.99 The procedures involved in the genetic modification of animals are described in paragraphs 5.43–5.55. Key issues for animal welfare are:

- the nature and extent of the genetic modification;
- the potential adverse effects of the genetic modification;
- the unpredictability of adverse effects associated with genetic modification; and
- wastage of animals.

5.100 Section 8.3 of the Discussion Paper stated that ‘the nature and extent of genetic modification will need to be assessed on a case-by-case basis to ensure that the animals retain the essential characteristics and dignity of their species’. Some respondents questioned the precise meaning of this statement. For example:

> … when does the Working Group consider the essence of an animal to be changed? When they look different? When they act different? When they are not able to reproduce naturally anymore? I think these questions need to be specified beforehand, so that each AEC does not have a different view.
>  
> Bernice Bovenkerk (Submission X052)

5.101 Whether the genetic modification has affected the essential characteristics and dignity of an animal is hard to determine, but will be assessed by individual AECs based on in-depth knowledge of the species. Monitoring of genetically modified animals will be required over many generations to ensure that adverse effects do not appear in subsequent generations (see paragraph 5.51).
**The potential adverse effects of genetic modification**

5.102 A number of respondents expressed concern about the distress caused to animals by genetic modification and cloning procedures:

> Animals also endure considerable manipulations and interventions during the surgical embryo retrieval and embryo transfer involved with genetic engineering technology … The significant manipulation of the animal’s ovulation and oestrus cycle can lead to over-stimulation of the ovaries causing painful ovarian cysts or enlarged ovaries. The exposure to additional hormones, collection of eggs and implantation of the fertilised eggs can also lead to considerable stress.

*Animals Australia (Submission X079)*

5.103 However, as noted in paragraphs 5.52 and 5.55, cloning methods are being used for genetic modification of pigs, using eggs obtained from sows killed at abattoirs and nuclei from permanent cell cultures grown in the laboratory. This reduces the need for any of the procedures described in paragraph 5.102.

**The unpredictability of outcomes**

5.104 Other respondents commented on ‘the assumption’ in the Discussion Paper that ‘the insertion of one or two human genes into a pig genome … is unlikely to alter the animal in a significant way’.

> The outcomes of the insertion of human genes into the pig genome are unpredictable, particularly given the lack of control over the insertion point of those genes. There is always the possibility that altering the pig genome will have a deleterious effect on the welfare of the animals involved and this should be acknowledged.

*Gene Technology Ethics Committee (Submission X084)*

> As the microinjection process is not always an efficacious one, genes can often fail to reach the correct cells within the embryo and this can cause painful abnormalities and death. *Animals Australia (Submission X079)*

5.105 Certainly, it has been reported in the literature that a significant number of animals born after genetic modification or cloning have genetic abnormalities:

> Data derived from Dolly the sheep and other cloned and transgenic animals have revealed that such animals often have weaker immune systems, and may be born with physical disabilities which cause them great pain. … Recently published studies in the *Journal of Cloning and Stem Cells*, cite a high mortality rate for cloned piglets at two American universities. *Campaign for Responsible Transplantation (Submission X067)*

5.106 An additional uncertainty that is created by genetic modification of pigs to make their tissues and organs more compatible with human transplant recipients is the possibility that pigs may become susceptible to human infections. This could have disastrous consequences for the Australian pig industry and for pigs in general.

**Wastage of animals**

5.107 A noted in paragraph 5.49, the gene modification, selection and breeding procedures involved in genetic modification of animals are difficult procedures with a high failure rate. A large number of animals are therefore required in order to develop a modified breed. However, the use of materials from abattoirs (such as eggs obtained from pig
ovaries) and cloning techniques involving cultured cells reduce the number of live animals used.

**XWP response (genetic modification of pigs)**

5.108 AECs should ensure that any proposed genetic modification is fully justified and that any welfare implications are taken into consideration.

5.109 Further detailed guidance on the creation, breeding, care and use of genetically modified animals is included in the draft GM Policy document (see paragraph 5.17).

**National oversight of animal use in xenotransplantation research**

5.110 The XWP has recommended that animal-to-human transplantation clinical trial proposals be assessed by a national committee based on the existing NHMRC Gene and Related Therapies Research Advisory Panel (GTRAP; see Section 11 of this Response Paper for a detailed explanation of this proposal).

5.111 However, as indicated in paragraph 5.21, the AEC system does not provide a mechanism for the national oversight of animal-based research. In relation to xenotransplantation research there is a particular need for national oversight of both animal-to-animal (preclinical) and animal-to-human (clinical) transplantation research to allow cross-communication between these two types of studies and ensure that NHMRC guidelines for xenotransplantation research can inform research at all levels.

5.112 The Animal Issues Subcommittee and the XWP considered this issue in detail. The XWP agreed that animal-to-animal studies need to be included in the national consideration of animal-to-human trials and in the formulation of guidelines for such research and that a central register of relevant animal studies should be maintained.

5.113 Such national oversight of animal-to-animal studies needs to take account of the following factors:

- only those animal-to-animal studies that are intended to further the use of animal-to-human studies (preclinical studies) should be required to be reported nationally;
- national oversight should focus on those studies that raise particular ethical questions, such as animal-to-nonhuman primate studies and studies involving the use of tissues or organs from animals bred as source animals for xenotransplantation into humans; and
- the final decision over the approval of any project involving the use of animals must remain in the hands of the relevant institutional AEC.

5.114 The XWP acknowledged that there may be confidentiality issues for the institutional ethics committees in making public the details of studies. Also, some privately funded units may not come within the NHMRC’s power to influence. However, the XWP recommends that the NHMRC consider these issues and introduce a general notification system for both private and publicly funded research.

5.115 This information should be forwarded to the national committee responsible for oversight of xenotransplantation research (ie the expanded GTRAP) and recorded in a central register. A mechanism to trigger notification of relevant animal-to-animal studies would also need to be established.
5.116 The notification of preclinical animal-to-animal studies to the national xenotransplantation committee would provide this committee with an oversight of developments leading to clinical studies in Australia. The committee could then use this information when making assessments of clinical guidelines or the approval of particular xenotransplantation therapies. Such a register would also provide an important central point of contact for researchers and AECs involved with assessment of animal-to-animal preclinical studies.

**Expertise required for national committee**

5.117 The Discussion Paper considered the expertise that would be required for the national assessment of animal-to-human transplantation trial proposals. It concluded that the relevant regulatory authority would need to include members with expertise in the following areas:

- ethical, regulatory and legal issues relating to the use of animals in research;
- veterinary considerations and animal husbandry; and
- animal welfare concerns.

5.118 The XWP also raised the question:

*Are there any other areas of expertise that may be needed by the regulatory authority responsible for xenotransplantation in order to address the issues addressed in this chapter [on animal welfare]?*

5.119 Submissions nominated several specialist members in addition to those flagged in the Discussion Paper, and included more details of the required expertise in veterinary science and animal husbandry:

I propose a contribution by an [animal] ethologist (on the national regulatory body). Bernice Bovenkerk (Submission X052)

An AWC member could not be expected to be truly independent … An independent committee requires a ‘devil’s advocate’: a representative of an animals rights group who will offer a different perspective. Heidi Nore (Submission X058)

The national committee … should include the following members … animal welfare science member with background in housing and husbandry issues; animal welfare proponent; veterinarian with laboratory animal expertise; and a veterinary pathologist to advise on the animal disease issues, particularly potential zoonoses and the phenotype of genetically modified animals. Bureau of Animal Welfare, Department of Natural Resources and Environment, Victoria (Submission X073)

Agree that committee should include additional members with animal welfare, veterinary and community expertise. Preterm Foundation (Submission X081)

5.120 RSPCA Australia and Animals Australia both considered that while the necessary areas of expertise were well covered by the inclusion of members as described in the Discussion Paper, it is important to ensure that these categories are clearly specified in the membership of the regulatory authority and that animal welfare is represented in its own right (see paragraphs 11.57–11.67):

5.121 The proposed membership of an expanded GTRAP, which would review animal-to-human transplantation trial proposals, is discussed in paragraph 11.66.
**Guideline on animal welfare**

5.122 The Draft Guidelines for xenotransplantation research released for public comment in 2002 did not include a specific guideline on animal welfare (although a requirement that preclinical animal-to-animal studies should be conducted in accordance with the Code of Practice was included in the guideline on efficacy).

5.123 Several respondents recommended that the guidelines should include a specific guideline on animal welfare. The XWP has therefore amended the Draft Guidelines to include a new guideline, as follows:

Guideline 1 (Animal welfare)

(a) All xenotransplantation studies involving animals (preclinical and clinical) must be conducted with due regard for high standards of animal welfare and in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and other associated policies.

(b) To assist national overview and decision making on animal-to-animal xenotransplantation research in accordance with the Code of Practice, researchers should submit information to a central register about all animal-to-animal studies that are directly related to the development of animal-to-human trials (eg pig-to-primate studies).

(A complete list of the revised draft guidelines is presented in Section 12 of this Response Paper.)

5.124 The information included in the Discussion Paper’s Table 8.1 (Information required for assessment of animal welfare issues) and reproduced in the ‘Advice regarding the application of the proposed guidelines’ section was regarded as helpful by some respondents but as inadequate by others. Animals Australia wrote:

In regard to the data required in the assessment questions, they are currently inadequate. First and foremost it is clear that the first question that needs to be asked relates not only to whether the use of an animal is justified in the current trial, but whether pursuing this line of research is acceptable and necessary. As mentioned above, whether xenotransplantation is ‘acceptable’ has yet to be debated and determined. Further, it can be seen from the national Code of Practice that further questions are required; in particular, relating to the justification of animal numbers, the effect of genetic modification (or other changes) to the animals (e.g. immune suppression of pigs), the effect of housing conditions on the animals, the effect of the interventions (breeding methods) etc. Animals Australia (Submission X079)

5.125 RSPCA Australia (Submission X050) also asked why nonhuman primates were listed as a possible source animal if the guidelines only cover clinical therapeutic trials. In response, nonhuman primates were included so that trial proposals could be assessed against the draft guideline on efficacy, which stated that clinical trials would have to be based on preclinical studies that show efficacy and are conducted in accordance with the Code of Practice.

**Conclusions**

5.126 As for the use of animals in other biomedical research, when assessing proposals to use animals in xenotransplantation research an ethical decision must be made about whether
any pain and suffering caused to the animals can be justified by the potential benefit of the research to humans or other animals. If so, experimental design should ensure that the animals are cared for in a way that provides for their social and environmental needs and minimises pain and suffering. These issues are reflected in the Code of Practice (NHMRC 1997a; update in progress, NHMRC 2003a), and its supplementary policies on the use of nonhuman primates (NHP Policy; NHMRC 2003b) and genetically modified animals (GM Policy; NHMRC 2003c).

5.127 Preclinical animal-to-animal studies involve many different types of procedures, from external procedures such as liver perfusion and skin grafting, to whole organ transplantation. Three areas of animal use identified as needing special consideration are the use of nonhuman primates, the use of pigs as source animals and the genetic modification of animals. In each case, the Code of Practice provides overall guidance and the NHP policy and GM Policy provide additional guidelines for the use of nonhuman primates and GM animals, respectively. The NHMRC Animal Welfare Committee has also decided to produce a policy statement on the use of animals in xenotransplantation research to assist AECs to assess and monitor such studies.

5.128 Respondents to the Discussion Paper identified the lack of national oversight of animal use in xenotransplantation research (both in animal-to-animal and animal-to-human transplantation research). Without such oversight, it is difficult for AECs to make the judgments required in paragraph 5.126 (ie whether the use of animals can be justified, based on the overall progress of the research towards a beneficial therapy for humans or other animals).

5.129 To help overcome this issue, the Animal Issues Subcommittee proposed a national notification system for the use of animals in animal-to-animal xenotransplantation studies that are intended to lead to clinical (animal-to-human) studies. This information should be provided to the national xenotransplantation advisory committee (based on an expanded GTRAP; see paragraphs 11.49–11.56).

5.130 The register of animal-to-animal studies should be available for AECs to review when assessing study proposals at their institutions and will also provide the national committee with an overview of animal-to-animal studies leading to clinical trials.
6 Alternatives to animal-to-human transplantation

Overview of issues from Discussion Paper and Draft Guidelines

Despite efforts to increase the number of human organ donors, demand outstrips supply: many people on waiting lists die before an organ becomes available (e.g., approximately 5% of kidney dialysis patients and 20–30% of potential liver and heart recipients die while waiting for a suitable transplant, NHMRC 1997bc). There is also a shortfall of cell and tissue products and new knowledge is opening up new therapeutic avenues, further increasing demand. It is in this context that animal-to-human transplantation is being considered as a source of cells, tissue products and organs for transplantation into humans.

Section 2.2.3 of the Discussion Paper provided information about six alternatives that have been suggested to overcome the shortage of human organs, tissues and cells available for transplantation:

- a ‘presumed consent’ policy for organ and tissue donation;
- changes to hospital procedures;
- payment for organs;
- living donor programs;
- artificial organs; and
- the use of stem cell and related biotechnologies (‘grow your own’ cells).

To obtain community views on the issue of alternatives to xenotransplantation, the Xenotransplantation Working Party posed the question:

Have the alternatives to xenotransplantation been adequately identified and put to one side?

In the submissions that addressed this issue, opinion was divided as to whether the alternatives had been adequately identified, with some submissions concerned that they had not been. There was general support for more actively pursuing the alternatives. Some of the respondents to this question were concerned about the wording; in particular, the notion of ‘putting the alternatives to one side’ (with the associated implication that the alternatives would not be given due consideration). This was described variously as ‘inappropriate’, ‘odd’, ‘unclear’ and ‘worrying’. These issues are discussed in greater detail in this section.

Introduction

6.1 The Discussion Paper identified a range of alternative approaches for treating people who are currently on transplant waiting lists or for providing treatments for diseases and conditions for which animal therapies are currently being investigated (such as diabetes and Parkinson’s disease). While some respondents felt that the alternatives had been covered and that it was clear why xenotransplantation could potentially provide a valuable additional therapy alternative for people in these situations, others did not think that the alternatives had been adequately canvassed. For example:

… it is the strong view of AA [Animals Australia] that, given the enduring ethical and animal welfare problems inherent in animal to human xenotransplantation (and the earlier pre clinical animal work) these ‘alternative’ approaches should be pursued vigorously. This is particularly so given that even if current work is allowed to proceed, it is a fact that xenotransplantation may not be efficacious, or indeed may be rejected in time by the community as a whole, or by individual patients.

Animals Australia (Submission X079)
It is not clear why the alternatives have to be ‘put to one side’. Techniques for both xenotransplantation and its alternatives will continue to evolve and develop and their relative suitability will be context specific and change over time. Alternatives have been adequately identified, however they have not been adequately discussed.

_NSW Health (Submission X090)_

6.2 The submissions proposed and/or supported several alternative strategies. Some supported strategies to increase the number of organ donors, including the system of presumed consent. Others considered stem cell technologies and gene therapy to be preferable alternatives to xenotransplantation; some thought them more likely to be successful. The use of artificial organs was also supported. There was also considerable support for investing in strategies that would help to reduce the reasons people seek transplants, with particular emphasis on preventive health care and lifestyle education. Investment in research that would improve allotransplant outcomes was also supported. These issues are discussed in more detail below.

**Human organ and tissue donations**

6.3 Whole organ transplantation depends upon donation of organs from people who have died, most often as the result of an accident. However, as the use of transplantation has grown, the supply of organs has not kept pace with demand. The addition of human tissue and cell therapies to the range of procedures available has also created demand for additional tissues (eg pancreatic islet cells for the treatment of diabetes).

6.4 The Discussion Paper flagged the various means used around the world to increase donations. These include changes to the legal definition of death; public awareness campaigns; in some countries, presumed consent (a person is assumed to ‘opt in’, unless they clearly indicated before they died that they did not wish to donate organs); and the development of live donor programs (adult-to-child and adult-to-adult).

6.5 Despite these efforts, for most tissues and organs, in Australia as elsewhere, there are not enough donor tissues and organs available for transplantation. The Discussion Paper concluded that this is not just a minor shortfall that can be overcome by greater effort or funding; it is extreme and is increasing.

6.6 The Discussion Paper asked whether the alternatives to xenotransplantation had been adequately identified. Submissions that dealt with this issue focused on options to address the shortage of organ donations for human-to-human transplantation. They include:

- improving donation rates;
- changing consent arrangements to favour donation unless the person has clearly indicated otherwise before they die (presumed consent);
- addressing institutional arrangements; and
- promoting living donor programs.
Improving donation rates

6.7 Some respondents noted that, as animal-to-human transplantation is not likely to be available as a routine therapeutic procedure for many years, xenotransplantation research should not distract attention or funding from current efforts to maximise human donation rates:

The Discussion Paper makes clear that xenotransplantation is not now a viable procedure and not likely to become so in the near future. Therefore, it is not an alternative in terms of the core issue of finding ways to increase the levels of organ donation. Queensland Health (Submission X014)

If the problem lies in a lack of organs for transplant, then wouldn’t it be better to put serious efforts into investigating means of increasing organ donation? Then there may be no need to even consider xenotransplantation.

(Respondent details confidential)

6.8 Australians Donate, the agency responsible for raising the profile of organ and tissue donation across Australia, is funded by the Australian and State/Territory governments. The Australian Government also initiated and supports the Australasian Donor Awareness Program (to facilitate the management of brain injured patients and their families) and funds the Australian Donor Register (where people register their intention to donate in the event of their death).

6.9 However, despite high levels of funding for these programs over many years, there has been little increase in organ donor numbers. This is due to many factors, including significant improvements in road safety, neurosurgery and intensive care, which have substantially reduced the numbers of donors who are victims of trauma. However, the rate of donation in Australia remains one of the lowest in the world (approximately 10 per million population per year, compared to 20 for the United States and over 30 for Spain).

6.10 To keep the donor rate stable, more marginal donors are being used (eg older people, and those with underlying conditions such as vascular disease or diabetes). Transplant surgery using these donors is less successful than when younger, healthy donors are used.

6.11 Usually, cadaveric donations are obtained only from people whose death has been determined by the brain function criteria (‘brain dead’); that is, their heart is still beating, thus maintaining the function of vital organs and tissues. However, one respondent drew attention to attempts that have been made to use kidneys from people who have died and whose heart has stopped beating.

Doctors at University Hospital Zurich have discovered that kidneys transplanted from ‘cardiac death’ donors are just as successful (in some cases more successful) than those transplanted from ‘brain dead’ donors. They have estimated that the use of such organs could increase the availability of donor kidneys by up to 30%. Research currently underw ay on the liver, pancreas and lungs indicate that these too may be transplanted from a donor shortly after the heart has stopped beating.

Humane Charities Australia (Submission X033)

6.12 So far, kidneys are the only organs to be trialled from this category of donor. The results have shown unresolved problems of initial functioning that are not experienced with transplants from brain-dead donors. However, for recipients where this problem does not occur, the prospects for long-term survival have been promising (Weber et al 2002). The approach is being considered for organs other than kidneys (Garcia-Valdecasas Salgado
2000). If successful, this method has the potential to significantly increase the number of donated organs and tissues available.

6.13 The Xenotransplantation Working Party (XWP) agrees that continued efforts are required to increase the number of human donations available. However, unless there is a dramatic increase in the number and quality of donations, the development of animal transplantation therapies may ultimately prove to be a valuable alternative that will maximise the number of people who can be successfully treated.

**Presumed consent**

6.14 In 1991, the World Health Organization issued principles for the removal of organs (WHO 1991). These principles state that organs may be removed from a body of a dead person if:

- any consents required by law are obtained; and
- in the absence of any formal consent given during life, there is no reason to believe that the dead person would have objected to such removal.

6.15 The Discussion Paper (Section 2.2.3) highlighted the different types of consent arrangements used in Australia and some other countries and how this relates to the availability of organ donations in those countries. These approaches are described in further detail in paragraphs 6.16–6.27, below.

6.16 In countries where transplantation is widely practiced, the law permits removal of organs from the cadaver of a person who made known the wish to donate while alive (prior consent, or ‘opt in’). In practice, however, most people have not made any such formal declaration and in these circumstances the law looks to the relatives for consent.

6.17 The power of relatives to influence the final decision in cases where the deceased did not formally declare their intention to donate before they died (and, sometimes, even if they did) varies under the law from country to country (Kennedy et al 1998). In countries such as Australia, the United States and the United Kingdom, donation cannot go ahead if the person registered an objection before death or if the relatives object. If the relatives agree, however, the donation can occur even with no consent before death.

6.18 Other countries have a system of presumed consent, which means that unless the person has formally registered an objection (‘opted out’) before their death, their organs can be used.

6.19 First introduced by Singapore in the 1980s, in its purest form, presumed consent does not take account of the views of relatives. This system was introduced in Austria and Belgium in the late 1980s and resulted in a large increase in the number of organs available for transplant (Kennedy et al 1998). In Italy, donation is not subject to objection by the deceased person during their lifetime, but is subject to objection by the relatives.

6.20 Spain also has a system of presumed consent, although families are still asked to confirm that their loved ones will be organ donors; in Norway only the views of the nearest relative are obtained. Spain also has a system of ‘active detection’, which means that transplant coordinators visit the intensive care unit on a daily basis to check the status of patients.
Several submissions (including X003, X019, X028, X063) referred to higher rates of organ donations that have been achieved in countries where a more liberal approach has been adopted as public policy (e.g., Spain and Norway):

Xenotransplantation is being considered in Australia because of low levels of organ donations throughout the world. In Austria the ‘Presumed Consent’ program effectively increased organs available for transplant four-fold by requiring that all people are potential donors unless they lodge an objection.

Tony Clunies Ross (Submission X003)

While presumed consent will not resolve the entire problem of organ and cell availability it would obviously make a huge difference to the number of organs that are currently available. My understanding is that in countries such as Spain there is almost a 2–3 times higher rate of human organ donation than in Australia.

A/Professor Peter Collignon (Submission X063)

A number of other respondents also advocated presumed consent (X033, X042, X040, X092):

I do not feel that ‘presumed consent’ has been adequately explored as I am unaware of any discussions in parliament or in the media on this issue; I consider that it has been too hastily disregarded as an option because of pressure to allow XT research.

Kerrie Donaldson (Submission X092)

Queensland Health thought the Discussion Paper was brief and unduly pessimistic when it came to options for increasing the supply of donor organs:

Systems that could address the short-term need — presumed consent, changes to hospital procedures and payment for organs — are not in place because it is assumed the social, emotional and ultimately political objections they raise cannot be overcome. However, as demonstrated by the recent public debate on embryo research, such subjectively based objections can be confronted and overcome.

Queensland Health (Submission X014)

However, in Australia and elsewhere, even if a potential donor has registered consent before death, there are obstacles to the recovery of organs and tissues that would not necessarily be overcome by a system of presumed consent. For example, relatives may refuse to proceed with the donation or suitable surgical facilities may not be available.

Also, the lower rate of donation in Australia may be a reflection of a lower fatal accident rate in this country than in some other countries.

Transplantation specialists who have many years of experience of working with intensive care staff and the families of deceased patients do not consider that the system of presumed consent would work well in Australia because of cultural factors associated with the diverse multicultural population and because the federal system of government makes uniform regulation difficult to implement across the country.

Even countries that have presumed consent arrangements in place have a shortfall of organ and tissue donations. For example, Spain has one of the highest organ donation...
rates in the world (see paragraph 6.9), yet the Spanish government is allowing animal-to-human transplantation trials to proceed in that country.\textsuperscript{7}

**Institutional arrangements**

6.28 The Discussion Paper observed that policies and procedures in hospitals could be changed to overcome the obstacles preventing recovery of organs and tissues from a person whose death has been determined by the brain function criterion and who registered consent before death. It concluded that, while improvements in this area may increase the number of available organs, the shortfall of transplantable organs and tissues is currently so great that this option is unlikely to greatly reduce the length of waiting lists.

6.29 However, some respondents, including Queensland Health, considered that improved institutional arrangements could increase donor rates.

6.30 The XWP agrees that it is a priority of health authorities to pursue this option as vigorously as possible. However, as noted in paragraphs 6.14–6.27 on presumed consent, such increases in donation rates will not completely overcome the shortage of organs, particularly with the development of new transplantation procedures involving a broader range of cells and tissues as well as organs. For example, in Australia in 2001, over 12,000 people were receiving kidney dialysis (equivalent to over 600 per million population) (ANZDATA 2002).

**Use of organs from living donors**

6.31 Another option for increasing the number of human tissues and organs available is the ‘living donor’ program. This has already expanded considerably over the past few years, particularly for kidney donations, where the risks to donors are very low. Already approximately 30% of kidney donations are from living donors (ANZDATA 2002).

6.32 Internationally, the use of live liver donors has also increased over recent years. The left lobe of liver can be removed from an adult and transplanted into a child with a relatively low risk of complications or death of the donor. However an adult recipient requires donation of the right lobe of the liver. This procedure has been associated with a significant complication rate and occasional deaths of donors, and is not in routine practice in Australia. Programs involved in live organ transplantation must ensure appropriate procedures for selection, medical and psychological evaluation and informed consent of both donors and recipients.

6.33 As stated in paragraph 6.13, animal-to-human transplantation should not preclude vigorous attempts to increase human organ and tissue donations by all the methods described in this section.

\textsuperscript{7} http://www.xeno.cpha.ca/english/legisla/page3.htm
Human cell research

6.34 Research using human cells has paralleled animal cell research both for external therapies and for cell therapies.

Human external therapies

6.35 Researchers are investigating several approaches to provide external liver support for patients with acute liver failure for whom a transplant is not available. At this stage, the systems that are best at detoxification and compensating for lost metabolic function pass the blood of the patient through a bioreactor containing live liver cells (animal or human).

6.36 Primary cultures of human liver cells can be set up from relatively small samples of human liver, such as transplant discards; secondary cultured cell lines derived from liver tumours can also be used. Such cultures have been maintained in bioreactors. Early trials using human cell external liver support therapy for people with liver failure have shown similar results to those obtained using pig cells (Gerlach et al 2002, Millis et al 2002). Paragraphs 8.35–8.40 of this Response Paper discuss this research in further detail.

Human cell therapies

6.37 Recent scientific work on the culture of human stem cells has raised hopes for future therapies to repair human organs and to treat a range of diseases. Human stem cells are early, unspecialised cells that can, under certain conditions, be induced to mature into specialised cell types (eg heart, muscle, liver). Researchers hope that such human cells can provide a range of human cell therapies (HCTs) for both autotransplantation (to the same person) and allotransplantation (to a different person).

6.38 The Discussion Paper described the extraction of stem cells from human embryos as ethically controversial. However, the Australian Parliament has since legislated for embryo use in research within strict limits by passing the Research Involving Human Embryos Act in September 2002. Under this Act, licensed researchers will be able to use human embryos considered ‘excess’ to in vitro fertilisation (IVF) programs (with consent from the persons responsible for the embryos) for medical research, including the extraction and culture of embryonic stem cells.

6.39 Comments in the submissions received were generally in favour of human stem cell research. Several respondents strongly voiced the opinion that these alternatives should be pursued rather than animal cell therapies (ACTs):

… I cannot see how research with single animal cells can be condoned rather than using human cell lines, given the potential risks associated with xenotransplanted animal cell lines are so much greater.
A/Professor Peter Collignon (Submission X063)

Gene therapy and stem cell research have numerous advantages over xenotransplantation e.g. cost savings, minimal clinical intervention and monitoring required, no risk of latent zoonotic infections, as well as less controversy in the scientific and wider community over their safety and efficacy.
Dr Anthony Raizis (Submission X034)

6.40 This support for HCTs ignores the fact that currently available human stem cell lines are grown on animal feeder layers and therefore come within the definition of
xenotransplantation. However, the recent legislation to allow research on human embryos that are excess to IVF programs will allow the development of new stem cell lines that do not need to be grown on nonhuman feeder cells, potentially providing the stem cell approach with an advantage over ACT:

There is a great deal of overlap between the two areas [animal and human cell therapies] and the committee has elected to regard stem cells as a form of xenotransplant because of the use of non-human cells in their cultivation. Non-human cells may not always be needed, in which case the use of stem cells could develop into a form of allotransplantation, with a less stringent set of biological and ethical criteria needing to be considered. Ethics and Research Committee, Armadale Health Service, WA (Submission X048)

6.41 The XWP was aware that human external and cell therapy research is targeting a similar range of diseases and conditions to research on animal therapies. However, at this stage there is no clear indication whether the human or animal therapies will have an advantage in any particular clinical circumstance.

**Artificial organs**

6.42 The XWP considered the use of mechanical or artificial organs for people suffering organ failure. Some mechanical devices are used as a short-term ‘bridging’ procedure for people waiting for an organ to become available but the XWP concluded that the production of safe and effective mechanical alternatives for long-term use is probably some decades away. However, some respondents supported the development of such artificial devices:

Whilst [artificial organs] may be in the very early stages of development and not likely to be used for some years — so too is xenotransplantation. Artificial organs do not carry the risk of zoonosis and are considered less likely to cause rejection from the recipient’s body, thus eliminating the need for immunosuppression.

_Humane Charities Australia (Submission X033)_

6.43 However, the XWP has subsequently become aware of trials of some artificial approaches to organ repair or assistance. One example concerns small mechanical heart assist devices, which have recently started clinical trials; initial results have shown promise (Nemeh and Smedira 2003, Patel and Pagani 2003). Another example involves trials of several noncellular procedures for artificially purifying blood (Kjaergard et al 2003).

6.44 Research on artificial organ therapies is an important alternative to xenotransplantation. However, as for the other alternative therapies discussed above, it is not clear at this stage which approach will be most effective.

**Improving transplant outcomes**

6.45 A proportion of transplants fail, mainly from viral complications. Some respondents thought that research to improve human transplant outcomes could offer a more realistic and beneficial outcome than animal-to-human transplantation. For example, they suggested that more effective immunosuppressive therapy regimens should be vigorously encouraged.

6.46 In response, the XWP noted that in Australia the rate of failure of kidney transplants in the first year after transplant is approximately 8% (Briganti et al 2002). The Discussion Paper did not specifically canvass improving transplant outcomes as an alternative to animal-to-human transplantation. However, the XWP acknowledges that this is a very
important area of ongoing research; there is no suggestion that this should stop or be reduced in favour of animal-to-human transplantation research.

Preventive programs and lifestyle education

6.47 Some respondents suggested that the need for interventions such as tissue or organ transplants could be reduced by investing in preventive programs and lifestyle education aimed at maintaining good health (for example, Submissions X003, X010, X026, X033, X040, X042 and X079):

… a proactive health system focused on preventative programs rather than experimental techniques for preventable diseases could provide real benefits in quality of life to people who would otherwise become transplant candidates in the future … Tony Clunies-Ross (Submission X003)

Many of today’s health problems are generated by our choice of lifestyles. Smoking, lack of exercise and consumption of animal products have all been acknowledged as being major contributing factors to such conditions as heart disease, stroke, cancer, diabetes and a range of other ailments. By using our resources to promote healthier lifestyles we would be reducing the number of people who are in need of organ or tissue transplants. Whilst we acknowledge that not all those on transplant waiting lists are there as the result of unhealthy lifestyles, with a healthier population, and thus fewer people waiting for transplants, the lower demand for organs and tissue would ensure that those people suffering from genetic ailments have a better chance of receiving a transplant. Humane Charities Australia (Submission X033)

6.48 However, many diseases and conditions that can potentially be treated using existing or developing transplantation therapies are not lifestyle related. For example, kidney failure frequently occurs in young, otherwise healthy, people as a result of an infection or other factors. Type 1 diabetes, which is usually first diagnosed in children or young adults, is an autoimmune disease not related to lifestyle. The cause of Parkinson’s disease is unknown but the illness is not related to poor lifestyle choices; other neurological diseases, such as Huntington’s disease, are genetic.

6.49 The Population Health Division of the Australian Department of Health and Ageing already funds extensive preventive health programs in relation to conditions that are related to lifestyle. The Minister for Health and Ageing recently released a paper that shows that these programs have been successful in reducing health care spending on preventable diseases (DHA 2003).

6.50 Overall — given the slow response times associated with preventive medicine and community education campaigns, the proportion of diseases and conditions treatable by transplants that are not lifestyle related, and improvements in transplant technology (leading to more people being offered this option) — there seems little chance that waiting lists will reduce in the near future.

Conclusion

6.51 Organ and tissue donations are required to overcome a large range of diseases and conditions. Xenotransplantation is only one of a number of approaches that might be used to overcome the current shortage of such donations.

6.52 Although vigorous efforts are needed to increase the number of human donations to transplantation programs, it is unlikely that such efforts will overcome the extreme
shortfall, especially as further new therapies are developed that use transplanted cells and tissues.

6.53 In terms of the various alternative therapies that are currently being researched, the XWP felt that Australia should be able to opt for the therapy that is considered the most efficacious and safest at the time. If human cells fulfil this role in a given circumstance, they will supplant animal cells for that particular therapy. Before agreeing to proceed with a trial of animal-to-human transplantation, the proposed regulatory committee will need to consider all alternative therapeutic options available at the time.

6.54 Attention to preventive strategies is always a worthwhile goal for health care systems, and could prevent the need for transplants for some patients. However, many diseases that are treatable by transplant therapies are not related to lifestyle or preventable by other public health measures (see paragraph 6.48). Also, preventive health programs have long lead times; in the meantime, many people are already in need of medical help.

6.55 Until we can more accurately identify the best option for particular diseases and conditions, it may be best to adopt an integrated approach involving a range of different options.
7 Resource issues

Overview of issues from Discussion Paper and Draft Guidelines

Increasing the supply of organs and tissues for transplantation by the use of animal transplantation products would inevitably lead to an increase in demand for such products. Section 3.4.1 of the Discussion Paper highlighted issues relating to research funding and allocation of health care resources. It concluded that 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 ongoing supervision and treatment of animal transplant recipients. Ideally, the costs of ongoing treatment and care would eventually be matched by the savings made in restoring recipients to healthy and productive lives, but it is too early to know whether this hope will be realised.

The Discussion Paper also flagged justice and equity issues: while altruistic human transplantation therapies are currently funded publicly, animal therapies may initially be available only commercially. It described these issues as complex, and said they were beyond its scope. The XWP posed the following question:

*Should there be a more extensive discussion of resource allocation for xenotransplantation research and clinical trials now, or can these issues be postponed until it becomes clearer that xenotransplantation is likely to become a reality?*

Most of the submissions that addressed resource issues relating to animal-to-human transplantation thought such matters need to be taken up now as part of the continuing public debate. Respondents also raised a number of other major issues that affect the funding of xenotransplantation research and the allocation of health care resources, including:

- the potential for xenotransplantation research to divert public attention and support away from organ donor programs and alternative therapies (paragraphs 7.1–7.5);
- private and public sector involvement in xenotransplantation research (paragraphs 7.6–7.16);
- public access to therapies (paragraphs 7.17–7.23);
- costs of research, including long-term monitoring and follow-up (paragraphs 7.24–7.33); and
- insurance, liability and legal issues (paragraphs 7.34–7.43).

Resource allocation

7.1 Respondents saw the allocation of resources, particularly money, as an important issue in considering alternatives to animal-to-human transplantation. People needed to be convinced that the benefits of investing in such research were likely to be at least commensurate with the benefits of pursuing the available alternatives.

There is some concern that medical research (not only xenotransplantation) is continually being extended when welfare/community service issues fail to receive adequate funding and attention. … How xenotransplantation research fits with the general scheme of medical research that should be funded must be explored and justified. While this may be beyond the discussion of this document, it is likely to be of significant interest to the Australian public. *Human Research Ethics Subcommittee of the Department of Human Services, South Australia (Submission X055)*
7.2 Some of the respondents who discussed research funding argued that it would be better to address the shortage of organ donations than spend money on animal-to-human transplantation research.

The urgency to proceed with exploring xenotransplantation however, is due to the extreme shortage of organ donors within Australia. As research into xenotransplantation will involve a great deal of time and money, we consider these resources would be of greater value if used to address the problem of human organ shortage. *Humane Charities Australia (Submission X033)*

7.3 Other respondents were concerned that investing in animal-to-human transplantation research would reduce the resources, especially funding, available to alternative forms of therapy and preventive health programs.

The money and time proposed for these trials should be spent on researching other methods for curing the diseases from which the transplant patients suffer, or better still, on researching and promoting preventative measures where possible. *(Respondent details confidential)*

7.4 In preparing the Discussion Paper, the XWP thought that it was beyond the scope of the working party to consider the full economic impact of animal-to-human transplantation research (Discussion Paper, Section 3.4). However, some respondents argued that the potential for animal-to-human transplantation studies to divert resources from other medical services must be discussed:

How could funding research into an uncertain and risky subject, which is likely to benefit only a select few (if any), possibly be justified when other medical procedures are likely to be sacrificed in order for it to proceed? … We do not consider that the public would agree to further cutbacks to allow research into xenotransplants and believe that this issue would need to be explored in full to determine the real financial costs. *Humane Charities Australia (X033)*

The issues of cost, availability and demand for these procedures have been dismissed as ‘complex and beyond the scope of this discussion paper’ (p 31). These issues cannot be ignored and consideration of the implications for our society must not be postponed. *Lene Martins (Submission X007)*

Discussions of resource allocation for xenotransplantation research and clinical trials should be embarked on now. By the time it is clear that xenotransplantation is likely to become a reality it will be too late to wind it back or change its trajectory. *Gene Technology Ethics Committee (Submission X084)*

7.5 On the other hand, the Gene Therapy Advisory Committee of New Zealand proposed that discussion of resource allocation for animal-to-human transplantation research and clinical trials could be postponed until it becomes clearer that such therapies are likely to become a reality (Submission X088).

**Research funding**

7.6 To consider the issue of research funding allocation in greater detail, it is necessary to consider how medical research is funded in Australia. Essentially, research funding comes in three forms:

- public funding provided by the government through the NHMRC Research Program, Australian Research Council, State and Territory governments, the cooperative research centre program and other programs;
- not-for-profit organisation funding (eg National Breast Cancer Foundation, National Heart Foundation); and
- commercial funding by biotechnology companies.

**Public funding**

7.7  The NHMRC is one of the major providers of funds for medical research to institutions such as hospitals, universities and research institutes. Like other public funded research, NHMRC-funded research has the broad strategic intent of better health for all Australians. Research grants are awarded on the basis of scientific quality, as judged by peer review.

7.8  To allocate resources, funding agencies must identify and prioritise developments in health and medical research, likely outcomes for the community and the needs of the Australian medical research community.

7.9  To assist with the task of priority setting, both for research funding and health care service provision, the Australian Health Ministers Advisory Council established the National Health Priority Areas (NHPA) Initiative in 1996. The initiative is managed by the National Health Priorities and Quality Branch of the Australian Department of Health and Ageing. The scope of the initiative includes the continuum of care from prevention and early detection, through to treatment, rehabilitation and continuing care in six national health priority areas that together constitute the cause of the majority of the burden of disease in the Australian community (cancer control, cardiovascular health, mental health, injury prevention and control, diabetes and asthma).

**Not-for-profit funding**

7.10  A proportion of medical research is funded by not-for-profit organisations (charities). These organisations raise money through public donations against specific stated aims to fund research in a particular area of medicine (cancer, heart disease, diabetes and so on). Grants are generally awarded in the same way as for publicly funded research.

**Commercial funding**

7.11  Private sector funding has as its aim the development of a technology that will ultimately be marketed and return the money spent on its development plus a profit. In this case, all the research and development costs, including the costs of clinical trials, are borne by the company (known as the research sponsor).

7.12  Because research and development costs are so high, the company needs to ensure that there will be a demand for the product once it is registered for marketing. This can bias the reporting of research findings in favour of the product, an issue which has been taken up recently by the journals that publish research findings, who now have strict conflict-of-interest disclosure policies for all publications.

7.13  Various submissions raised concerns about private sector involvement in research, in regard to profit, liability and accountability:

> … if funding is provided by the private sector (ie pharmaceutical companies) then there is a vested interest involved and then the best interests of the public may not be the main priority.  *Humane Charities Australia* (Submission X044)
Xenotransplantation should remain in the public domain. Eventually it is health services which pay for it either through government or commercial systems, but the knowledge should not be the property of private commercial interests.

*Preterm Foundation Ethics Committee (Submission X081)*

7.14 The Armadale Health Service Ethics and Research Committee fully supported the need for the basic research, including clinical trials, but questioned the need for animal-to-human transplantation technology to be made available to commercial operators (Submission X048).

7.15 Other respondents agreed:

… there are very large profits to be made by the owners of patents of genes, cloned animals as well as pharmaceutical companies marketing anti-rejection drugs. If something does go wrong however the cost will not be borne by the individuals who are making the profits. It will be borne by the community at large, because the costs are to do with infection control, quarantine and other social costs that will occur if a new organism does develop and is transmitted from person to person.

*Professor Peter Collignon (Submission X063)*

The debate could generally be seen to be an attempt to balance the rights and desires of a few people to undertake a procedure that may (or may not) benefit them, and the ability of researchers and companies who will financially gain from the commercialisation of the procedure, on the one hand, versus the right of the whole of the rest of society to protect itself from harm, on the other hand.

*Respondent details confidential*

7.16 On the other hand, the biotechnology companies themselves would argue that they provide the necessary research funds and incentives to help alleviate a real human problem and that commercialisation of their products is a necessary part of this process.

**Access**

7.17 The Discussion Paper noted that, while human-to-human (altruistic) transplants are currently funded publicly, if animal-to-human therapies come into normal clinical practice, they may only be available privately while companies recoup the high development costs of the procedures. In the submissions that addressed questions about access, there was a general perception that access to animal-to-human therapies would be restricted to those who could afford it and that this was undesirable.

7.18 The Human Research Ethics Sub-committee of the Department of Human Services, South Australia said:

The paper indicates that the involvement of private companies in xenotransplantation research may mean that only people with access to significant amounts of money would have access to xenotransplantation in the first instance. It is ethically unacceptable to accept [participants] based on socio-economic status. Public medical funds would be needed in the future to make such treatment equitably accessible.

*Human Research Ethics Sub-committee of the Department of Human Services, South Australia (Submission X055)*

7.19 Several submissions asserted that, while access to the procedures could be limited to those able to afford them, the community is likely to bear many related costs.
Other important ethical issues that are addressed are that in most of the world this technology will be subsidised at least in part by the Government, yet a very limited number of individuals will be able to access this technology.

_Professor Peter Collignon (Submission X063)_

Given that xeno products are intended to be sold as a therapeutic good, and hence may not be available to the most needy poor and sick, I have serious doubts that the end will justify the means. Xenotransplantation research would entail great costs in terms of money and animal lives, yet it will only benefit those who can afford it.

_Heidi Nore (Submission X058)_

If we look at a prospective xenograft recipient, even in Australia’s part socialist medical system, the public is footing the bill for what is seen to be a private-only procedure, as the costs are exorbitantly high. Thus, only the wealthy will have this as a choice, though the whole community is subjected to the disease impact and costs …

_Ratifiers for Democracy (Submission X040)_

7.20 In response, the XWP stresses that, during the research phase, animal-to-human transplantation trials would be funded by researchers and research sponsors (mainly biotechnology companies), as is the case for other clinical trials, with no cost to research participants. Such procedures would therefore be available generally and not limited to only those people who could afford private health care.

7.21 If new procedures and technologies move from research into established clinical practice in Australia, the Medical Services Advisory Committee (MSAC) reviews the safety, efficacy and cost-effectiveness of new technologies and procedures and determines whether the new technology or procedure should be listed on the Medical Benefits Schedule (MBS). This is a similar process to that for drug listing on the Pharmaceutical Benefits Scheme. MSAC is a large committee with broad stakeholder representation including researchers, health economists, consumer advocates and government representatives. MBS listing would allow patients to obtain reimbursement under Medicare for treatment.

7.22 However, many procedures that are not MBS listed are still available publicly and receive State/Territory funding at a public hospital or national funding at a national centre. Similar arrangements exist for human-to-human transplantation (allotransplantation), which is not funded under Medicare. For example, for liver allotransplants, one unit was initially set up, cooperatively funded by State and Australian governments. Further publicly funded units have been added as treatment has been shown to be successful.

7.23 As animal-to-human transplantation is at such an early stage of research, it is impossible to predict what public funding may be made available to set up transplant units in public hospitals, or to pre-empt the findings of MSAC for MBS listing. However, the pattern of funding is likely to be the same as that for other similar procedures, such as allotransplantation.
Costs

7.24 Several respondents commented on the absence of a cost–benefit analysis in the Discussion Paper.

No comparative analysis is undertaken of potential costs and benefits between xenotransplantation and the other options. The Discussion Paper’s pessimistic assessment of the options for increasing the supply of donor organs by potentially cost-effective extension of current practices (allocative efficiency) means that using research to develop new tools (technical efficiency) is favoured by default. This is unfortunate because neither the biotechnology approach based on genomic and proteomic manipulation nor xenotransplantation is likely to provide a short-term solution. Queensland Health (Submission X014)

7.25 Some anticipated that a cost–benefit analysis of animal transplants would be poor:

The cost could only be substantially higher [than allotransplantation] but with a substantially lower benefit (The human tissue has an 80% success at 1 year – insulin free — the xenotransplants to date for that purpose 0%). There will therefore be a very poor cost benefit if pig tissue is used (and it could never be expected to be as good as human tissue no matter what genetic engineering is done to pigs).

A/Professor Peter Collignon (Submission X063)

7.26 Various submissions identified a range of costs associated with animal-to-human transplantation and listed additional expenses that need to be considered in any discussion of the overall costs of such procedures:

The costs associated with xenotransplantation … are expected to be immense. In the long-term, these costs can in no way be met by recipients paying for the entire necessary infrastructure, which will be required for the procedure to be effective. Such costs can only be met by the taxpayer. There will be the hidden costs of breeding, housing, feeding, medicating, testing, transporting, rendering, and disposing of the waste and remains of herds of animals. Rearing pigs under germ-free conditions is extremely expensive and time-consuming and the production of germ-free pigs would greatly add to the cost of providing donor organs.

Dr Anthony Raizis (Submission X034)

7.27 The Campaign for Responsible Transplantation identified a range of costs associated with animal-to-human transplantation and questioned who would absorb these costs:

In addition to the operations themselves, there are hidden costs of: housing, breeding, feeding, medicating, testing, and disposing of the remains of herds of transgenic animals; of hiring skilled hospital personnel, surgical staff, infectious disease experts and veterinarians capable of properly monitoring xenograft patients, their close contacts and source animals; of government-mandated patient registries, blood and tissue archives, programs and technologies to screen for new viruses, and unpredictable medical and legal costs associated with disease outbreaks.

Campaign for Responsible Transplantation (Submission X067)

7.28 Monitoring issues are addressed in Section 10 of this Response Paper. However, several respondents identified a range of costs associated with the monitoring of animal transplant patients and their close contacts, as well as the pigs that would be the source of tissues and organs, and were concerned that these costs might fall on the community as a whole:
the whole community is subjected to the disease impact and costs, and for the ‘surveillance’ (NHMRC term) part of this process, it is both unstated as to who will pay and what the surveillance will be, but certainly the burden of public health monitoring for public health purposes, and notification for same, will fall on the taxpayer. 

Ratifiers for Democracy (Submission X040)

I believe that the cost of such follow-up should be met by those who intend doing the research as part of the application/licensing fee. (Respondent details confidential)

7.29 St Vincent’s Clinical Trials Centre noted that patients and contacts would need to be monitored even if their transplant failed or if the whole trial was cancelled (for example because of problems with the procedures or because the biotechnology company goes out of business):

The issue of potentially small biotechnology companies being involved at the outset raises the issue of the effect of a failed trial and who will assume financial and regulatory responsibilities for the ongoing monitoring of subjects. This might be particularly the case where, for example, in renal failure or diabetes alternative treatment options exist once the transplant has failed, but monitoring for infectious disease needs to continue. St Vincent’s Clinical Trials Centre (X056)

7.30 NSW Health discussed costs associated with the overall monitoring of the progress of clinical trials and pointed to the need for clearly defining what has to be monitored, in how much detail and by whom.

The monitoring of the conduct of clinical trials is the responsibility of the relevant Human Research Ethics Committee (HREC), as is currently the case. However, it may be necessary to provide additional resources to HRECs to ensure that such monitoring is effective. … The monitoring of the impact of xenotransplantation on recipients and close contacts over time will require the establishment of a registry and possibly an associated tissue bank. Consideration will need to be given to monitoring methods, such as how, what and when data and tissue is to be collected and stored, the possible future uses of the data and tissue, privacy and confidentiality issues, and capital and recurrent resourcing. NSW Health (X090)

7.31 Finally, the International Xenotransplantation Association noted that there is still considerable uncertainty about the practicalities of animal-to-human transplantation. However, they indicated that judicious infusion of funds into animal-to-animal research may improve the usefulness of results obtained and save money in the long term:

Although perhaps outside the scope of this paper, it is our view that an infusion of funds into the development of core facilities for measuring drug levels and producing biological reagents that are specific for non-human primate species used in xenotransplantation research, and into non-human primate research facilities with more sophisticated monitoring techniques, could go far in improving the clinical applicability of data obtained from non-human primate studies. In any case, an unbiased assessment of the potential for benefit and of the need for more pre-clinical studies that can realistically be performed, should be obtained before any clinical study proceeds. International Xenotransplantation Association (Submission X077)

7.32 In considering these issues, the XWP noted that all costs associated with xenotransplantation research should be borne by the research sponsors. Although some of the early development costs of research may be borne overseas (as is already the case for Hepatassist external liver perfusion devices), to date, research sponsors may not have adequately assessed all the costs involved in conducting animal-to-human transplantation research in Australia.
The XWP also noted that the current costs of treating people with diseases such as renal failure is also very high: one year of dialysis is estimated to cost $50,000–$70,000 per patient. The costs of developing other alternative therapies (e.g., artificial organs, human cell therapies) are also high.

**Liability**

If animal-to-human transplantation research goes ahead, and if a new infectious agent emerges in the human population as a result, or another such adverse event occurs (such as loss of animal species), a question of accountability may arise.

In the event that [there is a new epidemic], who will be held responsible? The research subject, his or her close contacts, the organization sponsoring the study, the ethics committee of the institution that allowed the study to proceed, and the government and its regulatory agencies which approved the study could all arguably be held responsible. … In addition, government-level approval of xenotransplantation procedures may be seen as an implicit form of social acceptance that the potential risks of xenotransplantation are outweighed by its potential benefits. For this reason, public input into the decision as to whether or not a country will proceed with xenotransplantation studies is of the utmost importance.

*International Xenotransplantation Association (X077)*

What legal liability is there for the NHMRC and scientists if a non-human virus crosses the species barrier? Would the NHMRC be considered negligent in their failure to protect public health and safety? I assume that an XT recipient would sign a form waiving (some of) their legal rights, but what happens if the disease(s) spreads into the broader community, to people that have not signed up for the risk?

*Kerrie Donaldson (X092)*

Respondents addressed a variety of issues and raised several important questions regarding liability, insurance and related legal matters. They expressed concern that the involvement and potential responsibilities of both governments and researchers (mainly from the private sector) have the potential to blur lines of responsibility and to complicate matters considerably.

Sovereign liability is already a reality, and given that governments are involved, both in permitting, regulating, and funding xenotechnology, they would be the most obvious targets for transnational legal suits, especially since a pandemic would cause a domino effect of corporate bankruptcies. Even now, how is insurance risk being calculated, and who is the final guarantor? Whatever the claims … the liability for purposely inserting the capacity for an unknown number of diseases into the human species is incalculable, for which it looks like society will pay, in all ways.

*Rattifiers for Democracy (Submission X040)*

Associate Professor Peter Collignon also stressed that because of the organisation of health care and quarantine arrangements, it will be the community (through governments) that may bear the costs if something goes wrong.

If something does go wrong however the cost will not be borne by the individuals who are making the profits. It will be borne by the community at large, because the costs are to do with infection control, quarantine and other social costs that will occur if a new organism does develop and is transmitted from person to person.

*A/Professor Peter Collignon (Submission X063)*

One respondent proposed that researchers should be required to carry insurance to cover any potential adverse events:
It may take decades to find any unintended consequences of xenotransplantation: Those who are the recipients of the xenotransplant may be asked to sign away their rights for compensation for adverse events by the individuals or company that undertakes or funds the research. I believe that the draft guidelines should address this issue and prevent this from happening. Furthermore, if adverse events are communicable to others, there could be a huge consequence to the community. I believe that the guidelines should address this issue as well, and cause the researchers to be liable for the consequences. Consequently, the researchers and their economic backers should be required to have considerable insurance to cover such a possible event. Otherwise, if something goes wrong, the community will have to pay for the damage. (Respondent details confidential)

7.38 NSW Health noted that the involvement of human participants in animal-to-human transplantation research will be required to comply with the NHMRC National Statement on Ethical Conduct in Research Involving Humans (National Statement; NHMRC 1999). Clause 12.7 of the National Statement provides that ‘An HREC must be satisfied, before approving a clinical trial, that arrangements exist to ensure adequate compensation to participants for any injury suffered as a result of participation in the trial.’ This clause clearly covers unforeseen side effects of the treatment in a clinical trial, but it is not clear that it would cover long-term effects and the involvement of close contacts, as may occur with animal-to-human transplantation.

7.39 The XWP therefore consulted further with the Therapeutic Goods Administration (TGA) on this issue. The TGA advised that, in processing clinical trial applications, the TGA has two legal requirements:

- the trial must comply with the National Statement (NHMRC 1999) (see paragraph 7.38, above); and
- the trial must comply with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Note for Guidance on Good Clinical Practice (CPMP/ICH 135/95; referred to here as the ICH GCP Guidelines).

7.40 Under the requirements of the ICH GCP Guidelines, trial sponsors must have insurance arrangements in place to ensure that liability for adverse events is covered, both for the immediate trial and in the future. The guidance also specifies in detail the information required to be given to trial participants before they sign a consent form, including information on the compensation and/or treatment available to the subject in the event of a trial-related injury.

7.41 However, NSW Health contends that:

Requiring the researcher to provide compensation to participants only is inadequate. However, if the guidelines required the researcher to obtain compensation for all possible victims of infections, it is doubtful that any clinical trials would proceed, as the risk is unquantifiable and potentially large, making it an unattractive proposition for researchers/ insurers. It is recommended that the Paper be amended to include a requirement that ‘An HREC (and any proposed regulatory committee) must be satisfied, before approving a clinical trial, that arrangements exist to ensure adequate compensation to participants and their close contacts, for any injury suffered as a result of participation in the trial.’ Close contacts should include sexual partners, close friends, family and health care workers. It should also include offspring born subsequent to the transplant. NSW Health (X090)
7.42 To ensure that compensation is available in the event of an adverse event such as an infectious disease outbreak, it may be necessary to classify contacts of the xenotransplant recipient as research participants for the purposes of the necessary insurance arrangements under the ICH GCP Guidelines. The definitions of research participant and close contacts are discussed further in paragraphs 10.1–10.60.

7.43 The XWP considers that the role of the regulatory system adopted for animal-to-human transplantation trials will be to ensure that mechanisms are in place to minimise the risk of an adverse event. Patients in early animal-to-human transplantation trials will be intensively monitored and screened to ensure that any potential infection is detected long before any spread to the community can occur.

**Conclusions**

7.44 When drafting the Discussion Paper, the XWP considered that full assessment of the economic impact of animal-to-human research was outside the scope of its terms of reference. However, the XWP shares the concerns expressed by many respondents in relation to various resource issues. In particular, it notes concerns about funding, particularly private sector involvement; the costs of research, including long-term monitoring; and liability for adverse events that affect individuals and also society and ecosystems more generally.

7.45 In response to these issues the XWP has concluded:

- Participation in animal-to-human transplantation trials will be free to the patients involved, as the costs of such research will be borne by the research sponsors.
- To date, research sponsors may not have adequately assessed all the costs involved in conducting animal-to-human transplantation research in Australia.
- Legal liability, insurance and compensation issues associated with animal-to-human transplantation are all very important and should be clearly stated in research protocols, as required by the ICH GCP Guidelines. However, appropriate regulations will be required to ensure that mechanisms are in place to minimise the risk of an adverse event occurring.
- For medical technologies and procedures that are approved for clinical use, MBS (Medicare) listing administered by MSAC provides public funding for the procedure. However, most transplants are carried out in public hospitals and many procedures that are not MBS listed (eg allotransplantation) are funded from State/Territory or Australian government health budgets, initially at small local units and later (as the benefits of the procedures become more apparent) at larger specialist centres.
8 Will animal-to-human transplantation work?

Overview of issues from Discussion Paper and Draft Guidelines

Guideline 1 (efficacy) of the draft NHMRC guidelines on animal-to-human transplantation provides for an assessment of the efficacy of proposed animal-to-human trials as follows:

Any proposed clinical (animal-to-human) xenotransplantation trial must be based on preclinical (animal-to-animal) studies that demonstrate therapeutic benefit to the participants.

The Discussion Paper provided information on the scientific background to animal-to-human transplantation, the obstacles that need to be overcome for it to be successful (Discussion Paper, Chapter 4), and the current state of research, in both animal-to-animal studies and animal-to-human trials, on each type of xenotransplantation procedure (external, cellular and organ). The issue of how to assess the evidence of benefit was discussed briefly in Section 5.6 and the Xenotransplantation Working Party (XWP) posed the following question:

Is it possible to define a reasonable criterion for success in animal-to-animal studies, on which progression to phase I clinical trials (animal-to-human) can be based?

The submissions received indicated that there is not a consensus on the criteria to use to judge the success (efficacy) of animal-to-animal or animal-to-human trials. However, respondents expressed considerable concern about the lack of evidence for benefit from xenotransplantation procedures that are currently being studied in animal-to-animal studies (particularly whole organ transplant research) and in the human clinical trials currently under way (mainly in the United States).

These concerns centred around the scientific rationale for such research, the validity of animal-to-animal studies as a model for human research, and the very limited benefits seen in any of the animal-to-human trials to date, especially in view of the infectious disease concerns associated with the procedures. These issues are described in detail below for animal external therapies, animal cell therapies and animal organ transplants.

Infectious disease risks are discussed in detail in Section 9 of this Response Paper.

Scientific methods and obstacles

Animal external therapies

8.1 As described in paragraphs 3.3 and 3.14, animal external therapies (AETs) are procedures that involve removing cells or tissues from the transplant recipient and treating them in a way that involves contact with cells from the transplant donor before returning them to the recipient.

8.2 One such potential therapy involves the perfusion of blood from patients with liver failure through a pig liver cell perfusion device so as to ‘buy time’ while waiting for a suitable liver allotransplant. The use of a whole pig liver for such perfusion invokes an immune response similar to that described for animal organ transplants (AOTs; see paragraphs 8.8–8.22), which means that the pig liver is quickly destroyed, preventing effective perfusion of the patient’s blood. However, the use of isolated liver cells in perfusion columns (bioartificial livers) does not cause such a strong immune response, thus allowing time for effective perfusion to occur.
8.3 Functional or anatomical barriers, such as those described for AOTs (see paragraphs 8.13–8.22), are less important for an external, short-term bridging procedure, and animal-to-human transplantation trials to date have shown that animal cells used externally in this way can remain functional (see paragraphs 8.35–8.40).

8.4 Another type of external therapy that has received a lot of attention is the growth of a layer of skin that can be used as a skin graft. Such skin layers can be grown from a patient’s own skin cells using a culture of animal cells as a feeder layer. Skin grown from the patient’s own cells is less likely to be rejected than other artificial grafts but can attach and function in the same way as other skin grafts.

Animal cell therapies

8.5 Animal cell therapies (ACTs) are defined in paragraphs 3.3 and 3.15–3.17. Proponents of these therapies have indicated that transplantation of isolated animal cells or cell clusters has the potential to treat many metabolic and genetic diseases associated with specific cellular dysfunction, including type I diabetes, Parkinson’s disease, Huntington’s chorea and other neurological disorders, as well as for repairing damaged tissues or organs, thus avoiding more invasive surgery.

8.6 As described in Section 5.3 of the Discussion Paper, the problems of immune rejection are not as severe for ACTs as for AOTs, especially if the cells are placed away from direct contact with the blood circulation or contained within a capsule made from a biological substance, such as agarose or collagen. ACTs can provoke an immune rejection response, however, and recipients of such transplants require immunosuppression. To minimise this response, researchers are testing a variety of chambers and microcapsules to contain the cell clusters, and new immunosuppression regimens and other methods to reduce the immune response.

8.7 Physiological and anatomical barriers such as those described for AOTs are less of a problem when very specific cell types are used. Early trials have shown that pig cells can survive and remain active for some time after transplantation into humans (see paragraphs 8.44–8.48).

Animal organ transplants

8.8 Animal organ transplants were defined in paragraphs 3.3 and 3.18–3.19. There are major obstacles to such interspecies transplantation, as was shown by the succession of failed attempts from the 1960s to early 1990s. However, the advent of modern biotechnology and the shortage of donated human organs for transplantation has encouraged researchers to try again. For AOTs to be successful, however, researchers need to prevent immune rejection and also ensure that the organ functions properly in the human recipient.

Immune rejection

8.9 As discussed in Section 4.3 of the Discussion Paper, when whole organs are transplanted from native (ie not genetically modified) pigs to primates, including humans, they are rejected within minutes or hours. This is because the cells of all animals apart from the higher primates (including baboons, chimpanzees and humans) are coated with a sugar (‘αGal’). This sugar stimulates a powerful innate immune response that causes very rapid,
‘hyperacute’, rejection (HAR) of the transplanted organ followed by a further so-called ‘delayed xenotransplant rejection’, or DXR (although it is still very rapid).

8.10 To overcome this problem, researchers have been using genetic technology and interbreeding to produce a strain of ‘gene knockout’ pigs that do not have αGal on their cells (see paragraphs 5.44 and 5.55 for further information about genetic modifications of pigs). This has provided hope that HAR and DXR will be overcome, especially when elimination of αGal is combined with other genetic modifications to pigs to make their organs more compatible with humans. Other methods of modifying immune responses are also being investigated. This work is still at an early stage but progress is being made and more recent pig-to-nonhuman primate organ transplantation studies have shown some slight improvements in survival times (see Table 8.3).

8.11 However, as noted in the Discussion Paper and confirmed by some of the respondents, even if the initial powerful immune responses are overcome, the immune system still presents major obstacles to AOTs:

> It is important to note that the issues of subacute and chronic rejection have not really been overcome at all. This again highlights that fact that any transplantation that will be done in humans is not very likely to have any therapeutic benefit in those individuals receiving the transplant. *A/Professor Peter Collignon (Submission X063)*

8.12 Certainly, if the transplant survives the initial HAR and DXR responses, it will be subjected to the same adaptive rejection processes that occur for human-to-human organ transplants (ie cell-mediated and chronic rejection). This may prove to be a more powerful rejection response than that seen for human organ transplants (HOTs). We will not know how big a barrier to successful xenotransplantation this will prove to be until HAR and DXR are overcome.

**Anatomical and physiological barriers to AOT**

8.13 The Discussion Paper explained that other major obstacles to AOTs include anatomical problems (eg structural issues, such as the size and growth rate of the animal organs) and physiological problems (eg biochemical, pharmacological and endocrinological factors that affect whether the transplanted animal products can function properly). However, Section 4.2 of the Discussion Paper stated that ‘there appear to be no insurmountable physiological barriers to the use of pig hearts and kidneys’ and that ‘life-preserving pig heart and kidney transplants have been performed in baboons without obvious major physiological incompatibility’.

8.14 Several respondents thought that this assessment of the issues facing researchers was too simple and that, in fact, very considerable obstacles need to be overcome before whole organ xenotransplantation will be successful:

> … the statement in Section 4.2 (p36) ‘Life-preserving pig heart and kidney transplants have been performed in baboons without obvious major physiological incompatibility’ glosses over the stark details of mean survival times provided later in Section 5.2.2 (p51–52). *Individual (confidential) (Submission X059)*

8.15 Indeed, as described in Section 5.2.2 of the Discussion Paper, pig-to-baboon kidney, heart, lung and liver transplants performed to date have all been lost due to immune rejection within short time spans (mostly less than one month, with a maximum of three months), which may not be enough time for anatomical or physiological problems to show up.
8.16 Some respondents described potential anatomical and physiological problems in greater detail.

Incompatibilities in the complex cascade of reactions which leads to blood clotting will also tend to trigger organ failure, with possible fatal consequences. The blood vessel walls of a pig not only activate human clotting factors by more than one process, they also suppress normal anti-clotting mechanisms. This means that as a patient’s blood circulates through the pig xenograft, blood clots may form continually. (Respondent details confidential)

Subtle differences in molecular structures of key proteins may be sufficient to render pig organ transplants in many clinical settings involving complex signals and pathways ineffective. Dr Anthony Raizis (Submission X034)

8.17 Submission X017 included a report prepared jointly with the British Union for the Abolition of Vivisection (Animal Organs in Humans: Uncalculated and Unanswered Questions). This report includes a detailed literature review on whether animal organs can sustain human life. Some other respondents also described the potential problems for each organ (see paragraphs 8.18–8.21).

8.18 A pig kidney may not be able to handle the levels of uric acid found in the human bloodstream, so a human patient with pig kidneys may be prone to kidney stones or kidney failure. Also, the renal hormones formed in a pig kidney may not be able to control blood pressure as the human hormones would, and may also produce an antibody response.

8.19 For the heart, it is essential that a grafted heart matches in size the needs of the recipient. This may be difficult with animal organs. Even within different breeds of pigs, heart weight-to-bodyweight ratios can vary significantly. An animal heart will need to pump the right volume of blood round a human body at the right pressure. Despite a faster heartbeat, a pig’s heart normally pumps lower amounts of blood per minute than required by a human patient. If the output of the heart is too low, multiple organ failure and death would result.

8.20 For lungs, the problems revolve around the size of the organs and gas exchange. If the organs are too small, there may be persistent leakage of gases and fluid; if they are too large, there is a risk of collapse. Gas exchange depends on many features, including the rate of air movement through the lungs compared to the rate of blood circulation. In a human these rates are balanced, but in a patient with a pig’s lungs the rates will be mismatched, which may be fatal.

8.21 For pig livers, there may be major problems for transplant into humans because pig livers have different metabolic pathways from those of the human liver (eg due to different dietary sources, essential foodstuffs and biochemical activities). As a result, the recipient may require genes for many hepatic functions that are not found in the pig liver cells.

8.22 The Xenotransplantation Working Party (XWP) has been advised that researchers in the field are aware of these issues, which will be tested more formally when the immunological barriers are overcome. For some organs, such as the liver, major obstacles are expected because of the complex functions they perform; researchers are not actively pursuing studies on these organs. However, researchers hope that pig hearts and kidneys may function appropriately despite the significant size and other incompatibilities between the two species (Dobson and Dark 2002).
Use of genetically modified pigs

8.23 Pigs can be genetically modified using a variety of gene insertion, silencing or cloning methods (see paragraphs 5.43–5.55 for a more detailed description of these methods). These ‘founder’ pigs are then bred normally to produce a stable ‘line’ with the required genetic modification. Researchers believe that this approach will help to overcome many of the obstacles to AOTs, and also improve the outcomes for AETs and ACTs.

8.24 Some respondents to the Discussion Paper expressed concerns about the efficacy of using transplant products from genetically modified (particularly cloned) pigs, because the health profile of such animals is still largely untested:

Apparently healthy cloned animals may have undetected abnormalities. This raises serious questions about the safety of the technology whether for the animals themselves or for human use of food, pharmaceuticals or organs derived from them. Cloning experts believe there is a need for a full evaluation of the health of cloned animals. (Respondent details confidential)

The historical record of genetically engineered animals … is that they often have inherent health problems and high death and failure rates … As the microinjection process [used to create transgenic animals for xenotransplantation] is not always an efficacious one, genes can often fail to reach the correct cells within the embryo and this can cause painful abnormalities and death …

Animals Australia (Submission X079)

8.25 Animal welfare issues associated with genetic modification procedures are discussed in paragraphs 5.99–5.109. However, transgenic and cloning procedures are only used to produce the founder generation of pigs, which are then used for normal breeding of subsequent generations of pigs for xenotransplantation. Researchers hope that any genetic abnormalities identified in founder pigs can therefore be screened out and that other possible problems may be overcome by cross-breeding.

Animal-to-animal studies

8.26 Researchers are working out the science of xenotransplantation in a step-by-step way, using laboratory studies (eg cell cultures) and small-animal studies (eg mice, rats, rabbits). This is the same approach as used for other medical research (eg cancer research, new drug development). The difference for xenotransplantation research is that, once promising results are obtained using laboratory and small animal studies, researchers must undertake animal-to-animal studies that more closely simulate the situation that will occur in human clinical trials. This most commonly involves studies of pig-to-nonhuman primate transplants.

8.27 The submissions reflected the concern many people feel about animal-to-animal studies involving nonhuman primates. This includes concern about animal welfare and ethical considerations about the status of nonhuman primates and the source and number of animals that are being used in this way. These issues are discussed in detail in Section 5 of this Response Paper.

8.28 The submissions also raised the possibility that primate experiments yield limited, if any, useful information that is relevant to the safety or efficacy of animal-to-human transplantation in humans. For example:
It is disheartening that the NHMRC guidelines call for more gruesome pig-to-primate experiments to be conducted in Australia. They should not proceed. Hundreds of these experiments have already been performed, and are ongoing around the world with dubious outcomes. Researchers have acknowledged that such experiments may not provide information relevant to the safety or efficacy of xenotransplantation in humans, and that nonhuman primates are poor models for humans. *Campaign for Responsible Transplantation (Submission X067)*

8.29 On the other hand, some researchers and medical professionals indicated that pig-to-baboon studies are a good model for pig-to-human transplantation. For example:

> Large animal studies are helpful, and the use of nonhuman primates in this regard may provide useful data. The reasons for this is that they (especially old world monkeys), like humans, possess preformed antibodies to gal alpha 1,3, gal, and hence the rejection process is akin to that which would be expected to occur in humans.

*Professor Bernie Tuch (Submission X016)*

8.30 Overall, most researchers in this field agree that the preclinical testing of xenotherapies can best be carried out using primates, particularly baboons, as recipients. The immune incompatibilities between pigs and baboons are very similar to those seen between pigs and humans. Furthermore, primates provide the only realistic model to test the effect of genetic manipulations in pigs that have been designed to work in humans.

8.31 Professor Tuch also expressed concern that the researchers in Australia may be restricted to using only baboons for animal-to-animal studies. He thinks this would be unwise because the supply of baboons in Australia is limited and might not meet xenotransplantation demands. He noted that baboons are only one example of Old World monkeys, all of which have preformed antibodies, and that many xenotransplantation researchers overseas are using other Old World monkeys (eg cynomolgus monkeys).

8.32 The Transplantation Society of Australia and New Zealand endorsed this view:

> While it is recognised that baboons are probably the best current recipients for preclinical studies, it is also considered that their limited availability in this country will place inordinate and quite possibly impractical constraints on any proposed clinical trials in xenotransplantation. The guidelines need to allow for some flexibility — for example, other old world monkeys (eg cynomolgus) may be deemed suitable if the investigators provide suitable evidence; or the possibility of other suitable animal models to test certain aspects of the xenoresponse should be considered.

*Transplantation Society of Australia and New Zealand (Submission X053)*

8.33 The use of primates other than baboons in xenotransplantation research is discussed in paragraph 4.42.

8.34 The XWP felt that any xenotransplantation therapy should be tested in baboons before human trials can be undertaken. Furthermore, the working party noted that this view is shared by most of the comparable regulatory authorities overseas and by the International Xenotransplantation Association. The XWP realises that, in many circumstances, these experiments will occur overseas.
Effectiveness of animal therapies

Animal external therapies

Bioartificial livers

8.35 Section 5.4 of the Discussion Paper discussed the use of animal liver cells in bioartificial liver devices (Hepatassist devices). Researchers hope that AETs such as liver perfusion can provide life-saving temporary liver function for people waiting for a liver transplant (see paragraphs 8.1–8.4).

8.36 Bioartificial liver devices to treat acute liver failure have been extensively tested in animal models over many years, with promising results. Since the 1960s, whole pig, calf and baboon livers have been used intermittently to externally perfuse blood from patients with liver failure, but such trials have been largely discontinued because of concerns about infection and problems of immune rejection.

8.37 Since the 1990s, the United States Food and Drug Administration (FDA) and relevant regulatory authorities in some European countries have approved small clinical trials of bioartificial liver devices. Examples of these trials are shown in Table 8.1. There were some improvements for patients with liver failure and successful bridging to liver transplants. However, the preliminary trials did not include any controls (ie patients who received normal intensive care rather than external liver perfusion), so it is impossible to know whether the similar results represent a true benefit of the bioartificial liver treatment or not.

Table 8.1 Examples of animal-to-human external liver perfusion studies using bioartificial liver devices with pig liver cells for patients with liver failure

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Results</th>
<th>Study/country</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Some improvement and 18/21 participants suitable for liver transplant were successfully bridged to a transplant</td>
<td>Chen et al (1997), Watanabe et al (1997) United States</td>
</tr>
<tr>
<td>7</td>
<td>Improved symptoms and 6/7 successfully bridged to a liver transplant. No severe adverse events</td>
<td>Morsiani et al (2002) Italy</td>
</tr>
<tr>
<td>7</td>
<td>6/7 successfully bridged to a liver transplant. 1/7 recovered. No severe adverse events</td>
<td>van de Kerkhove et al (2002) The Netherlands</td>
</tr>
<tr>
<td>10</td>
<td>A significant improvement in symptoms. All bridged to a liver transplant but 2 died after transplantation. No severe adverse events</td>
<td>Samuel et al (2002) France/Germany</td>
</tr>
</tbody>
</table>

a No controls

8.38 Importantly, the use of pig liver cells in the bioartificial liver devices tested has not caused significant adverse effects, suggesting that AETs may be one of the first viable animal-to-human transplantation procedures to reach clinical practice.

8.39 As indicated in paragraphs 6.35–6.36, similar research is being done using human liver cell bioreactors. As expected, human liver cells have been shown to give better outcomes for bioartificial liver therapy than pig liver cells (Pascher et al 2002). However, human liver cells are usually only obtained as offcuts from liver surgery or other liver transplants, so there are significant problems of availability.
A systematic review by the Cochrane Collaboration Hepato-Bilary Group showed some overall benefit of artificial and bioartificial liver support systems compared with standard medical therapy (Kjaergard et al 2003). However, at this stage we do not know which of a number of possible procedures will be the most effective.

**Skin grafts**

Growth of skin grafts on animal cell feeder layers provides a valuable technique for producing skin for the treatment of burns victims and other skin graft recipients. This technique has been trialled, in several countries, including Australia, since the 1980s with promising results (Stoner and Wood 1995, Carsin et al 2000, Elliot and Vandervord 2002).

**Animal cell therapies**

Since the mid-1990s, much xenotransplantation attention has focused on ACTs (see paragraphs 8.5–8.7). Research on human cell therapy is in its early stages, but preliminary animal-to-animal studies and animal-to-human trials have shown some encouraging results, with good survival of the cellular transplants and minimal unwanted side effects.

**Animal-to-animal studies**

There have been numerous animal-to-animal ACT studies carried out to date (further details of these studies were given in the Discussion Paper, Section 5.3). The ACTs have not caused unwanted side effects in the recipient animals, and in some studies the transplanted cells have not been rejected and have remained viable. Some functional improvements have been recorded in the recipient animals, although these have often been slight and poorly defined because of relatively low numbers of animals in the trials or lack of controls.

**Animal-to-human trials**

Because some success has been achieved in animal-to-animal ACT studies, the United States FDA and the relevant authorities in Europe have approved a number of animal-to-human (clinical) trials of ACT. Some of these trials were described in Section 5.3 of the Discussion Paper but some respondents criticised this section for lacking important information, such as patient numbers. Table 8.2 therefore shows a summary of all the clinical studies that have been attempted to date.
Table 8.2  Examples of pig-to-human cell therapy trials to date

<table>
<thead>
<tr>
<th>Pig cells</th>
<th>Recipients/indication</th>
<th>Site</th>
<th>No. of patients</th>
<th>Results (MST)</th>
<th>Country/study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encap neonatal pancreatic islets</td>
<td>Type 1 diabetic</td>
<td>Peritoneal cavity (in alginate capsules)</td>
<td>6</td>
<td>Some evidence of graft function in 2 patients reported</td>
<td>New Zealand Elliot et al (2000)</td>
</tr>
<tr>
<td>Fetal pancreatic islets</td>
<td>Type 1 diabetic (adolescents)</td>
<td>Subcutaneous (into preformed vascularised collagen tube)</td>
<td>12</td>
<td>In progress; some improvements reported in media</td>
<td>Mexico</td>
</tr>
<tr>
<td></td>
<td>Focal epilepsy</td>
<td>Brain</td>
<td>3</td>
<td>1 improved</td>
<td>United States</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>Brain</td>
<td>5</td>
<td>2 no effect</td>
<td>United States</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 improved</td>
<td>United States</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 strokes (trial discontinued)</td>
<td>United States</td>
</tr>
</tbody>
</table>

Note: Detailed information about some of these trials is not yet available as the trials are still in progress or the full data have not been published.

8.45  Although these early trials have reported some improvements, the results are difficult to interpret at this stage because of the lack of control subjects in some trials and the small numbers of subjects involved.

8.46  Some respondents to the Discussion Paper thought that these results, combined with the animal-to-animal data, did not show enough improvement to warrant further clinical (animal-to-human) trials, particularly in the light of potential infection risks (see Section 9 of this Response Paper). For example:
The track record [for xenotransplantation] shows effectively no success to date. In the single case reports, where there may be some benefit, my view is that no control group has been used and it is well known that with sham surgery (eg for Parkinson’s disease) as well as in newly diagnosed diabetics themselves, there is a marked fluctuation in the natural history of these diseases, including apparent dramatic responses. A/Professor Peter Collignon (Submission X063).

In the case of islet xenotransplantation, the level of benefit demonstrated in the previous clinical trial and in nonhuman primate studies is not, in our view, sufficient to justify further clinical trials using the same approach. We believe that demonstration of long-term freedom from insulin requirements would be needed in a nonhuman primate study of porcine islet transplantation before a clinical trial using a particular approach could be justified. International Transplantation Association (Submission X077)

8.47 Another respondent also raised the possibility that the few improvements recorded in a handful of ACT trials (ie for Parkinson’s disease) could be the result of a strong placebo effect. This highlights the importance of trials that include either placebo controls or comparison with another treatment.

8.48 The XWP agreed that the available data do not support the view that ACT is necessarily an effective treatment for Parkinson’s disease or type 1 diabetes. Nevertheless, the clinical trials to date have provided some encouragement for researchers. For example, in many cases, the cells survived well in the recipient, were not rejected and did not cause unwanted side effects. Further animal-to-animal research is being carried out to find out how to promote function as well as survival of the cells. While this may well be a very steep learning curve, the obstacles are not as great as for whole organ transplantation.

Animal organ transplantation

8.49 Animal organ transplantation was first tried at the beginning of the twentieth century and there have been many attempts since that time. Table 5.1 in the Discussion Paper showed a summary of the main human trials of whole organ transplants that have been carried out since the 1960s. At this time, human organ transplantation (HOT) was also being developed. Like HOT, AOT was carried out in an attempt to save the lives of patients with potentially fatal organ failure. With the exception of one remarkable case reported by Reemtsma et al (1964), in which a chimpanzee kidney functioned for nine months after transplantation to a young woman, xenotransplants failed within a few weeks due to immune rejection.

8.50 When HOT procedures were improved in the 1970s and 1980s, and other medical procedures, such as kidney dialysis, were also improved, AOT was not trialled further.

8.51 Research on AOT recommenced in the 1990s as the demand for organ transplants outpaced supply. However, the potential infectious risks of live animal tissues, particularly tissues from nonhuman primates, became apparent at about the same time. This infectious risk meant that nonhuman primates were no longer considered to be suitable donors for AOT. Researchers therefore turned their attention to pigs as the source animals. However, the use of transplantation products from pigs causes more serious problems of rejection and malfunction than the use of products from nonhuman primates. A single pig-to-human heart transplant carried out in the early 1990s survived for less than one day.
Animal-to-animal studies

8.52 Since the early 1990s, there have been many studies of animal-to-animal whole organ transplants. With the advent of genetic modification technologies, researchers have made considerable progress in genetically modifying pigs, in an attempt to overcome the most severe forms of immune rejection. The first stage has been to introduce the genes for human complement regulation.

8.53 Table 8.3 shows a summary of animal-to-animal studies of AOT that have been carried out to date (further details were given in the Discussion Paper, Section 5.2). Clearly, these studies show only short survival times, even when the recipient animals were heavily immunosuppressed, their blood was treated to remove antibodies that might cause rejection and, in some cases, their spleens were removed to further suppress their immune response. These short survival times were noted by some respondents:

The creation of genetically redesigned pigs has been met with dismal failure, with no significant advances in over five years. The big obstacle of transplanting complex organs such as kidneys or liver from pigs to primates appeared to be the violent immune response known as hyperacute rejection, in which grafted tissues are starved of blood. Despite this problem having been to some degree overcome, the transplanted organs still don’t survive. No matter how many immunosuppressants the primates have pumped into them, none of the modified pig organs lasted more than two months. Dr Anthony Raizis (Submission X034)

8.54 However, researchers argue that the results show an increase in survival times from a baseline of minutes or hours, to days or weeks, and that these times will continue to improve as the science is better understood and new modifications are made to the donor animals, the immunosuppressive drug regimens and other ancillary treatments.

8.55 The XWP acknowledges that pigs expressing human complement regulatory genes alone are not suitable for clinical trials, particularly for AOT. Although these pigs have answered important biological questions, they are not the definitive answer on genetic manipulation for animal-to-human transplantation. The studies showed that preventing complement activation was of benefit but anti-αGal antibody and thrombosis remain major obstacles.

8.56 Further genetic manipulation strategies to overcome these issues are currently being developed. For instance, pigs have been modified to silence (knockout) the genes responsible for producing anti-αGal antibodies (see paragraphs 8.9–8.10) but transplant products from these pigs have not been tested in animal models yet. This will take time as pigs have relatively long gestation periods and take seven months to reach sexual maturity. However, in most of these areas there is ongoing progress.
<table>
<thead>
<tr>
<th>Organ</th>
<th>Recipient</th>
<th>Donor pigs</th>
<th>Other treatment</th>
<th>Results (MST)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>Baboon</td>
<td>Non-GM GM</td>
<td>Imm</td>
<td>30-90 minutes 7.6 days (max 15 days)</td>
<td>Diamond et al (1997)</td>
</tr>
<tr>
<td></td>
<td>Baboon</td>
<td>Non-GM GM</td>
<td>Imm</td>
<td>45 minutes 7.5 days (6–10 days)</td>
<td>Lawson et al (1997)</td>
</tr>
<tr>
<td></td>
<td>Baboon</td>
<td>Non-GM GM</td>
<td>Imm</td>
<td>6.5 days (8 hours –30 days)</td>
<td>Zaidi et al (1997)</td>
</tr>
<tr>
<td></td>
<td>Baboon</td>
<td>Non-GM GM</td>
<td>Imm + splenectomy</td>
<td>5 days (max 15 days)</td>
<td>Schmoeckel et al (1998)</td>
</tr>
<tr>
<td>Heart</td>
<td>Baboon (heterotopic)</td>
<td>Non-GM GM</td>
<td>Imm</td>
<td>30-90 minutes 5 days (max 15 days)</td>
<td>Diamond et al (1997)</td>
</tr>
<tr>
<td></td>
<td>Baboon (heterotopic)</td>
<td>GM</td>
<td>Imm + Ig depletion</td>
<td>Max 29 days (with no HAR or DXP in 5/6 animals) and animals died of other complications</td>
<td>Lin et al (1998)</td>
</tr>
<tr>
<td></td>
<td>Baboon (orthotopic)</td>
<td>Non-GM GM</td>
<td>Imm + Ig depletion + splenectomy</td>
<td>30 hours 5 days 12 hours to 10 days</td>
<td>Kroskus et al (1997)</td>
</tr>
<tr>
<td></td>
<td>Baboon (orthotopic)</td>
<td>Non-GM GM</td>
<td>Imm</td>
<td>5: &lt; 24 hours (technical failures) 5: 4–9 days (2 x complications; 3 x DXP)</td>
<td>Bhatti et al (1997)</td>
</tr>
<tr>
<td></td>
<td>Baboon (orthotopic)</td>
<td>GM</td>
<td>Imm</td>
<td>5 days 26 days</td>
<td>Bhatti et al (1998)</td>
</tr>
<tr>
<td></td>
<td>Baboon (unilateral)</td>
<td>Non-GM GM</td>
<td>None</td>
<td>30 minutes 5 hours 17 hours</td>
<td>Daggett et al (1997)</td>
</tr>
<tr>
<td></td>
<td>Baboon (orthotopic)</td>
<td>Non-GM GM</td>
<td>Ig depleted</td>
<td>Rejected by HAR 4–8 days (no HAR; failed metabolically)</td>
<td>Ramirez et al (1999)</td>
</tr>
</tbody>
</table>

MST = mean survival time; GM = genetically modified (with human complement regulation genes); Imm = immunosuppressed (usually with three immunosuppressive drugs); Ig deleted = immunoglobulins (including $\alpha$-Gal antibodies) removed from blood; splenectomy = spleen removed; orthotopic = organ replaces recipient’s organ; heterotopic = transplanted organ does not replace recipient’s organ.

Notes: GM pigs were all modified to include at least one and up to three human complement regulator genes. Since the Discussion Paper was prepared, $\alpha$-Gal knockout pigs have been bred but no results have yet been published about the survival of organs from such pigs in pig-to-baboon studies.
8.57 There is also a better understanding of the pathogenesis of hyperacute rejection and the gene manipulations required to overcome these problems, and there have been considerable improvements in methods to genetically modify pigs. Some researchers have therefore suggested that the rate of development may accelerate in the near future. On the other hand, after reviewing the alternatives, UKXIRA (2001) concluded: ‘It seems, therefore, that the likelihood of whole organ xenotransplantation being developed within a clinically worthwhile timeframe is increasingly remote’.

**Definition of therapeutic benefit**

8.58 Draft Guideline 1 (efficacy) required that any clinical trials of animal-to-human transplantation must ‘demonstrate a therapeutic benefit to the patient’. Further discussion of therapeutic versus nontherapeutic research is given in paragraphs 3.24–3.30 of this Response Paper. It is stressed that it is the intention of the XWP that clinical trials should not be allowed to proceed unless a real therapeutic benefit is demonstrated in animal-to-animal studies and that the ‘bar’ should be set high for assessment of such effects.

8.59 Section 5.6.1 of the Discussion Paper highlighted the difficulties of defining ‘success’ in animal-to-animal or animal-to-human transplantation research. In particular, it stressed that, because of difficulties with animal-to-animal studies and interpretation of the results, there is a point where little or no further progress can be made without proceeding to a clinical trial. The XWP asked if it was possible to define a reasonable criterion for success in animal-to-animal studies, on which progression to clinical trials (animal-to-human) can be based.

8.60 Responses to this question varied. Some respondents did not think it was possible to set specific criteria and stressed that any such assessment would need to be made case by case:

No. This must be a purely subjective decision and left to the regulatory authority to make the decision. Armadale Health Service Ethics and Research Committee (X048)

It is our position that these criteria should not be predefined, but should be determined on an individual basis. International Xenotransplantation Association (Submission X077)

8.61 The Gene Technology Advisory Committee (GTAC) of the Health Research Council of New Zealand acknowledged that assessment may be needed on a case-by-case basis but nevertheless felt that this should be done within internationally agreed, peer-reviewed criteria:

It is important that preclinical [research] is analysed to meet international peer review standards. Are primate studies needed? … These decisions we believe need to be made by GTRAP/GTAC on a case-by-case basis as they will vary from one type of XTP to another. It will be important to review the burden of evidence. Criteria will be needed and will need to be published. Gene Technology Advisory Committee (Submission X088)

8.62 Other respondents suggested that clinical trials should not be permitted unless animal-to-animal studies have achieved a defined level of effectiveness:
… there needs to be some defined criterion for success in animal-to-animal studies on which progression to phase 1 clinical animal-to-human trials can be based. For example, a survival time of months rather than days or weeks. However, this would be a matter for experts, but underlines the need for the inclusion of animal-to-animal studies in the regulatory model. Gene Technology Ethics Committee (Submission X084)

It should be possible to reasonably define criteria, at least for pig-to-human xenotransplantation. Phase I studies should not proceed until such criteria are clearly stated. NSW Health Department (Submission X090)

8.63 In the Discussion Paper, the XWP proposed that, if animal-to-human transplantation research were to go ahead, it would be the responsibility of a national committee on xenotransplantation to assess proposals for trials and to thoroughly review all the preclinical data before approving a clinical trial. Researchers would not be able to start a clinical trial until they had convinced the national committee it was warranted. The XWP purposely avoided being overly prescriptive about the level of effectiveness of the preclinical studies. There were several reasons for this:

- The level of effectiveness will vary depending on the type of transplant. For instance, the criteria would be different for an AET (e.g. Hepatassist device) and an AOT (e.g. heart transplant).
- Issues other than the overall length of survival are important. The reasons for the death of the animal and the cause of graft failure are likely to affect the decision as much as the length of survival.
- Meaningful long-term survival should be demonstrated, but the interpretation of this could be left to the experts on the national committee, who would be in a better position to assess the potential benefits against current available alternatives.

8.64 However, the evidence would have to be comprehensive enough to convince such a committee, and the levels of evidence presented would have an impact on any decision. For instance, published data in respected peer-reviewed journals would be more persuasive than small series of unpublished results. Such a committee would be in a position to demand to review all the data from relevant studies and request information beyond that seen in any publication.

8.65 Clearly, benefits to the patient from animal-to-human transplantation procedures would need to be compared to all possible therapeutic alternatives in terms of both quality and quantity of life. For example, some of the conditions for which cellular transplantation is being considered can be treated by other means (such as insulin treatment for diabetes, dialysis for renal failure or dopamine treatment for Parkinson’s disease).

8.66 However, there are patients with diabetes, renal failure or Parkinson’s disease who have failed conventional therapy and for whom there is no therapeutic alternative, or who have considerably reduced quality of life. Also, many older people do not survive indefinitely with kidney dialysis: median survival time (50%) is 7.3 years for 45–54-year-olds, 4.6 years for 55–64-year-olds and 3.1 years for 65–74-year-olds (ANZDATA 2002) and some patients are no longer able to dialyse because of lack of access. Therefore, if there is a viable animal therapy available, it may be possible to select a subgroup of patients for whom the potential benefits would be worth the risk.
8.67 Other side effects of the therapy (such as the known serious side effects of immunosuppression) would also need to be taken into account in both the decision to allow a trial and individual patient selection.

8.68 The XWP considers that these issues highlight the importance of having guidelines in place, supported by a regulatory system and with strong international links to ensure that, if possible, the same principles are also applied in other countries. Because of the checks and balances that such guidelines would provide, it would be hard for clinical trials to gain approval without substantial preclinical data supporting efficacy. In addition, initial trials would be registered with the Therapeutic Goods Administration’s Clinical Trial Exemption Scheme (see paragraphs 11.14–11.16). This would add an additional layer of audit, oversight and emphasis on quality control.

**Conclusion**

8.69 Animal-to-animal transplantation research is occurring in all developed countries, funded by biotechnology companies as well as medical research institutions and national and international funding bodies. Some animal-to-human transplantation trials of AETs and ACTs have also been carried out or are in progress in the United States and Europe. The results so far do not show clear benefits of the therapies but there have been some improvements and few adverse events.

8.70 Further advances in gene technology, such as the recent development of an α-Gal knockout pig (see paragraphs 8.9–8.10 and 8.56) are allowing the development of new approaches to overcome the obstacles to human xenotransplantation. The next few years will be crucial in this respect. If no real progress is made, researchers may not find it worthwhile to continue with xenotransplantation research.

8.71 Similarly, if other approaches such as stem cell research, gene therapy or artificial systems yield more promising results over this timeframe, these alternative therapies may overtake animal therapies as the preferred option. However, none of these approaches have delivered a successful therapy at this stage and it is not possible to predict which therapy, if any, is more likely to be better and safer than others for a particular condition in the future. Rather, the XWP proposes that, to ensure the best outcomes for the patients concerned, all clinical trial proposals, including animal-to-human transplantation, should be evaluated against other routine and experimental therapies available at the time to ensure that patients are offered the procedure that offers the most prospect of benefit for their condition.

8.72 Finally, the NHMRC is concerned to make sure that if any animal-to-human transplantation trials proceed on this basis, they occur within a framework that ensures the highest ethical standards possible for the animals and humans involved and that protects the safety of the community at large.
9 Risks of infection (safety)

Overview of issues from Discussion Paper and Draft Guidelines

All procedures involving living tissues carry the risk of infections. The major concern for animal-to-human transplantation is that infectious disease agents (particularly viruses) from animal products may infect transplant recipients. Such viruses may initially cause no obvious signs of disease and spread into the general population before the infection is identified and contained. Therefore, in addition to risks for animal transplant recipients themselves, there are potential health risks for close contacts, carers and the general public. Such risks must be assessed and weighed against the benefits of animal-to-human transplantation, and options considered for their management.

The Discussion Paper (Chapter 6) openly discussed the infectious risks associated with animal-to-human transplantation; Draft Guidelines 2, 5, 6 and 7 provided for the assessment and management of health risks associated with such procedures, as follows:

Guideline 2 (Safety):

The public health risks of any proposed animal-to-human xenotransplantation trial must be minimal and must be acceptable to the community.

Guideline 5 (Monitoring and surveillance):

The research protocol must include processes based on the most up-to-date procedures available. It must also show that resources and facilities are available for the timely monitoring and surveillance for public health risks of research participants and, if required, their close contacts.

Guideline 6 (Data and tissue storage):

The research protocol must include procedures which, when followed, ensure that:

(a) all research participants are informed about, and have consented to, their clinical data being entered on a central register maintained by the national committee; and

(b) the necessary clinical data are collected to enable future analysis; and

(c) all necessary tissue samples are collected and securely stored for an appropriate period to allow tracing of public health risks.

Guideline 7 (Management of public health risks):

The research protocol must include procedures for the management of public health risks if they should occur (such as an emerging infectious disease), including an appropriate policy of containment.

The Discussion Paper indicated that risk analysis methodology could be used to assess proposed animal-to-human transplantation trials on a case-by-case basis. However, as this is an emerging area, the XWP acknowledged that criteria to assess risks have not yet been defined. The working party posed the following question:

Are there clear criteria that should be used or developed to allow decisions to be taken about infectious risks involved in human trials of xenotransplantation?

The submissions indicated that the potential for a new infectious disease to cross the species barrier from animals to humans is of great concern to many members of the public, as well as to a proportion of researchers and medical practitioners. Such fears are very real and many respondents expressed concern that another deadly viral disease such as HIV/AIDS may sooner or later emerge if animal-to-human transplantation research is allowed to proceed.

Hence, it was clear that respondents to the public consultation require very high standards of safety for animal-to-human transplantation research. Any risk that a novel infectious disease could emerge and trigger a new epidemic is clearly considered not acceptable, especially given the limited benefits that animal-to-human transplantation procedures currently offer. These issues are discussed in more detail in this section.
Main community concerns

9.1 Many respondents to the public consultation expressed their concerns about infectious risks associated with animal-to-human transplantation, in terms of comparisons with previous infectious disease disasters. The following are typical extracts:

There is a frightening potential for viruses to cross the species barrier if these sorts of transplants become the norm. We need not tell you that the AIDS and influenza viruses are both of animal origin. It places not only the recipients of the organs at risk but the rest of us also … we believe that the risk far outweighs the perceived benefits.

*Naomi and Michael Mairou (Submission X013)*

Pigs, the preferred donor animals are notorious sources of zoonosis, including anthrax, botulism, influenza, rabies, salmonellosis, swine vesicular disease and many others. A recent example that animal diseases can and do cross the species barrier has been proven most vividly by ‘BSE’ [bovine spongiform encephalopathy] or mad cow scares throughout the world … The deadly human influenza virus of 1918 that killed more than 20 million people worldwide was a mutation of a swine flu virus …

*Astrid Herlihy (Submission X066)*

9.2 For these and other respondents, the risk of a new infectious disease emerging in humans, however small, is not acceptable: their preferred approach would be not to permit animal-to-human transplantation research at all.

9.3 Such concerns were not confined to people without professional involvement in transplantation medicine, microbiology or other related fields. Medical professionals also expressed concerns:

In the last century we have witnessed the swine flu epidemic of 1918 and the Malaysian Nipah virus of 1998. The swine flu epidemic caused the deaths of millions of people. The Nipah virus infected hundreds of people, killing over one hundred, and resulted in 1 million pigs having to be destroyed … Moreover, only one AIDS-like variant is required in order to give rise to a major catastrophic event.

*Dr Anthony Raizis (Submission X034)*

9.4 The International Xenotransplantation Association was also frank in its admission of the potential risks:

However, potential pathogens which have not been previously identified and which therefore cannot be screened for, and particularly those that do not cause disease in their non-human hosts, still impose a potential risk to humans under such conditions. Viruses that do not cause disease in their original hosts may modify themselves once transmitted to humans and become severely pathogenic. HIV-1, which originated from non-human primate species, is an example of such a virus.

*International Xenotransplantation Association (Submission X077)*

9.5 Hence, for the general public and some professionals alike, the ‘worst-case scenario’ was expressed in terms of a comparison with an HIV/AIDS-like epidemic. The Xenotransplantation Working Party (XWP) shares these concerns. It intends that the NHMRC guidelines will provide a regulatory mechanism to prevent research that has not clearly shown minimal risks, and to manage the risks of research that is permitted.

9.6 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.
General infection risks from animal-to-human transplantation

Known disease agents

9.7 Animal-to-human transplantation procedures are likely to be associated with the same wide range of viral, bacterial and other infections that are associated with human-to-human transplantation and its accompanying immunosuppressive drug therapy. The Discussion Paper (Section 6.3) stated that such diseases could be dealt with in the same way as for human-to-human transplantation (ie rigorous screening of donor animals, and appropriate treatment of transplant recipients in the event of an infection occurring).

9.8 However, a number of respondents were concerned that known pig diseases may be a greater problem than indicated in the Discussion Paper. For example, the Armadale Health Service, Western Australia noted that the Discussion Paper did not include a discussion of all the pig diseases that may be important in animal-to-human transplantation:

Apart from a few viruses with emphasis on porcine retrovirus, other pathogens that can be potentially transmitted from pigs to humans are not mentioned … there is no suggestion that the committee is aware of the protozoa such as Toxoplasma, Cryptosporidium, Neospora all of which are of zoonotic significance and common in pigs in Australia. Armadale Health Service, Western Australia (Submission X048)

9.9 The United Kingdom Department of Health has published a review of infection risks in animal-to-human transplantation (Muir and Griffin 2001). The review lists all the viruses, bacteria, fungi and parasites that are found in pigs and, of these, those that are known to also cause disease in humans (zoonoses), particularly in an immunosuppressed host. The list is a long one. However, it is a compilation of all the disease agents that pigs are known to be susceptible to, not a list of all the agents that are found in every pig. Most individual pigs can be expected to have none or very few of these disease agents at any one time, in the same way as humans do not carry all the disease agents that could be listed for human diseases (mumps, chickenpox, measles, hepatitis, HIV, influenza, tuberculosis, salmonella and so on).

9.10 The United Kingdom review highlighted the fact that human-to-human transplantation physicians have a long history of minimising the risk of infection from the many human disease agents that could infect transplant recipients, and managing infections when they occur.

9.11 However, it is certainly the case (as stressed by several respondents) that any pigs used for animal-to-human transplantation would need to be free of major infections, including those of significance to immunocompromised patients:

A herd of pigs free of specific pathogens will need to be developed and quality controlled according to very strict protocols. The specific pathogens will need to include those of significance to immunocompromised humans. As an example the protozoan parasite Cryptosporidium is of minor importance in healthy humans but very important in AIDS sufferers (various strains of Crypto are also very prevalent in Australian pigs). Armadale Health Service, Western Australia (Submission X048)

9.12 The XWP acknowledged the broad spectrum of diseases associated with pigs and the need for very closely controlled conditions for rearing pigs for use in animal-to-human transplantation trials. However, the working party noted that the United States Food and Drug Administration (USFDA) has developed detailed guidelines for industry on the
animal husbandry requirements for rearing pigs for use in animal-to-human transplantation (USFDA 2003; see paragraph 3.41). The United Kingdom’s Xenotransplantation Interim Regulatory Authority is developing similar guidelines (UKXIRA 1999; see paragraph 3.39). Most regulatory authorities agree that strict adherence to such animal husbandry guidelines will prevent infection of transplant recipients with these agents.

**Novel and evolving disease agents**

9.13 As indicated in the United Kingdom review of infectious risks (Muir and Griffin 2001), however, more serious public health concerns about the risks of animal-to-human transplantation relate to the possibility of new, not currently known, infectious organisms emerging and infecting humans. Indeed, there are numerous examples of viruses that appear to have emerged over recent years. These organisms can be divided into those that are newly recognised (ie that have been around for a long time but have remained undetected) and those that are genuinely newly emerged.

9.14 Many respondents were concerned about the long-term potential for emergence of new and dangerous viruses:

> Unlike drugs that have a limited biological half-life, latent zoonotic infectious agents that can propagate via permissive human tissues without necessarily causing viraemia may be stable for the lifetime of the recipient. More importantly, time is the one thing that the viruses will have plenty of, to increase the likelihood of forming a rogue variant. Dr Anthony Raizis (Submission X034)

9.15 Such emerging viruses pose a particular problem because they may not be diagnosed with current tests and, by definition, their pathogenic behaviour is unknown. Recent experience with Hendra, bat lyssa, Nipah and Menangle viruses demonstrates the potential for continued emergence of new zoonoses from unexpected sources (Mackenzie 1999). Viruses are of most concern in this respect because they may be difficult to identify, there may not be effective therapies against them and they have various routes of transmission. Certain pig viruses may have the potential, if given the opportunity, to infect new host species such as humans through a process of adaptation (eg rotavirus, influenza).

9.16 The animal husbandry guidelines developed by the USFDA and UKXIRA (see paragraph 9.12) include detailed guidelines for minimising the risk of novel or evolving infections. The measures recommended include maintaining a closed herd (to allow close monitoring and containment of any new infections), regular screening using validated state-of-the-art tests, and adherence to strict infection control guidelines.

9.17 The XWP agreed that while these measures would be helpful in identifying any novel or emerging infections in the source animals, careful case-by-case risk analysis would also be required for animal-to-human transplantation trial proposals. This analysis would need to ensure that the proposed protocol does not involve any unacceptable infection risks, takes full account of all relevant animal husbandry guidelines and includes procedures to manage any infections if they should occur.
Porcine endogenous retrovirus (PERV)

The issue

9.18 The retrovirus family of viruses is a large and diverse group of viruses that includes the immunodeficiency viruses (eg human immunodeficiency virus, or HIV; and simian immunodeficiency virus, or SIV), the T-cell lymphotropic viruses (HTLV, STLV), various leukaemia viruses (eg gibbon, cat, mouse), human foamy virus and others.

9.19 Active (or exogenous) retroviruses are transmitted in various ways, including ‘horizontally’ from animal to animal in a population via sexual contact or blood, and ‘vertically’ from mother to offspring. A feature of this group is their ability to move across species barriers and emerge in the new species with a different pattern of disease and mode of transmission. For example, SIVs are transmitted horizontally between monkeys in the wild and are not associated with clinically apparent disease. However, following transmission to other nonhuman primates or to humans, clinical disease occurs and the modes of transmission may change. Most scientists now believe that this is what happened with HIV and possibly also with HTLV.

9.20 Pigs do not have any known active retroviruses, which is why researchers initially thought that they would be a good source of animal transplantation products (compared to nonhuman primates, for example, which have a number of active retroviruses). However, it is now recognised that pigs carry an inactive (or endogenous) retrovirus called porcine endogenous retrovirus, or PERV (see Discussion Paper Section 6.3.3). Endogenous retroviruses are integrated into the genome of their host and only replicate with the genome. They are passed vertically from generation to generation as inactive proviruses. They are present in many animal species, including humans, nonhuman primates and pigs.

9.21 In some circumstances, endogenous viruses become active and produce infectious virus particles that cause disease. Such activated retroviruses can remain clinically latent in the host for a long time before emerging to cause varying types of disease. They can also be transmitted to others by various routes (often different from the routes of transmission in the animal host).

9.22 The XWP has attempted to be frank and honest about this risk scenario, which is a credible potential risk to public health. However, the magnitude of the risk is the subject of considerable debate among experts (see paragraphs 9.23–9.28).

The evidence

9.23 Central to the debate about PERV is research that shows that, to date, of over 200 human patients who have received animal-to-human therapies, none has become infected by PERV. The patients included 160 external-device patients who were specifically tested for PERV up to 12 years after the procedures. However, many of these patients were found to have some pig cells circulating in their bloodstream, which was unexpected (Paradis et al 1999).

9.24 Some experts have cited the presence of circulating pig cells in the patients in Paradis’s study as evidence that the patients have been ‘infected’ with PERV (Collignon and Purdy 2001). However, this is not strictly the case as the evidence only shows the ongoing presence of pig cells (microchimerism), not that PERV has been activated and transferred.
to the human transplant recipients. However, the continuing presence of the pig cells means that the potential for infection remains.

9.25 As reported in the Discussion Paper (Section 6.3.3), in the past two years, researchers have reported that when they mixed pig cells with human cells in the laboratory, the human cells became actively infected with PERV and were able to infect other cells. This raises the possibility that, if such active transfer can occur in laboratory cell cultures, it could also occur in transplant recipients at any time in the future while live pig cells are in contact with human cells in the recipient’s body. Other researchers have also reported PERV viral expression (activation) in pig-to-mouse transplant experiments (Van der Laan et al 2000).

9.26 Furthermore, genetic modifications of pigs that make their cells and organs more compatible with humans may also create conditions that allow the emergence of retroviruses in transplant recipients. For instance, in order to overcome the problems of hyperacute rejection (Discussion Paper, Section 4.3.2), researchers have genetically modified source pigs to delete a cell surface sugar called alpha-galactose (α-Gal), which is one of the main triggers for the immune rejection response. However, this sugar is also the first line of defence for humans against invading microorganisms. If pig cells carrying PERV are modified so that their cells do not have their usual sugar coating, any virus particles produced and secreted by these cells will be packaged up without an α-Gal coating. Such virus particles may not be recognised by the human immune system and may be more likely to cause an infection than virus particles that have their natural sugar coating.

9.27 However, further research is being carried out to improve knowledge of PERV and related viruses, including their possible mechanism of activation in human cells and the likely infective properties of active strains. Alternatively, some researchers are turning their attention to pig breeds (eg ‘minipigs’) that do not carry the type of PERV genome that has been shown to infect human cells in culture.

9.28 Tests are also being developed to screen for any possible early signs of virus infectivity in transplant recipients so that measures can be taken well ahead of the emergence of an active virus to prevent the spread of a novel infection.

**Therapy-specific considerations**

*Animal external therapies*

9.29 If animal external therapies are perfected so that no animal cells are transferred to the recipient during a procedure, the risk of transferring PERV or other pathogens may be considered minimal. If an active disease agent is transferred during the procedure, it is likely that disease would be seen or the presence of the disease agent would be detected quickly. However, it may be difficult to rule out transfer of a disease agent that remains dormant for many years before emerging and causing disease; each procedure would therefore need to be carefully reviewed on a case-by-case basis.

*Animal cell therapies*

9.30 In animal cell therapies (ACTs), risks may vary according to the procedure used. For example, encapsulation of the transplanted cells may help to block the transfer of any infectious agents from the transplant to the recipient, and also avoid the need for
immunosuppression (thus reducing the susceptibility of the recipient to infection). However, Dr Anthony Raizis mentioned the need for caution about the assumption that encapsulation of pig cells before implantation into a human recipient would protect the recipient from possible pig infectious agents:

There are several alginate-based membranes used for microencapsulation in xenotransplantation clinical trials. Alginate/aminopropyl-silicate/alginate (Alg/AS/Alg) membrane is the latest technology to emerge, which is more stable than the well-known Alg/poly-L-lysine (PLL)/Alg microcapsule. However, even after just 30 days of soaking in simulated body fluid, the percentages of intact microcapsule were 98% and 88% respectively. Such results indicate that current microencapsulation techniques will not be sufficiently robust to contain infectious agents, which remain viable for as long as the transplant. Dr Anthony Raizis (Submission X034)

**Animal organ transplants**

9.31 Animal organ transplants (AOTs) present the highest risk of infection because more tissue is transplanted than in ACTs and because of the higher level of contact between animal and human tissues, including direct association with the blood supply of the recipient, which would continue over the long term if the transplant were successful. Also, the high level of immunosuppression required for the transplant recipient would increase their susceptibility to infection should an activated disease agent emerge.

9.32 With our current knowledge of infection risks, such procedures could therefore only be allowed under extremely strict infection control guidelines.

9.33 However, other problems and obstacles associated with AOTs (such as overcoming hyperacute rejection reactions and ensuring the functioning of the transplant) mean that such procedures are unlikely to progress to clinical trials for several years to come. By that time, researchers may know more about PERV and related viruses and a decision will need to be made in the light of knowledge at that time.

**XWP response**

9.34 It is clear that the lack of consensus about the interpretation of the current research evidence on viral infection risks will make decisions about proposed research very difficult for some time to come. This position was echoed by some respondents who felt that animal-to-human transplantation research should not be allowed until the risk of infection has been better researched:

It is of grave concern that the risks associated with xenotransplantation have not yet been fully researched. It is recommended that before xenotransplantation research takes place in animals to humans, more analytical research is conducted to assess the risks of transfer of infective particles. Human Research Ethics Sub-committee, Department of Human Services, SA (Submission X055)

9.35 The XWP envisages that the role of the national xenotransplantation committee, working according to NHMRC guidelines, will be to engage the necessary expertise to independently review the evidence in detail and to assess animal-to-human transplantation proposals case by case, in the light of the most recent research evidence as it becomes available.
How safe is safe?

Risk analysis

9.36 The Discussion Paper (Section 6.6) described a risk analysis framework that could be used to assess the risks associated with animal-to-human transplantation procedures. This would require the research applicant (investigator) and sponsor of a proposed trial to submit data on risk analysis as indicated in the Advice section of the Draft Guidelines and Discussion Paper (pages xxv–xxx). The national xenotransplantation committee would assess submissions case by case.

9.37 The XWP acknowledged that this would be a difficult task and that there are no existing criteria that can be used to allow decisions to be taken about infectious risks involved in human trials of animal-to-human transplantation. The working party posed the question:

*Are there clear criteria that should be used or developed to allow decisions to be taken about infectious risks involved in trials of xenotransplantation?*

9.38 There were no direct responses to this question, although several respondents commented on the risk analysis framework overall. For example:

> Thought especially needs to be given to whether the risks are acceptable and whether people will be willing to consent to taking those risks. … There is little currently known about the risk of infection to the recipient of xenotransplanted organs and beyond that to others. The limits of the medical system to deal with any unforeseen infections/diseases are not known and still need to be investigated further. The Committee would like to see a significant amount of research carried out to investigate such risks to determine whether in fact xenotransplantation will be beneficial.

*Human Research Ethics Sub-committee, Department of Human Services, SA (Submission X055)*

9.39 The Gene Technology Ethics Committee commented on the need to assess any risks that may arise from the use of genetically modified animals:

> The Discussion Paper does appear to suggest that there is a potential for additional risks in these cases [when the animal is genetically modified], although in the risk analysis section of the document (chapter 6) there is only brief mention of risk analysis for xenotransplantation from genetically modified sources (page 71, paragraph 2 & p 73, 6.5 paragraph 2). While it is possible that the general risk analysis framework captures these risks adequately, the Discussion Paper could highlight more obviously how any special infection risks from xenotransplantation involving genetically modified source animals (identified in 4.5, 4.5.1 and 4.5.2) are adequately addressed within the risk analysis framework.

*Gene Technology Ethics Committee (Submission X084)*

Risk versus benefit

9.40 Many respondents stressed that the risk of a new infectious disease emerging is too high a price to pay for the unproven benefits of animal therapies to date. The following statements are typical of the responses on this issue:
The draft guidelines do not include any statement demonstrating a benefit to the human population which would outweigh the potential risks … The draft guidelines contain many statements which indicate that there are too many unknown factors in xenotransplantation to allow any confidence in the safety of the procedures, even under the best circumstances and with heavy regulation.

*Maren Child (Submission X030)*

I think the risk:value ratio is too high … It seems to me that on balance the biological unknowns make the risks too high when there are other ways already at the experimental stage nearly ready to go to Phase 1 trials.

*Emeritus Professor David Allbrook (Submission X039)*

9.41 An important aspect of risk assessment is the seriousness of the consequences, or impact, if the risk event occurs. A level of risk for an event that poses relatively minor consequences is clearly much more acceptable than an equivalent level of risk for an event that has very serious consequences. Clearly the outcome of the infectious disease risk scenario for xenotransplantation has the potential to be extremely serious, so even a very low level of risk is much less acceptable than for a less serious threat.

9.42 As noted in paragraph 9.35, the XWP envisages that the role of the national xenotransplantation committee, working according to NHMRC guidelines, will be to engage the necessary expertise to independently review the evidence in detail and to assess animal-to-human transplantation proposals on a case-by-case basis, in the light of the most recent research evidence and risk analysis.

**Risk management**

9.43 Factors that affect the risk of infection, from both known and potential zoonoses, include the conditions under which source animals are reared, genetic modification of source animals, how the xenotransplantation product is produced, what health care infection control procedures are used during and after the procedure, the type of procedure involved, and the level of immunosuppression of the patient. These issues all need to be taken into account in assessing potential for exposure to infection, and any investigator undertaking animal-to-human transplant trials would be required to submit documented procedures that address these issues.

**Source animal husbandry and production of animal transplantation products**

9.44 The Discussion Paper (Section 6.5.1) indicated that good manufacturing practice principles will need to be applied to xenotransplantation products to minimise infection risks. They should specifically include documented procedures to detect potential infectious agents, the maintenance of pedigreed source animals in specific pathogen-free environments, assessment of personnel who manage the animals and prepare the xenotransplant products, assessment of safeguards for the transport of animals and/or xenotransplantation products, and continued monitoring for infectious agents. Many of these procedures do not apply to animals used for food production.

9.45 Some respondents were sceptical about how easy it would be to achieve this:
Pigs currently grown for meat in Australian factory farms have infection rates of no less than 90% of Pleuropneumonia. They have rates as high as one third infected with proliferative enteritis, a disease caused by a campylobacter-like organism that is responsible for the majority of food-poisoning cases in humans … Breeding pigs have been identified by the Queensland Dept of Primary Industries as the source of most introduced disease problems in Australian piggeries [Quotes from ref by Cutler and Spencer]. Sarah MacNabb (Submission X002)

9.46 As indicated in the Discussion Paper, there are precedents for the type of vigilance that will be required for the production of xenotransplantation products. Examples are the blood transfusion service and existing procedures to minimise the risk of infection through human-to-human transplantation procedures.

Screening and monitoring of infectious agents

9.47 It has been widely agreed that if animal-to-human transplantation research is permitted, post-transplantation clinical and laboratory surveillance will be essential. Transplant recipients would need to be evaluated for life for transplant-related adverse events. This monitoring would need to be done within a framework of accredited laboratory facilities and using validated test methods, as described in the Discussion Paper (Section 6.5.3).

9.48 Some respondents were concerned that the Discussion Paper did not give enough detail of the proposed monitoring processes and recipient registry:

The monitoring of xenotransplantation therapeutic research needs to be clearly defined in terms of what has to be monitored, in how much detail and by whom. … The monitoring of the impact of xenotransplantation on recipients and close contacts over time will require the establishment of a registry and possibly an associated tissue bank. Consideration will need to be given to monitoring methods, such as how, what and when data and tissue is to be collected and stored, the possible future uses of the data and tissue, privacy and confidentiality issues, and capital and recurrent resourcing. This registry and tissue bank will require statutory protection. A mechanism should be established whereby relevant HRECs are kept informed of the progress of the monitoring of recipients and close contacts.

NSW Health (Submission X090)

9.49 Some respondents cautioned about the practicalities of these procedures, including the considerable cost, optimal location, and appropriate duration of archiving patient specimens. The issue of the degree to which close contacts should be monitored and their specimens archived is also unclear.

9.50 Furthermore, the assays for PERV have been under continual development, and, as assay sensitivity and specificity improves, the necessity of re-analysing previously studied samples should be considered. The development of an internationally standardised assay for PERV is an important goal. This would also apply to any other new organism identified as a risk in xenotransplantation.

9.51 The XWP agreed that detailed arrangements will be needed for the oversight of animal-to-human transplantation clinical trials, including monitoring and surveillance, and maintenance of a register of transplant recipients and contacts. These issues are discussed in detail in Section 10 of this Response Paper. All animal transplant recipients would need to be recorded on a national xenotransplant register and their information updated regularly (see paragraph 11.80).
**International cooperation**

9.52 As infectious agents do not respect international boundaries, there will be a need for a high level of international cooperation so that animal-to-human transplantation research carried out anywhere in the world does not pose a threat to the whole world.

9.53 The International Xenotransplantation Association suggested that to combat ‘xenotourism’ there would also need to be a register of xenotransplant recipients who had received a xenotransplant overseas:

This ['xeno-tourism'] is where a person receives a transplant in one country and then moves to another either permanently or as a visitor. The problem is the potential dissemination of a viral infection … We think that individuals should be questioned about xenotransplantation upon entry to a country, and that receipt of a xenotransplant should become ‘reportable’; to public health authorities so that appropriate monitoring may be instituted in the country of residence … we note that this has not been addressed by other countries, but we will endeavour to draw this to their attention. *International Xenotransplantation Association (Submission X077)*

**Management of an infectious disease incident**

9.54 The Draft Guidelines indicated that animal-to-human transplantation research protocols should include procedures for the management of a public health risk if an adverse event occurs, including measures for appropriate containment. Section 6.5.4 of the Discussion Paper discusses measures that would need to be considered. The Australian Infection Control Association commented on this section as follows:

We would like to see the infection control component more explicit and defined … Methods of transmission of any new virus/bacteria [is] unknown therefore infection control measures need to cover all modes of transmission … Restrict xenotransplantation to limited facilities who have a multi-disciplinary infection control team. The recipient must have a single room with own ensuite and adequate handbasins ie in the room and outside room. The respiratory route may be a factor for transmission of a new virus/bacteria therefore consideration needs to be given to negative pressure rooms with airlocks incorporated. *Australian Infection Control Association (Submission X093)*

9.55 The XWP agrees that these aspects of a trial protocol need to be carefully defined. The working group envisages that detailed infection control guidelines would form part of the guidance documents that would need to be developed by the national regulatory agency responsible for xenotransplantation (see Section 11).

**Conclusions**

9.56 Like other animals, including humans, pigs carry many disease agents. Most of these are well known to microbiologists. Although some can infect humans, it is widely agreed that, with careful husbandry of the animals, good manufacturing practice for preparation of transplantation products and prudent management of transplant recipients, based on the same principles as those used to minimise infections in human-to human transplants, there should not be a significant risk of dangerous infections in animal transplant recipients. The same considerations would apply to other source animals.

9.57 However, some disease agents have only recently been identified and are less well known. These include the endogenous retroviruses, such as PERV, which are inactive in
the source animal genome but may become active in the transplant recipient. In the light of the submissions received, it is clear that the risk of such a virus becoming active and emerging as a novel infectious disease in humans is a very serious concern for the community. For many people, such a risk appears unacceptable, especially when the benefits that can be delivered through animal therapy procedures are uncertain.

9.58 However, the researchers stress that since concerns were first raised about the potential infective risk of PERV much has been learnt about its potential infectivity for humans and how this could be managed. Tests have also been developed to monitor transplant recipients for infection.

9.59 The XWP therefore considers that a careful risk analysis should be required for each research proposal for animal-to-human transplantation. The analysis should include the following components:

- evidence of benefit for the procedure under consideration;
- characterisation of PERV and other relevant infectious agents from the source animals, including the amount of the agent (titre), potential infectivity of human cells and the ability to evade the immune defence of the transplant recipient;
- characterisation of procedure-specific factors that will influence risk (see paragraphs 9.29–9.33);
- an estimation of the magnitude of the risk involved for the procedure (including a statement of any uncertainties in the available data); and
- a clear risk management strategy, including monitoring of patients and close contacts, appropriate infection control guidelines and a strategy for handling noncompliance with these requirements.

9.60 Trials with an unacceptable level of risk should not be allowed to proceed.
10 Managing animal-to-human transplantation trials

Overview of issues from Discussion Paper and Draft Guidelines

The potential risk of infections associated with animal-to-human transplantation raises important ethical issues for clinical trial management, particularly in relation to definition of the trial participants, information giving and consent, and monitoring and surveillance requirements.

Chapter 7 of the Discussion Paper addressed these issues, starting with consideration of who should be considered to be research participants in such a trial. The Xenotransplantation Working Party (XWP) proposed that close contacts of the transplant recipient should not be considered to be ‘participants’, although they would need to be closely involved in the information-sharing and decision-making process. This position was reflected in Draft Guidelines 3 and 4:

Guideline 3 (Information giving):

The research protocol must include:

(a) clear patient information sheets that allow potential research participants to make an informed decision about the proposed procedure; and
(b) procedures which, when followed, ensure that appropriate information and counselling are provided to potential participants and that no coercion is used; and
(c) procedures which, when followed, ensure that appropriate information and counselling are provided to close contacts, including carers, of the xenotransplant recipient; and
(d) procedures which, when followed, ensure that research participants and their close contacts, including carers, are aware of the need for ongoing and long-term follow-up and surveillance for possible emerging personal and public health risks.

Guideline 4 (Consent):

The research protocol must include:

(a) procedures which, when followed, ensure that the consent of potential research participants is obtained after the necessary information is provided (Guideline 3) and which allow the participant to take a reasonable period to think things over and discuss the information provided with their close contacts; and
(b) consent forms that clearly set out what is being consented to, including the need for ongoing and long-term surveillance for possible emerging personal and public health risks; and
(c) procedures for collection of signed information sheets (or equivalent) from close contacts of research participants.

Because the definition of research participant is a difficult issue in the context of animal-to-human transplantation, however, the XWP posed the question:

*Do you agree that only xenotransplant recipients themselves, and not their close contacts, should be regarded as ‘research participants’?*

Most respondents to this question considered that close contacts of the transplant recipient should be included as research participants and that their consent should be required before the trial is carried out. The definition of research participants is discussed further in paragraphs 10.1–10.11. Many respondents also stressed the need for a process of broader public consultation and ‘consent’ commensurate with the risk to the community.

To ensure that the key issues relating to informing and consulting with close contacts of transplant recipients had been covered in the discussion paper, the XWP also posed the question:

*Does the discussion adequately cover the key issues for informing and consulting with close contacts of xenotransplantation research participants?*
Responses to this question related to the definition of a close contact, the type of consent they would be giving (ie whether they would be actively involved in the decision about whether a trial should go ahead or not) and close contacts who may not be in a position to make an informed choice (such as young children, the aged or the mentally ill). This is discussed further in paragraphs 10.20–10.22.

The Discussion Paper highlighted the need for long-term monitoring and surveillance of research participants and close contacts, which was reflected in Draft Guidelines 5 and 6 (see Section 9 of this Response Paper). However, the XWP acknowledged the ethical difficulties inherent in this approach and requested input from the community to the following questions:

Are trials that require lifelong monitoring and follow-up for emerging infectious diseases acceptable?

Do you agree that there should be an ethical and social responsibility on the research participant to remain in the trial for long-term follow-up?

Is it acceptable for close contacts of a research participant to be identified and screened before the trial and contacted and tested if a novel infection emerges at a later date?

On the whole, respondents thought that whatever measures possible should be taken to ensure that participants and their close contacts would remain in the trial for long-term follow-up and that opting out should not be an option. Screening and testing of close contacts were seen as essential to any management strategy. These issues are discussed further in paragraphs 10.29–10.39.

Who are the ‘research participants’?

10.1 Section 7.1 of the Discussion Paper considered the issue of who should be considered to be a research participant in an animal-to-human transplantation trial. The Xenotransplantation Working Party (XWP) argued that although the National Statement on Ethical Conduct in Research Involving Humans (National Statement; NHMRC 1999) defines participants as including ‘those upon whom the research impacts, either concurrently or retrospectively’, it was not necessary to include close contacts of animal transplant recipients as ‘research participants’ because it would not be practical to rely on the long-term involvement of close contacts.

10.2 The issue of who should be considered a research participant drew many responses. Most did not support the XWP view that close contacts should not be considered as research participants. Two reasons were put forward: the risk to the rest of the community if they should contract an infectious disease from the transplant recipient, and their right to say ‘no’ to a trial that could have an adverse impact on their health and freedom. In addition, several respondents noted that the scope of the National Statement (quoted on page 80 of the Discussion Paper) appeared to include close contacts: ‘Close contacts should also be regarded as research participants, they should be included in the protocol as such and they should be fully consented and monitored. NSW Health (Submission X090)’

If close contacts are required to be monitored and undergo testing, then they must be considered participants. It states that the working party have not defined close contacts as participants because ‘it is not practical to rely on the involvement of contacts.’ I don’t care if it’s practical – practicality is not the issue and the National Statement should not be re-interpreted simply because it doesn’t suit the agenda of XT supporters … The scope and definition of ‘participants’ [in the National Statement] clearly involves close contacts as well, and to disregard this is misleading and dishonest. Kerrie Donaldson (Submission X092)
10.3 The Gene Technology Ethics Committee, which agreed with this position, also thought that making close contacts research participants would encourage their long-term participation:

Making [close contacts] research participants may encourage their long-term involvement and follow up. Since they are also the conduit for infection to the wider community it is important to impress upon them the importance of long term follow up. Gene Technology Ethics Committee (Submission X084)

10.4 Some respondents took an opposite view (ie that close contacts should not be considered participants):

Consideration needs to be given from whom consent is required. This should be the recipient and his/her partner. Other close contacts, for example, parents, should also be involved in the discussions, but ultimately it is not their decision. What is required of them is that they follow the guidelines re blood collection etc. The involvement of their son/daughter in the trial should not require their consent, although this would be helpful. Professor Bernie Tuch (Submission X016)

10.5 Others thought it was an issue that needed to be explored further:

… the issue is not whether they are to be included as research subjects, but whether there is duty of disclosure in relation to them. They might not have the right to withhold consent from the patient participating as a research subject, but they do have a right to know that the patient may become infectious with a new type of human infection and then might be infectious to them. Whether the relatives also have a right to refuse consent would seem to depend on the nature of the relationship. It has been in the past thought, for instance, in relation to sterilization, that marriage confers certain rights such that the consent of the spouse is required in relation to sterilization. Dr Nicholas Tonti-Fillipini (Submission X001)

10.6 Some respondents proposed that criteria need to be developed to define a ‘close contact’. NSW Health (Submission X090) argued that close contacts should include sexual partners, close friends, family and health care workers. Offspring born subsequent to the transplant would also need to be included.

XWP response

10.7 The XWP agrees that the definition of participants in an animal-to-human transplantation trial is complex. These issues were already taken into account in the draft guidelines on safety, monitoring and surveillance, data and tissue storage, and management of public health risks (see Section 9: Overview of Issues from Discussion Paper and Draft Guidelines).

10.8 To comply with revised draft Guideline 3 (Safety) (see revised draft guidelines included at the end of Section 12 of this Response Paper) and the accompanying advice, researchers would be required to submit a detailed analysis of the risk of infectious disease emergence and spread for the particular procedure to be trialled. Different risk considerations would apply to each type of animal-to-human transplantation therapy (external, cellular or organ), which are discussed in paragraphs 9.29–9.33. The trial protocol would also need to include a plan indicating how any identified risks would be managed.
Further definition of close contacts may vary from procedure to procedure. The XWP therefore considered that such definition should form part of the risk management plan for a particular trial protocol.

Furthermore, the XWP noted that any attempt to include close contacts as research participants would undermine the autonomy of the person who was making the decision about their own treatment.

Close contacts would need to be identified as appropriate for a particular procedure and provided with detailed information about the trial, including the need for prospective record keeping to enable tracking for monitoring and surveillance in the future if required. However, contacts should be considered as research participants for the purposes of complying with compensation and insurance arrangements under the National Statement and international good clinical practice guidelines (see paragraphs 7.39–7.40).

Selection of research participants

Selection of research participants is an important issue for any clinical trial. The National Statement, Section 1 requires researchers to design research so that the selection, recruitment, exclusion and inclusion of research participants are fair. It also requires that each research protocol be designed to ensure that respect for the dignity and wellbeing of the participants takes precedence over the expected benefits to knowledge. Other sections of the National Statement provided further guidance on the selection as research participants of children or young people, people with an intellectual or mental impairment, people who are highly dependent on medical care, and other groups where special care may be required.

When selecting participants for animal-to-human transplantation trials, an important issue that will need to be considered is whether there are other options available for potential participants, including conventional therapy or other alternative therapies (see paragraph 6.53), the need for immunosuppressive drug treatment (and any related long-term effects of this treatment), the expected outcome of the treatment, and any other relevant health and quality-of-life issues relating to the proposed treatment.

Information sharing and consent

Section 7.2 of the Discussion Paper discussed the issue of providing information and obtaining consent from potential animal transplant recipients. It was stressed that such decisions should be voluntary (free and uncoerced) and informed (based on a sound understanding of what is at stake). These principles, which are set out in the NHMRC General Guidelines for Medical Practitioners on Providing Information to Patients (NHMRC 1993) and the National Statement, require that great care be taken in the provision of information and obtaining consent from research participants.

A number of respondents expressed concern about the difficulties that may be experienced in obtaining genuinely voluntary and informed consent from seriously ill patients and their relatives. Pressures that will be faced by participants relate both to their own potential quantity and quality of life and to the risks to their close contacts.
... once the possibility of xenotransplantation exists, it will not simply be an uncoerced, voluntary choice for prospective recipients. A dilemma is created for them and this could cause great emotional and mental stress. Also, people who are terminally ill, will not be able to weigh the benefits to themselves against the risks for the community. Bernice Bovenkerk (Submission X052)

Strict guidelines will be required when obtaining informed consent to ensure a balance between the desires of a dying individual with no treatment alternative and the potential risks to the community of infectious diseases. At a minimum consent will be required from a participant and his/her partner. Transplantation Society of Australia and New Zealand (Submission X053)

10.16 The Federation of Ethnic Communities Councils of Australia stressed that information must be provided in the first language of the individual, through either interpreters or bilingual counsellors, as well as through translated information reference materials. These costs therefore need to be identified in the budget. The federation also stressed that researchers would need to take care not to make uninformed value judgments about a person’s suitability as a research participant, based on their religion or ethnic background:

... those involved in xenotransplantation research should not exclude individuals belonging to those faiths [for whom pigs are a taboo] from the opportunity to participate in the research by assuming a universal unwillingness to do so because of religious convictions. Nor should it be assumed that individuals identifying their country of birth or language as being one commonly associated with a particular faith necessarily belong to that faith. ... In every case, it must be up to the individual to make an informed decision. It is the obligation of the researcher to ensure that the individual is fully informed of the source animal of the organs and/or tissues for transplantation, as well as any risks involved in the research. The Federation of Ethnic Communities Councils of Australia (Submission X047)

10.17 Other respondents stressed the need to involve both the transplant recipient and their families in the information sharing and consent process:

With respect to the consent process we would advocate having all potential recipients and their families assessed by a consultation-liaison psychiatrist, in keeping with procedures applied to solid organ transplants. St Vincent’s Hospital Clinical Trials Centre (CTC), Sydney (Submission X056)

10.18 The need for counselling was also stressed:

The taking/giving of consent needs to be an extended process, independent counsellors must be available, and there should be an assessment of the emotional and cognitive impairment that potential participants are likely to be experiencing (to ensure that consent is fully informed). NSW Health (Submission X090)

10.19 Possible feelings of loss of identity that might be experienced by animal transplant recipients should be addressed during the information sharing process. Some respondents recommended that counsellors should be specifically trained on the psychosocial issues arising from animal-to-human transplantation:

It is important to ensure that these concerns [loss of identity] are managed through referral to bilingual counsellors [in the case of people who have English as a second language], such as those contracted by the NSW Transcultural Mental Health Centre to provide consultation on transcultural mental health issues. It is recommended that these counsellors who are qualified psychologists, social workers and nurses, be provided with training on psychological issues arising from xenotransplantation. Federation of Ethnic Communities Councils of Australia (Submission X047)
Some respondents did not think that the Discussion Paper adequately covered the key issues for informing and consulting with close contacts of animal-to-human transplant recipients:

Close contacts are likely to include people who are not capable of understanding the issues or making an informed decision, such as children, the aged and the mentally ill. Current and future contacts such as transient sexual partners may not be identified at all, or may be unwilling to cooperate. There is no opportunity for consent for future contacts such as a baby born into the family after the research commences or someone who becomes a carer for the research participant later when they become ill.  
*Maren Child (Submission X030)*

Others thought that the issues were covered, but with a note of caution from NSW Health:

Yes [the issues have been covered], but should be extended to fully informed consent. There is also a need to ensure that close contacts are not placed in a position of coercion. Issues will arise if the close contact(s) do not wish to participate in the research. A potential recipient should not be xenotransplanted unless both he/she and the close contact(s) consent. It would also be useful to have a clear definition of what constitutes a ‘close contact’.  
*NSW Health (Submission X090)*

The XWP agrees that if animal-to-human transplantation trials are to be allowed to proceed, protocols for information sharing and consent need to be extremely thoroughly prepared, taking account of the difficulties highlighted in the Discussion Paper and raised by respondents. However, not all of the issues raised will apply to all types of animal-to-human transplantation. Therapy-specific considerations are discussed in paragraphs 10.24–10.29.

Participants should also be clearly informed that, while they will retain their right to withdraw from the clinical trial itself at any time (ie to not receive any further medical treatment), they will not be able to withdraw their consent to long-term monitoring and follow up and will not be able to donate their organs or tissues to others in the future or after their death. Close contacts should also be made aware that they will not be able to withdraw from long-term surveillance (see paragraph 10.34 and 10.46–10.48).

**Animal external therapies**

Depending on the nature of the animal external therapy involved, the patient may or may not be terminally ill when invited to join the trial. Also, these therapies do not include invasive surgery on the patient, so there may be other options if the treatment is not successful.

The XWP considered that the information sharing and consent arrangements for AETs should be similar to those for research on other health technologies that do not carry significant additional risks for the patient and minimal infection risks for contacts.

**Animal cell therapies**

Although many of the potential participants in animal cell therapy trials will be suffering from serious diseases or conditions such as type I diabetes, Parkinson’s disease or spinal nerve damage, they may not be terminally ill at the time they are invited to participate in the trial.
A sensitive and thorough approach to information sharing will therefore be required, as for other health technology research, including discussion of the results of the infection risk assessment. This information should be provided in consultation with family and close contacts of the transplant recipient, who may be required to consent to long-term monitoring and follow-up.

Animal organ transplants

Patients who are considered for participation in a trial of animal organ transplants are likely to be very sick, with no other options for treatment. However, it has already been noted that no such trials are proposed at the current time or expected in the near future. If such a trial were proposed, the same approach would be required as that described above for animal cell therapies.

Ethics of monitoring and follow-up of trial participants and contacts

Is lifelong monitoring and follow-up acceptable?

Some respondents did not think that lifelong monitoring and follow-up of xenotransplant recipients (defined as research participants) and their close contacts would be acceptable. Some thought that it would not be possible anyway:

No. It is not possible to do this in real life. Research participants and their close contacts may become unwilling or unable to continue to cooperate.

Maren Child (Submission X030)

Some felt that the mere fact of asking for lifelong monitoring indicated that the potential risks were too great:

No – lifelong monitoring indicates that the risk is too high if participants need to be monitored for the rest of their lives for emerging diseases. If the lifelong monitoring was specifically related to the illness (i.e. lifelong management of epilepsy to lower the chance of the person having an epileptic attack) then that is acceptable – monitoring for infectious diseases reflects the high risk of XT.

Kerrie Donaldson (Submission X092)

Others expressed uncertainty:

There seems no alternative to life-long monitoring but it is hard to envisage how it can be managed and harder to judge how we would react in a worst-case scenario in which an Ebola-like disease emerged. Armadale Health Service Ethics and Research Committee (Submission X048)

Still others thought that lifelong monitoring would be acceptable, or should even be mandatory:

Yes, even though participants may be being asked to relinquish the right to privacy and the right to freedom of movement. This needs to be very clearly addressed in the consent process. NSW Health (X090)

Lifelong monitoring would not merely be prudent, but mandatory. I certainly agree that there is need both for ethical and scientific reasons for lifelong followup of xenotransplant recipients. David Allbrook (Submission X039)
10.33 The Gene Technology Ethics Committee also supported mandatory lifelong monitoring, but agreed that it might not be prudent to assume that participants will abide by such promises. However, the committee also pointed out that if participants were able to opt out of their commitment to ongoing surveillance, more attention should be paid to the investigators’ evidence of safety:

Xenotransplantation trials, at least in the initial period, should require life-long monitoring and follow up for emerging infectious diseases in both the recipients and their close contacts … If this is to be the prevailing position [that organ recipients should be allowed to withdraw from the ongoing surveillance], more should be made of the sort of evidence that the investigators could provide to show that there is no undue risk should some participants withdraw from the trial. This would need also to be summarised better in Guidelines. Gene Technology Ethics Committee (Submission X084)

10.34 The XWP noted that patients who are at greatest risk, such as cell or organ transplant recipients, would already be under a lifelong system of regular check-ups, monitoring of immunosuppression, and so on. Although patients would retain their right, under the Declaration of Helsinki and the NHMRC National Statement (NHMRC 1999a) to withdraw their consent for further medical treatment (ie to withdraw from the trial), they would not be able to withdraw their consent to long-term monitoring and surveillance or donate organs and tissues to others in the future or after their death.

Ethical and social responsibility of the research participant

10.35 Section 7.2.4 of the Discussion Paper suggested that, while investigators should make every effort to ensure that research participants maintain lifelong monitoring, transplant recipients would have an ethical and social responsibility to provide information on a long-term basis, even if the trial is unsuccessful. Respondents who answered this question agreed, but most qualified this with some concerns about the difficulties inherent in such follow-up. For example:

Yes, though I do not consider that it can or should be enforced. I believe that someone who has agreed to participate would have done so at an extremely vulnerable time, when their choices were extremely limited. We cannot force someone to participate in a lifelong trial, when the full details of this trial cannot be provided — only time will determine what the requirements of ‘participation’ will be. Kerrie Donaldson (Submission X092)

10.36 Some respondents were concerned that the current draft guidelines are too ‘soft’ on the issue of long-term follow-up and that reliance on the ethical and social responsibility of xenotransplant recipients to maintain long-term surveillance would not be adequate:

GTRAP acknowledges that it is unlikely that individuals can be compelled to observe a long term follow-up regimen. However, it is reasonable to expect patients to enter an XTP program with the knowledge that long term follow up is part of the overall medical care. An innovative, Australian based mechanism then needs to be developed to ensure patients, investigators and sponsors comply with long term follow up. Gene and Related Therapies Research Advisory Panel (Submission X041)

… not everyone in society is ethical or responsible. Some are exactly the opposite … Consequently, I would recommend that the guidelines contain the requirement that all xenotransplant recipients sign a legally binding document that they agree to their details being entered into a national database, and a thorough six-monthly clinical assessment that looks for a variety of specified signs and symptoms. This may also need to occur for the recipients’ immediate friends and family. (Respondent details confidential)
10.37 The International Xenotransplantation Association added:

… it will be essential to select research subjects who appear capable of fully understanding the potential impact of their behaviour on the rest of society, and who seem genuinely motivated to minimize these risks.

*International Xenotransplantation Association (Submission X077)*

### Is identification, initial screening and follow-up of close contacts acceptable?

10.38 Several respondents agreed that the identification, screening and follow-up of close contacts would be acceptable:

- It would have to be done if the research goes ahead, but it would be extremely intrusive and could not be effective as there would be contacts who would not cooperate or would not be identified. *Maren Child (Submission X03)*

- Yes, provided close contacts are fully consented and become a research participant. The screening should be part of the research proposal. *NSW Health (Submission X090)*

10.39 Others thought that this question contradicted the exclusion of close contacts from the definition of research participants:

- If close contacts need to be screened before the trial and contacted if infections emerge, then surely they fall within the scope of ‘*upon whom the research impacts, whether concurrently or retrospectively*’ (NHMRC definition of ‘participant’ on pg 80 of discussion paper). How can the working party truthfully conclude that people that require monitoring are not participants? *Kerrie Donaldson (Submission X092)*

### Privacy and confidentiality

10.40 Section 7.2.5 of the Discussion Paper noted that the need to inform a recipient’s contacts of the procedure gives rise to some special issues to do with privacy and confidentiality. It suggested that potential recipients should be clearly informed of these issues before their involvement in any trial. Respondents to the Discussion Paper supported this view. Some respondents commented on this issue:

- This [confidentiality] could be a particular issue where an individual wishes to participate in the research but fears a negative reaction from his/her community for religious or cultural reasons. *Federation of Ethnic Communities Councils of Australia (Submission X047)*

10.41 The Human Research Ethics Sub-committee of the Department of Human Services, South Australia, felt that the issue needed to be explored further:

- Xenotransplantation appears to have significant confidentiality issues that must be addressed before the debate progresses any further. *Human Research Ethics Sub-committee of the Department of Human Services, SA (Submission X055)*

10.42 The XWP believes that these issues are sufficiently covered by the National Statement.

### Costs and compensation

10.43 Cost and compensation issues are discussed in Section 7 of this Response Paper.
Ongoing patient care

10.44 The Consumers’ Health Forum (X086) noted that the Draft Guidelines did not include any guidance on ongoing medical care for animal-to-human transplant recipients:

… Further protocols relating to long-term patient care must accompany the seven draft guidelines – including clarification of responsibility for any ongoing post-trial medical expenses and/or care. *Consumers’ Health Forum (Submission X086)*

10.45 The XWP agrees that this is an important issue, but believes it is sufficiently covered by the National Statement, international guidelines for good clinical practice (see paragraphs 7.39–7.40) and by normal medical care associated with clinical trials (see paragraph 7.20).

Overall XWP response (ethics of long-term monitoring and surveillance)

10.46 The XWP noted that respondents who were against animal-to-human transplantation trials considered the need for long-term follow-up as further evidence for the risks of the procedures, which were considered unacceptable.

10.47 However, those who were prepared to consider the possibility of trials considered that long-term follow-up was a necessary part of the trial protocol, with a strong feeling that it should not be left to chance and that procedures should be in place to ensure that it is done properly.

10.48 The XWP felt that, where risk assessment showed a potential for emergence and spread of infection, the practical need for monitoring and follow-up in trials should prevail if such trials are allowed to go ahead. However, such trials should only proceed if:

- the trial protocols include procedures for thorough information sharing with the transplant recipient, including the need for long-term monitoring;
- the trial protocols include procedures for consultation with the relatives and carers (close contacts) of the transplant recipient, including for sharing information about infection risks and the need for long-term follow-up;
- all parties give voluntary (uncoerced) consent to their part in the trial, including the requirement for long-term monitoring and follow-up, and for not donating their organs and tissues to others in the future or after their death;
- part of the selection and eligibility criteria for research participants is an assessment of their ability to adhere to lifelong monitoring, and their likelihood of doing so;
- the participants understand that although they retain their right to withdraw their consent for further medical treatment (ie withdraw from the trial) at any time, they will not be able to withdraw from long-term monitoring and surveillance; and
- the close contacts also understand the requirements for long-term monitoring and surveillance.
Conclusion

Definition of research participants and close contacts

10.49 After considering the submissions, the XWP concluded that the research participants in animal-to-human transplantation trials should be defined to include the transplant recipient only, as any attempt to include close contacts would be too difficult to administer and would have serious implications for the autonomy of potential transplant recipients in making decisions about their own health.

10.50 However, close contacts should be closely involved in the information sharing process, which should include a clear explanation that they may need to be contacted in the future for testing, particularly if the research participant develops an infection.

10.51 A more precise definition of close contacts would vary for different procedures and for particular participants, and will need to be worked out on a case-by-case basis.

Selection of participants

10.52 Participant selection would need to follow the general guidance set out in the National Statement, Section 1 and more specific guidance relating to specific groups of participants (eg children, the intellectually impaired). Care would also be needed to ensure that potential participants would not gain more benefit from an alternative type of therapy (including conventional therapy).

10.53 Procedures will also be needed when selecting participants to assess the likelihood of them complying with the long-term monitoring and follow-up procedures required.

Information sharing and consent arrangements

10.54 As for any clinical trial proposal, proposals for animal-to-human transplantation trials will need to meet all the ethical standards set out in the National Statement. In addition, the arrangements for information giving will need to be sensitive to the potentially serious health problems of the proposed participants, the possible lack of other options, and the ongoing implications, both for themselves and for their close contacts, of contracting an infectious disease of animal origin.

10.55 The XWP concluded that animal-to-human transplantation trials should only be allowed to proceed if they include clear patient information sheets and procedures to be followed for appropriate information sharing, counselling and consent. These procedures should involve both the research participants and their close contacts and include information and counselling on the need for ongoing and long-term follow-up and surveillance.

10.56 Consent forms for participants, and signed information sheets for close contacts, should set out clearly the conditions of the trial, including long-term follow-up. Consent to participation in the trial should be separate from consent for long-term monitoring and surveillance as participants will retain the right to withdraw from the former but not from the latter.
Monitoring and follow-up of participants and contacts.

10.57 However slight the risk of infectious disease spread may be for a particular trial proposal, monitoring and follow-up of participants and contacts should be an essential part of the risk management strategy. To be effective, such a strategy must be based on validated, up-to-date tests and procedures that allow early detection of the emergence of a potential infection in the participant, or its spread to a close contact.

10.58 In this regard, it will also be important that all trial participants are entered in a national register and that all necessary clinical data (including tissue samples) are collected and stored to allow later assessment and tracing of public health risks.

10.59 Prospective record keeping of close contacts will also be important to allow easier tracking at a later stage if an infectious disease emerges.

10.60 Overall, the XWP concluded that animal-to-human transplantation trials should be allowed to proceed only if the trial protocols include validated processes for monitoring and surveillance of public health risks of research participants and close contacts, and procedures for the collection and storage of sufficient clinical data and tissue samples to allow tracing of data concerning public health risks.
11 Regulation of animal-to-human transplantation research

Overview of issues from Discussion Paper and Draft Guidelines

Chapter 9 of the Discussion Paper described the current regulatory arrangements for animal research and for human clinical trials. It focused on the regulatory and administrative responsibilities of the NHMRC, and the regulatory powers of the Therapeutic Goods Administration (TGA) and the Office of the Gene Technology Regulator.

The NHMRC Research Program covers the full spectrum of health and medical science. The Research Committee administers public research funding, the Animal Welfare Committee oversees the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (under revision, 2003), and the Australian Health Ethics Committee administers the National Statement on Ethical Conduct in Research Involving Humans (1999).

The TGA is responsible for the regulation of supply of therapeutic goods under the Therapeutic Goods Act 1989 (TG Act). Under the TG Act, unregistered therapeutic goods can be used in a clinical trial after assessment by either a human research ethics committee (HREC) and the TGA, or by a HREC alone. Individual use of unregistered therapeutic goods is also allowed in some circumstances under the Special Access Scheme.

The Xenotransplantation Working Party (XWP) was concerned to clarify whether the TG Act would cover xenotransplantation products under the definition of ‘therapeutic goods’ and posed the question:

Does the TGA Act need to be revised to specifically cover xenotransplantation products?

The TGA responded that xenotransplantation products would be covered under the TGA Act but that, if tighter regulation is needed than is currently the case for other therapeutic goods, changes to the legislation will be required. These issues are discussed further in paragraphs 11.12–11.23 and 11.40–11.43.

The Discussion Paper also included a detailed discussion of the current arrangements for the regulation of research involving gene technology. This was a complex task as the Gene Technology Act 2000 (GT Act) is a relatively new act and the administrative arrangements under the Office of the Gene Technology Regulator are still being worked out for a range of different circumstances. To obtain further information, the XWP posed the question: Is this an accurate summary of the Gene Technology Act and the role that the Gene Technology Regulator will play in the regulation of xenotransplantation research in Australia?

The responses to this question indicated that the regulation of genetically modified source animals in xenotransplantation research and of GM xenotransplantation products will require very careful oversight for some time, until all the issues become clearer. These issues are discussed further in paragraphs 11.22–11.23.

The XWP did not consider that the current arrangements under the TGA and OGTR provide sufficient oversight for effective regulation of animal-to-human transplantation trials. Therefore, in Chapter 11 of the Discussion Paper, three potential models for the regulation of such research were presented. Models 1 and 2 both involved the formation of a national committee to assess animal-to-human research proposals, either based on the existing Gene and Related Therapies Research Advisory Panel (model 1) or separately constituted (model 2). Model 3 suggested TGA as the sole regulatory agency. The XWP asked several questions relating to these models, culminating in:

Which model do you favour and why?

These models and the responses received are discussed further in paragraphs 11.30–11.39.
General considerations

11.1 The Discussion Paper identified three regimes that would be involved in the national regulation of xenotransplantation research:

- regulation and administration of medical research, including animal experimentation, by the National Health and Medical Research Council (NHMRC) (see paragraphs 11.4–11.11);
- regulation of the supply and manufacture of therapeutic goods by the Therapeutic Goods Administration (TGA) (see paragraphs 11.12–11.16); and

11.2 Animal welfare is legislated at a State and Territory level based on a nationally developed code of practice. At a local level, institutional animal ethics committees (AECs), human research ethics committees (HRECs) and biosafety committees are responsible for overseeing research at each institution. Table 11.1 summarises the regulatory arrangements that apply to animal and human research.

11.3 The focus of the Discussion Paper and of this Response Paper is on research (animal-to-animal preclinical studies and animal-to-human transplantation clinical trials) because, even if such research is allowed to proceed, it will be many years before any therapies involving animal-to-human transplantation become routine clinical practice.

Regulation and administration of medical research

11.4 Public funding for medical research is administered by the NHMRC through its Research Committee, which awards grants on the basis of scientific quality and provides research support through a variety of mechanisms, including support for individual projects, broad programs of research, training awards and fellowships.

11.5 The NHMRC Animal Welfare Committee (AWC) oversees the development of the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (under revision, 2003) (referred to in this paper as the Code of Practice). Under this code, all proposals involving the use of animals in research and teaching must be approved and monitored by an institutional AEC. Legislative administration of the Code of Practice is a State/Territory responsibility under individual State/Territory legislation. It is also a requirement of the NHMRC that all NHMRC-funded research be conducted in compliance with this code and any other related NHMRC policies on the use of animals. Compliance with this requirement is overseen by the NHMRC AWC.

11.6 Research involving humans is overseen by the NHMRC through its Australian Health Ethics Committee (AHEC), which administers the National Statement on Ethical Conduct in Research Involving Humans (National Statement; NHMRC 1999). Under this statement, all proposals involving human research must be approved and monitored by an institutional HREC.
Table 11.1 Administrative and legislative arrangements for medical research

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<thead>
<tr>
<th>Research Level</th>
<th>Organisation</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANIMAL National</td>
<td>NHMRC Animal Welfare Committee</td>
<td>Oversees development of the Code of Practice&lt;sup&gt;a&lt;/sup&gt; Ensures compliance for NHMRC-funded research</td>
</tr>
<tr>
<td></td>
<td>OGTR</td>
<td>Regulates use of genetically modified organisms and products</td>
</tr>
<tr>
<td>State/Territory</td>
<td>State/Territory governments</td>
<td>Legislate compliance with Code of Practice for all animal research (animal welfare legislation)</td>
</tr>
<tr>
<td>Local</td>
<td>Animal ethics committees</td>
<td>Approve and oversee animal research at each institution</td>
</tr>
<tr>
<td></td>
<td>Institutional biosafety committees</td>
<td>Approve and oversee research involving genetically modified animals</td>
</tr>
<tr>
<td>HUMAN National</td>
<td>NHMRC – Research Committee</td>
<td>Funds research proposals</td>
</tr>
<tr>
<td></td>
<td>– Australian Health Ethics Committee</td>
<td>Administers the National Statement&lt;sup&gt;b&lt;/sup&gt; for NHMRC-funded and privately funded research</td>
</tr>
<tr>
<td></td>
<td>– GTRAP</td>
<td>Reviews proposals for clinical trials of gene therapy and related technologies (including xenotransplantation)</td>
</tr>
<tr>
<td></td>
<td>TGA</td>
<td>Administers the Therapeutic Goods Act, which regulates the supply and manufacture of all therapeutic goods in clinical practice and in clinical research</td>
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<tr>
<td></td>
<td>OGTR</td>
<td>Administers the Gene Technology Act, which legislates the use of GM organisms</td>
</tr>
<tr>
<td>State/Territory</td>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Local</td>
<td>Human research ethics committees</td>
<td>Approve and oversee clinical research at each institution</td>
</tr>
</tbody>
</table>

OGTR = Office of the Gene Technology Regulator; GTRAP = Gene and Related Therapies Research Advisory Panel; TGA = Therapeutic Goods Administration

<sup>a</sup> *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (under revision, 2003)

<sup>b</sup> *National Statement on Ethical Conduct in Research Involving Humans* (1999).
11.7 With the development of gene technology in the 1990s, the NHMRC Research Committee formed a subcommittee known as the Gene and Related Therapies Research Advisory Panel (GTRAP) to provide the NHMRC and HRECs with advice on matters relating to human gene therapy. In 1999, the terms of reference of this subcommittee were expanded to include xenotransplantation.

11.8 The formation of GTRAP introduced an additional step into the system for review and monitoring of clinical trial applications, since HRECs (with guidance from AHEC) usually undertook this work independently. However, it was considered that HRECs would need specialised advice about gene and related therapies because the short or long-term potential for harm was not well defined for such new technologies.

11.9 GTRAP provides the NHMRC with advice on gene therapy and related technologies, and asses human research protocols involving these technologies so that HRECs have expert independent advice for each trial.

11.10 GTRAP assessment covers medical, scientific, technical, safety and other matters related to a research trial proposal in humans. Although GTRAP is an advisory body, AHEC defined its role in the approval process for clinical trials involving gene therapy. In this framework, HRECs should not approve research that involves gene and related therapies without the prior approval of both the institutional biosafety committee and GTRAP.

11.11 However, as this framework is not backed by legislation, there is currently no guarantee that GTRAP’s decision will be final.

**Regulation of therapeutic goods**

11.12 The TGA is the Australian Government agency responsible for regulating the manufacture and supply of therapeutic products under the *Therapeutic Goods Act 1989* (TG Act), including the supply of nonregistered therapeutic goods in clinical trials and for individual use in special circumstances (Special Access Scheme).

11.13 The TGA has confirmed that most xenotransplantation products would be considered to be ‘devices’ and be covered by the requirement in the TG Act that ‘devices of human, animal or bacterial or recombinant origin for use in, or on, the body of a person’, must be included in the Australian Register of Therapeutic Goods (ARTG). Some viable animal tissues could, however, be described as medicines (eg pig pancreatic cells to deliver insulin) and, as such, would also need to be included on the ARTG.

**CTN/CTX approval**

11.14 Under current arrangements, research sponsors must submit applications for the use of nonregistered therapeutic goods in clinical trials in one of two forms. A Clinical Trial Notification Scheme (CTX) application must be considered first by the TGA before forwarding to the HREC for local approval. A Clinical Trial Exemption Scheme (CTN) application is forwarded directly to the HREC for approval, with only a notification to the TGA.

11.15 Whether a clinical trial application can be submitted as a CTX or a CTN application depends on the nature of the application and the expertise of the HREC to consider the issues involved. GTRAP has indicated that it considers that clinical trial applications involving gene and related therapies should be submitted as CTX applications. In the
Discussion Paper, Section 9.3.2, the XWP also indicated that animal-to-human transplantation clinical trial proposals should be submitted as CTX applications.

11.16 Respondents who commented on this section of the Discussion Paper agreed that applications for clinical trials of animal-to-human transplantation should follow the CTX Scheme. That is, applications should initially be submitted to the TGA for assessment before being assessed by the HRECs at the institutions involved in the research.

Special Access Scheme

11.17 Under the TG Act, there are situations in which individual patients and their physicians may access unregistered products (ie outside of a clinical trial) under the Special Access Scheme (SAS). Under the category A provision of the SAS, the treating physician certifies that the patient meets the category A definition (ie, the patient has a life-threatening condition) and has consented to treatment. In this case, the TGA only has to be notified of the intended use of the product and approval is not required. The category B provision allows use of an unregistered product for patients with less serious conditions, but approval must first be obtained from the TGA. Currently, the TGA has no power to refuse a category A request but may reject a category B request. There are additional provisions that give practitioners access to products for patients under their care and individuals access to goods for personal use.

11.18 Both GTRAP and the XWP have indicated that none of these schemes is appropriate for gene and related therapeutic products, including xenotransplantation products.

11.19 The XWP was concerned that, under the current legislation, the use of xenotransplantation products would be possible using these provisions. However, the ethical and safety issues involved in animal-to-human xenotransplantation strongly indicate that these schemes would not be appropriate for xenotransplantation products. The XWP therefore posed the following question:

*Does the Therapeutic Goods Act need to be amended to specifically ban the use of the Special Access Scheme for xenotransplantation?*

11.20 Respondents agreed that it would not be appropriate to allow the use of animal transplantation products under the SAS and other schemes that allow the use of unregistered therapeutic goods. The TGA noted that this would require a change to the TG Act to exclude animal transplantation products from the SAS.

The recommendation … that the TGA reviews the Special Access Scheme to exclude XTP is timely. Gene and Related Therapies Research Advisory Panel (Submission X041)

… consideration should also be given to amending the TG Act so as to specifically ban the use of the Clinical Trial Notification (CTN) scheme and the personal use or other schemes for xenotransplantation. NSW Health (Submission X090)

11.21 In its submission (X075), the TGA indicated that more rigorous regulation of the use of unregistered xenotransplantation products, such as requiring CTX applications or prohibiting the use of xenotransplantation products under the SAS (category A and/or category B) would require changes to the TGA Act and/or Regulations.
Regulation of research involving gene technology

11.22 The Discussion Paper included a discussion of the current arrangements for the regulation of research involving gene technology. This was a difficult task, as the Gene Technology Act 2000 (GT Act) is a relatively new act and the administrative arrangements under the Office of the Gene Technology Regulator (OGTR) are still being worked out for a range of different circumstances.

11.23 Overall, after discussions with the OGTR, the XWP assessed that:

- source animals that are not genetically modified are not regulated by the OGTR;
- source animals modified by gene technology are classified as genetically modified organisms (GMOs);
- research involving production of GM animals is classified as a ‘dealing’ with a GMO under the GT Act and will be regulated as either a notifiable low-risk dealing or as a licensed dealing, according to the circumstances (in the latter case, the researchers will need to obtain a licence from the OGTR);
- xenotransplantation of genetically modified material does not involve an ‘intentional release’ of a GMO; and
- live animal transplantation products for use in humans would be classified as GM products under the GT Act, which means that they would not be further regulated by the OGTR but would be regulated by the relevant agency (in this case the TGA), taking into account any advice from the OGTR (however, because of the unusual nature of xenotransplantation products under the definitions of the GT Act, some further assessment may be required by the OGTR on a case-by-case basis).

Regulation of medical services

11.24 As indicated in paragraph 11.3, the focus of the Discussion Paper and of this Response Paper is on research because it is considered that it will be many years before any therapies involving animal-to-human transplantation become routine clinical practice. If that happens, however, and xenotransplantation products are registered on the ARTG for general marketing and supply for clinical use, they may be approved for Medical Benefits Scheme listing and other sources of public funding will also be considered, such as through designated transplant units as has occurred for human-to-human transplants. This issue is discussed in further detail in Section 7.

International regulation

11.25 Some respondents mentioned the need for international harmonisation of xenotransplantation research:

> It would be appropriate to seek global harmonisation of controls and guidelines, particularly given the infection control issues.  
> *St Vincent’s Clinical Trials Centre (Submission X056)*

11.26 In preparing the Discussion Paper and Draft Guidelines and this Response Paper, the XWP has taken close account of international developments in the regulation of xenotransplantation. The International Xenotransplantation Association confirmed that the draft guidelines being developed by the NHMRC are in line with international practice in this area of research:
We are aware of guidelines from other countries and it appears to us that NHMRC is in agreement with virtually all the points covered by guidelines/draft guidelines in other countries, ie there appears to be a growing international consensus of what the guidelines should be. International Xenotransplantation Association (Submission X077)

11.27 The recent TGA discussion paper (see paragraphs 11.40–11.43) noted that the Australian and New Zealand governments are currently investigating the formation of a joint agency to regulate therapeutic products. At present, therapeutic products may not be traded freely between the two countries unless there is parallel regulation in New Zealand.

Therapy-specific considerations

11.28 Paragraphs 3.1–3.4 of this Response Paper distinguish three different types of xenotransplantation: animal external therapies (AETs), animal cell therapies (ACTs) and animal organ transplants (AOTs).

11.29 The XWP recognises that the different types of therapy have different levels of risk. Accordingly it suggests that the regulatory regime adopted should focus on safety, efficacy, animal welfare etc, on a case-by-case basis.

Proposed models for regulation of xenotransplantation research in Australia

Regulation of animal-to-human trials

11.30 In the Discussion Paper, the XWP put forward three possible models for regulation of animal-to-human transplantation research, as discussed below.

11.31 The respondents indicated no clear consensus for any one of the three models, although most respondents agreed that a national committee is needed.

Model 1

11.32 Model 1 proposed that animal-to-human transplantation research proposals should be overseen by a modified and expanded GTRAP, which would become a national committee for the assessment of gene therapy and animal-to-human transplantation research proposals. Under this model, research proposals would only be allowed as CTX applications and would initially be forwarded to GTRAP from the TGA for approval. The committee would liaise with the OGTR on issues relating to any genetic modifications of the source animals. If the committee approved a research proposal, the normal institutional approval processes through AECs and HRECs would follow.

11.33 Several respondents, including GTRAP itself, supported the general thrust of model 1.
There are a number of reasons favouring an extension of the existing GTRAP [model 1]. The committee is independent, it is established within the NHMRC structure, it now interacts well not only within the NHMRC but in relation to the TGA and the OGTR … Many of the issues in relation to animal to human xenotransplantation trials are not substantially dissimilar to the medical, technical, public health and scientific issues addressed by GTRAP currently. In addition, there is a limited pool of independent expertise in this country. It may be difficult to identify sufficient members for Model 2’s proposed Xenotransplantation Committee.

Gene Technology Ethics Committee (Submission X084)

[The GTRAP model] would make considerable sense in view of the common issues that GTRAP faces with gene therapy (ie registers, long term surveillance) as well as the overlap between gene therapy and XTP when issues for XTP come from genetically modified animals containing human genes.

Gene and Related Therapies Research Advisory Panel (Submission X041)

Model 1 as suggested, but with [with the addition of a zoonotic disease specialist as a member of the committee] seems the best approach. Armadale Health Service Ethics and Research Committee, WA (Submission X048)

We agree that a central body to vet all proposed clinical trials is crucial and we favour model 1 where the role of GTRAP is extended. Transplantation Society of Australia and New Zealand (Submission X053)

Of the models presented, model 1 is preferred by NSW Health. However, with a longer-term view, it may be appropriate to re-examine the use of a national committee structure for the management and monitoring of xenotransplantation … The establishment of a single regulatory and monitoring body to manage all such research could be an alternative model. Such a body would be ‘expansible’ to incorporate new technologies and new responsibilities as these technologies move from research into clinical practice. NSW Health (Submission X090)

Model 2

11.34 Model 2 proposed that animal-to-human transplantation research should be overseen by a newly constituted national xenotransplantation committee. The TGA would forward CTX applications to the national committee, which could obtain further scientific and technical advice from GTRAP as required. As for model 1, only after approval is granted nationally could research proposals be reviewed locally by institutional AECs and HRECs.

11.35 The TGA expressed concerns about this model because it felt that GTRAP already has the expertise necessary to assess proposals and that therefore a new national committee is not required:

TGA would … have difficulties with Model 2 as proposed … Acknowledging the considerable expertise of GTRAP, the TGA believes it would be possible to capture the scientific expertise of the committee members, using GTRAP as an existing NHMRC advisory committee to ensure consistency of regulation of these products. and still have the TGA recognised as the primary regulator.

Therapeutic Goods Administration (Submission X075)

11.36 Other respondents favoured model 2 over model 1 because they saw it as providing a more independent decision-making body:

CHF believes the added safeguard provided by the formation of a national xenotransplantation committee, as proposed in Model 2, … may serve the public good more effectively than current arrangements.

Consumers Health Forum (Submission X086)
If I had to choose, I would choose model two because it seems to provide more independence from the already existing framework. *(Bernice Bovenkerk X052)*

11.37 The RSPCA suggested a slightly different variation on model 2 that retained the existing expertise of GTRAP within a new national committee:

It might be better to approach the model in a slightly different way by replacing the existing GTRAP with the new NXGTC rather than renaming and expanding GTRAP. This would retain the efficiency and the accumulated knowledge and experience of GTRAP, while enabling the new committee to set up appropriate operating procedures and structures in line with its new role. *(RSPCA Australia X050)*

**Model 3**

11.38 The XWP proposed a third model with the TGA as the sole regulatory agency. The XWP did not discuss this option in detail in the Discussion Paper, because at that time it thought the other models were clearly preferable. As a result, few respondents commented on this model. However, the following responses are relevant:

TGA believes it must be part of any integral regulatory system.  
*Therapeutic Goods Administration (Submission X075)*

The TGA is not the appropriate body for the purpose of approval of xenotransplantation trials. The complexity of both scientific and ethical issues are more appropriately dealt with within the existing HREC system, subject to oversight by a single national committee.  
*Gene Technology Ethics Committee (Submission X084)*

The NHMRC is likely to have another principal committee which will specifically regulate [cloning and stem cell] technology. In this circumstance, a more global approach to regulation of medical research by the NHMRC will be beneficial so that the various regulatory processes … can be captured by a single national committee thereby ensuring adequate infrastructure and long term corporate knowledge is available to this committee.  
*Gene and Related Therapies Research Advisory Panel (Submission X041)*

11.39 Since publication of the Discussion Paper, the Australian Government has foreshadowed that the TGA may be given new powers to regulate a range of biological therapies. Public opinion on this issue has been sought by the TGA in a public discussion document, which is described in paragraphs 11.40–11.43 below.

**Therapeutic Goods Administration discussion paper**

11.40 To stimulate discussion about the regulation of a range of current emerging technologies using human and animal tissues, cells and genes for potential therapeutic application, the TGA released a discussion paper in March 2003 on *The Regulation of Human Tissues and Emerging Biological Therapies*. The discussion paper:

- described the range of current and emerging technologies utilising human and animal tissues, cells and genes for potential therapeutic application, the current regulatory arrangements and overseas experience;
- identified three types of drivers for changes to TGA legislation: issues relating to safety, issues relating to efficacy and issues relating to the administration of any regulatory system, including international harmonisation;
• proposed three classes of ‘activities’, based on comparative levels of risk (low, medium and higher risk);
• outlined a possible system of regulation for human cell and tissue therapies and proposed the addition of a new part to the TG Act to cover the regulation of these therapies; and
• questioned whether gene therapy and xenotransplantation should be included in the same general system of regulation for tissue and cell therapies.

11.41 The TGA has now received responses on its discussion paper. There was general agreement with the proposed new regulatory framework and with the proposal that this would be best achieved by the addition of a new part to the Therapeutic Goods Act 1989 to cover the regulation of biological therapies:

... it was proposed that a separate part of the TG Act be developed to address ‘biological therapies’. It was proposed that this new Part include separate sections to regulate human cell and tissue products; blood and blood products; xenotransplantation (if required); and gene therapy. There was general support for this approach, rather than trying to ‘weave’ the new regulatory requirements into the existing Act.8

11.42 The TGA reported the following summary of the responses received on the question of whether the new arrangements should include xenotransplantation:

Workshop participants generally agreed that the regulation of xenotransplantation should be kept separate from that of human cells and tissues. In that way, when the community and Parliament has debated the ethical arguments surrounding this issue, the TG Act would have the necessary regulatory force if required, or the relevant section could be easily removed, if not required. It was agreed that consideration of the ethical issues is outside the scope of the TG Act.9

11.43 It now appears likely that xenotransplantation and gene therapy will be included as high-risk therapies under a revised TGA Act. The new legislation will ensure that clinical trial applications will have to follow the CTX application route (see paragraph 11.14) and that there will be no access to the Special Access Scheme (see paragraph 11.17–11.21). However, the regulation of xenotransplantation will be kept separate from the regulation of other types of biological therapies, as it involves specific ethical considerations, which need to be debated independently of other therapies.

Comments from Gene and Related Therapies Research Advisory Panel

11.44 Based on the information provided in the Discussion Paper, GTRAP supported model 1 as the preferred model for the assessment of animal-to-human transplantation trial proposals. The Discussion Paper proposal in model 1 is for GTRAP’s membership to be expanded and its regulatory powers enhanced. However, GTRAP noted that the current working arrangement, involving a core group and two expert scientific groups (one for gene therapy and the second for xenotransplantation), has worked well. It provides an

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9 ibid.
opportunity through the core group for broad representation (including medical, scientific, community, ethical and legal). This existing framework also allows for additional membership if necessary.

11.45 GTRAP did not consider that model 2 would be appropriate as it would be comparable to a HREC in terms of scientific expertise and would duplicate GTRAP unless GTRAP no longer dealt with xenotransplantation matters. Importantly, it could also prove unworkable if the two bodies came to different conclusions. Overall, a second body, in addition to GTRAP, would be wasteful of limited resources.

11.46 GTRAP stressed that the funding or resources to be provided for the regulatory body should be clearly identified to allow adequate planning and development. The OGTR will be required to operate at full cost recovery within the next year (as the TGA already does). A new national xenotransplantation committee may also be required to recover all costs, placing an additional funding burden on individual researchers and research institutions.

11.47 Unlike the work covered by the OGTR, xenotransplantation and gene therapy involve relatively few scientists and organisations and it is difficult to see how full cost recovery will be possible. If so, the regulatory process will need to be highly efficient so that it is functional with the limited NHMRC resources that it will have access to.

11.48 Finally, GTRAP stressed that the recently passed cloning and embryo research legislation has led to the formation of another NHMRC principal committee to regulate this technology. In this circumstance, a more global approach to regulation of medical research by the NHMRC may be beneficial so that the various regulatory processes (stem cells, xenotransplantation, gene therapy and whatever comes up in the future) can be captured by a single national committee, thereby ensuring that adequate infrastructure and long-term corporate knowledge is available to this committee.

Xenotransplantation Working Party proposal for the regulation of xenotransplantation research

National assessment and approval for animal-to-human transplantation trial proposals

11.49 The XWP considered the submissions and the new developments with respect to revised TGA legislation for biological therapies and decided to propose model 1 as its preferred model for the regulation of xenotransplantation research. That is, that GTRAP will be expanded with revised terms of reference to act as a national committee to assess animal-to-human transplantation trial proposals.

11.50 Under this proposal, researchers will submit their trial protocol and supporting information to a national committee — the National Xenotransplantation and Gene Therapy Committee (based on an expanded GTRAP) — who will assess the proposal in terms of the proposed NHMRC guidelines for xenotransplantation research involving humans (see Section 12). The national committee may seek to clarify some issues with sponsors or recommend changes to the trial protocol. If the national committee approves the trial, the trial sponsors will need to submit it to the TGA as a CTX application.

11.51 The TGA will further review issues of safety and efficacy, particularly with respect to the production and supply of the xenotransplantation product (and may also commission any other internal or external evaluations that the TGA requires). The TGA will also raise any
issues identified with the sponsors. If TGA approval is granted, institutional ethics committees (HRECs and AECs) will be able to consider the trial for inclusion in the research program of their institution. These proposed arrangements are shown in Figure 11.1.

![Flowchart showing proposed regulatory process](image-url)

**Figure 11.1** Flowchart showing proposed regulatory process
11.52 The XWP also proposes that the changes to the TGA Act foreshadowed by the TGA public consultation (see paragraphs 11.40–11.43) should include:

- a requirement for all animal-to-human transplantation trial proposals to be submitted as CTX applications;
- a ban on access to animal-to-human transplantation therapies under the Special Access Scheme or other similar arrangements for single patient use (see paragraphs 11.17–11.21); and
- any relevant changes to the legislation and regulations to allow exchange of information between the TGA and the national committee (for example, if the TGA fails to approve a trial that has previously been approved by the national committee).

National oversight of animal-to-animal studies

11.53 The Discussion Paper described the current regulatory controls on animal experimentation and proposed that the existing controls also apply for xenotransplantation research. In Section 11.2.1, it said:

The current regulatory controls on animal experimentation will continue to apply for animal-to-animal (preclinical) xenotransplantation studies (ie those not involving any human research component). Research proposals will need to be consistent with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes … and must be approved by the animals ethics committee (AEC) of the institution in which the research will be conducted …

11.54 Many respondents criticised this aspect of the Discussion Paper as being too imprecise with respect to the role of AECs in the regulation of preclinical and clinical xenotransplantation research:

… proposed models 1 and 2 would need to be altered to include, at the institutional level, that both the AEC and the HREC would consider applications … it should not be considered that animal welfare concerns have adequately been met by the inclusion of an AEC representative on an HREC. NSW Agriculture Animal Welfare Unit (Submission X070)

AECs will be unable to identify from this document whether they have any additional responsibilities over and above their legal responsibilities … and how they are meant to interact with the proposed national xenotransplantation committee.

… In Victoria … the establishment which kills the animal would require licensing under the [Prevention of Cruelty to Animals Act 1986]. The procedure would also have to be approved by the AEC for that establishment before it was conducted. Bureau of Animal Welfare, Department of Natural Resources and Environment, Victoria (Submission X073)

11.55 In particular, respondents noted that it is difficult for AECs to uphold the principles outlined in the Code of Practice because individual committees do not have access to the ‘bigger’ picture of what research has been done elsewhere, with what results and whether the animal-to-animal research they are being asked to approve is likely to lead to the development of a worthwhile human therapy or not. As human cell research develops further, the same issues will arise for preclinical animal studies using human cells (human-to-animal studies).
Respondents representing animal welfare organisations were therefore unanimous in their call for some form of national oversight of preclinical xenotransplantation research. This is discussed in detail in Section 5 of this Response Paper (see paragraphs 5.110–5.116).

Committee membership

Chapter 11 of the Discussion Paper outlined the proposed membership of the National Xenotransplantation and Gene Therapy Committee based on an expanded GTRAP (model 1). The XWP posed the questions:

Is the suggested membership of the proposed ‘National Xenotransplantation and Gene Therapy Committee’, based on GTRAP, suitable for assessment of human xenotransplantation research proposals? and

If not, what other expertise would be required to provide a balanced input to decision making?

Many respondents commented on the composition of the committee. The Federation of Ethnic Communities’ Councils of Australia thought that there should be expertise on transcultural issues:

I would strongly recommend that this authority include membership with expertise in cross-cultural issues, such as FECCA, as well as in transcultural mental health issues such as the NSW Transcultural Mental Health Centre. Federation of Ethnic Communities’ Councils of Australia (Submission X047)

The Thoracic Society of Australia and New Zealand thought that the committee should include representatives of the colleges and specialist societies:

With respect to the potential formation of a national xenotransplantation committee it would be appropriate to seek representatives from the colleges and special societies who may have insight into the practical development of xenotransplantation and research. Thoracic Society of Australia and New Zealand (Submission X029)

NSW Health recommended the addition of someone with expertise in risk assessment:

Expertise in epidemiology and risk assessment may be advantageous. NSW Health (Submission X090)

The Armadale Health Service Ethics and Research Committee, WA stressed the need for a zoonotic disease specialist:

It is explicit in the discussion paper that risk of transfer of pathogens from the donor species (probably pigs) to the recipient humans and then possibly to the wider community is a major concern. For this reason a zoonotic disease specialist should be a member of the committee. New pathogens are being discovered and assessed in all species of animal (eg porcine circovirus) and it requires special interest and expertise to maintain full knowledge of these developments and the ability to assess their possible significance to human health. Armadale Health Service Ethics and Research Committee, WA (Submission X048)

However, the majority of submissions on this subject related to animal welfare, and included personnel with various veterinary, animal husbandry, animal ethology and animal welfare expertise. This is discussed in more detail in paragraphs 5.117–5.125 of this Response Paper:
I propose a contribution from an ethologist. 
*Bernice Bovenkerk (Submission X052)*

An AWC member could not be expected to be truly independent … An independent committee requires a ‘devil’s advocate’: a representative of an animals rights group who will offer a different perspective. *Heidi Nore (Submission X058)*

The national committee … should include the following members: animal welfare science member with background particularly in housing and husbandry issues; animal welfare proponent; veterinarian with laboratory animal expertise; and a veterinary pathologist to advise on … potential zoonoses and the phenotype of genetically modified animals. *Bureau of Animal Welfare, Department of Natural Resources and Environment, Victoria (Submission X073)*

Agree the committee should include additional members with animal welfare, veterinary and community expertise. *Preterm Foundation (Submission X081)*

11.63 RSPCA Australia and Animals Australia noted that the necessary areas of expertise are well covered by the inclusion of the members described, but that it is important to ensure that these categories are clearly specified in the membership of the regulatory authority and that animal welfare is represented in its own right:

… it may not be enough to have animal welfare concerns represented by a cross-member with the AWC, unless that member’s primary interest is animal welfare. The AWC, as with many such committees, has members whose primary interest (eg biomedical research) is different from the main aim of the committee but whose role is to provide relevant advice and a balanced viewpoint. *RSPCA Australia (Submission X050)*

11.64 A former member of animal ethics committees, Bernice Bovenkerk, noted that the scientists on ethics committees tend to have an optimistic picture of progress and are biased towards research. She argued that experts (scientific, ethical and social) should play an advisory role and have no decision-making power. The ultimate decision-making power should rest with the public:

Simply including one or two representatives of consumer groups or the public is not enough. Firstly, consumer groups are not the same as the general public. Secondly, lay persons are not in a position to assess the credibility of the claims of the experts in their committee. Therefore, broader-based enquiries need to be held, which include viewpoints from alternative experts … Also, there should be a role for risk communication. *Bernice Bovenkerk (Submission X052)*

11.65 The Department of Human Services, South Australia also supported this view:

It is recommended that the Regulatory Authority be constituted to reflect public opinion. *Human Research Ethics Sub-committee, Department of Human Services, South Australia (Submission X055)*

11.66 Taking into account these comments, the XWP now recommends the following membership for the National Xenotransplantation and Gene Therapy Committee:

- a chairperson;
- member(s) with knowledge of research in or related to xenotransplantation;
- a member in common with the AWC;
- a member with knowledge of animal ethics and welfare issues;
• a member in common with AHEC;
• a member with knowledge of ethics and related issues associated with xenotransplantation;
• a representative each of the TGA and the OGTR;
• an infectious disease specialist(s);
• a person with veterinary expertise;
• a person with epidemiology and public health expertise;
• a person with legal training;
• a person who has knowledge of and current experience in the professional care, counselling or treatment of people with organ failure;
• members who are not currently in medical, scientific or legal work but who are actively involved in the consumer movement or patient advocacy; and
• up to two coopted members with specific skills for the assessment of specific trial proposals.

11.67 This broadly based membership includes people with skills across all the areas identified in the Discussion Paper and submissions and also allows for additional members to be coopted if another area of expertise is required or if a particular member has a conflict of interest for a particular proposal.

Terms of reference

11.68 The Discussion Paper proposed the following xenotransplantation-specific terms of reference for the National Xenotransplantation and Gene Therapy Committee based on an expanded GTRAP (ie these terms of reference would be in addition to the terms of reference for work on gene therapies):

• to advise on the data required to assess safety and efficacy in xenotransplantation procedures;
• to assess the safety, efficacy and any other preconditions for proceeding with animal-to-human xenotransplantation procedures;
• to assess the acceptability of specific applications to proceed with xenotransplantation trials in humans;
• to authorise and monitor the conduct of xenotransplantation clinical trials, including the imposition of any conditions deemed necessary for their safe conduct;
• to maintain a register of all trials and all participants;
• to monitor overseas developments in xenotransplantation; and
• to liaise with the AWC over the use of animals in preclinical studies and clinical trials.

11.69 RSPCA Australia and Animals Australia both noted that the terms of reference for the national committee included: ‘to liaise with the Animal Welfare Committee (AWC) over the use of animals in preclinical studies and clinical trials’. However, these organisations submitted that the AWC will not be able to provide a comprehensive view of animal use
and they suggest that the only way to ensure that the use of animals in such studies is appropriately monitored would be to expand the terms of reference, as follows:

… to authorise and monitor the conduct of xenotransplantation preclinical (animal-to-animal) and clinical (animal-to-human) trials, including the imposition of any conditions deemed necessary for their safe conduct.

RSPCA Australia (Submission X050)

11.70 Similarly, these animal welfare organisations felt that it should be made clear here that institutional AECs have similar powers to HRECs to refuse permission for a particular study to go ahead rather than that the decisions of the AEC are secondary to those of the HREC. They also asked: ‘How will HRECs and AECs be able to make decisions jointly if they are at different institutions? For example, where the source animals are bred by a private company and bought by another institution for clinical trials?’

11.71 In the Discussion Paper, the XWP posed questions concerning the role of a national committee based on GTRAP in overseeing the monitoring of xenotransplantation clinical trials by HRECs (including the power to audit the trials, conduct onsite visits, and so on). RSPCA Australia and Animals Australia both suggested that the national committee should have such powers for both animal-to-human transplantation trials and animal-to-animal studies.

11.72 The issue of national oversight of animal-to-animal xenotransplantation research relevant for the development animal-to-human transplantation therapies is discussed in Section 5 (paragraphs 5.110–5.116) and in Section 11 (paragraphs 11.53–11.56). The XWP proposes that the NHMRC should develop procedures to collect information from researchers and maintain a register of relevant animal-to-animal xenotransplantation studies. This information should be made available to GTRAP, the AWC, AECs and HRECs to inform decision making, as required.

11.73 The National Xenotransplantation and Gene Therapy Committee will also need to maintain close contacts with the TGA and the OGTR to ensure that both these regulatory agencies are aware of all relevant xenotransplantation research.

11.74 As described in the Discussion Paper, the present GTRAP is a subcommittee of the NHMRC Research Committee and its chairperson and membership is determined by the Research Committee. Given the potential seriousness of the decisions which will be expected of the expanded GTRAP, the XWP wishes to receive submissions as to the appropriateness of this such arrangement.

11.75 An alternative arrangement that should be carefully examined is to have the National Xenotransplantation and Gene Therapy Committee report directly to the NHMRC Council and to have its chairperson and membership appointed by council.

11.76 The NHMRC has handled other issues of national concern, such as bovine spongiform encephalopathy and variant Creutzfeldt–Jakob disease (through the Special Expert Committee on Transmissible Spongiform Encephalopathies).

Conflicts of interest

11.77 One respondent noted the potential for conflicts of interest to arise in the decision-making process because so few Australians work in the xenotransplantation area:
We are concerned that there is a large potential for conflict-of-interest to occur in this industry given the limited number of players.

*St Vincent’s Clinical Trials Centre (Submission X056)*

11.78 Professor Bernie Tuch, who favoured model 1 overall, made several suggestions to overcome this problem:

Membership of the Committee needs to change every (say) 3 years. Experts in specific areas, e.g., xenotransplantation, who are to sit on the Committee at the same time should not be major collaborators.

An expert in another area, for example, Infectious Diseases, ideally should come from a different institution to that [from] which the xenotransplant experts are drawn. A clinical expert in the relevant area of the proposed human xenotransplant should be co-opted on to the Committee for the specific meetings where the proposal is being considered. Thus if perfusion of blood across pig liver cells is to be considered, then a hepatologist not involved in the trial should be co-opted. This allows a better assessment of the clinical alternatives and the necessity of the trial.

*Professor Bernie Tuch (Submission X016)*

11.79 The XWP agrees that strict procedures will be required to minimise conflict-of-interest problems.

**Registry for recipients of xenotransplants**

11.80 An additional role for any national xenotransplantation committee may be to maintain a registry of recipients of xenotransplantation. This would require recipients to submit to regular blood tests each year (or more frequently) and possibly, when they die, undergo an autopsy. Their close contacts would also need to be monitored.

**Appeals**

11.81 Some respondents commented on the need for an appeals process both for researchers and for the public, and suggested possible mechanisms:

… The potential for appeals against decisions made by the XTP regulatory body is real … GTRAP would strongly recommend that the appeals process is built into the Guidelines. *Gene and Related Therapies Research Advisory Panel (Submission X041)*

Appeals of decisions made by the AXGTC [ = proposed national xenotransplantation committee] … should be allowed. The appeal panel should include the chairman of AXGTC, the lawyer from AXGTC, and experts in those areas for which the applicant feels they have been unfairly treated. Such experts should be different from those who sat on AXGTC at the time the original decision was made.

*Professor Bernie Tuch (Submission X016)*

11.82 The XWP agrees that an appeals process will be required and will recommend to NHMRC to ensure that an appropriate process is incorporated into the arrangements adopted.
Need for timely decisions

11.83 Some respondents commented on the need for timely consideration of applications to meet the commercial needs of the research sponsors and ensure that local companies are able to participate in international research efforts:

… timely consideration of applications is going to be extremely important to make clinical trials a viable prospect for local companies … We suggest that the model of regulation include a pre-application meeting of all parties … in order to gain consensus between groups … Clear timelines for the decision making process are essential. St Vincent’s Clinical Trials Centre (Submission X056)

Conclusion

11.84 The respondents to the Discussion Paper did not indicate a clear consensus for any of the three models offered by the XWP, although most respondents agreed that a national committee was needed.

11.85 The submission from GTRAP (see paragraphs 11.44–11.48) and further discussions since the release of the Discussion Paper, however, have convinced the XWP that model 1 (expansion of GTRAP to form the National Xenotransplantation and Gene Therapy Committee) would be the best model to pursue for national overview and approval of animal-to-human transplantation clinical trial proposals, as it draws on the existing expertise of GTRAP while maintaining valuable links with the NHMRC Research Committee and Australian Health Ethics Committee.

11.86 The XWP therefore now proposes that model 1 be adopted and that the membership and terms of reference of the existing GTRAP be broadened to include the new task of a national regulatory committee for xenotransplantation research, including providing advice on data requirements, assessing trial proposals against NHMRC guidelines, monitoring the conduct of authorised trials, maintaining a register of all trials and participants, and monitoring overseas developments.

11.87 Under this model, animal-to-human transplantation trial proposals will be forwarded to the national committee for assessment against NHMRC guidelines for the conduct of such studies. If the national committee approves the proposal, it will be able to be considered further by institutional HRECs and AECs and a CTX application for use of the xenotransplantation product in a clinical trial can be forwarded to the TGA.

11.88 The XWP considers that a CTX application to the TGA will be needed, even after approval has been granted by the new national committee, because of the high-risk status of the technology. Planned changes to the TGA legislation for biological products should ensure that application must be made by the CTX application route and that single-patient use is not allowed for xenotransplantation products under the Special Access Scheme or other similar schemes.

11.89 Under the recommended arrangement, neither the institutional ethics committees nor the TGA would be able to approve trials that have not been approved by the national committee. However, either organisation could reject an application already approved nationally (but should notify the national committee of the reasons). An appeals process will need to be developed so that researchers can appeal decisions that do not allow their research to proceed.
11.90 The XWP also recommends that a national register be set up of animal-to-animal xenotransplantation studies that directly relate to the development of animal-to-human transplantation therapies. Once this register is set up, researchers would be required to notify the register of relevant animal-to-animal studies that they conduct and the information would be made available for the national xenotransplantation committee, AWC, HRECs and AECs, as required, to aid decision making about new research proposals.
12 The way forward for Australia

Introduction

12.1 In order to develop xenotransplantation as a possible therapy for humans, a great deal of research must be undertaken, initially on animals (animal-to-animal studies) and later on humans (animal-to-human trials).

12.2 The terms of reference of the Xenotransplantation Working Party (XWP) called on it to provide advice to the NHMRC Council on scientific, ethical, technical and animal issues related to xenotransplantation research involving humans and to produce guidelines based on its findings.

12.3 The Draft Guidelines and Discussion Paper, released for public consultation in June 2002, explored the ethical and scientific principles that apply to xenotransplantation research and proposed guidelines against which animal-to-human transplantation research proposals could be assessed.

12.4 The inclusion of the draft guidelines with the Discussion Paper at that time was not intended to indicate that the XWP had decided that animal-to-human transplantation trials should be allowed in Australia, thereby pre-empting public opinion on this matter. Rather, the guidelines were included to indicate the conditions that the XWP considered would be required, if such research were to be permitted, and to give the public a chance to comment on the draft guidelines, as is required under NHMRC legislation.

12.5 Since the release of the Discussion Paper, the XWP has carefully considered the submissions received and gathered much additional information on the issues involved in animal-to-human transplantation research, including animal welfare issues. It has also considered developments in regulatory processes overseas and the consequences for Australia of banning animal-to-human transplantation research or of not preparing any guidelines to deal with this issue (see paragraphs 2.27–2.31).

12.6 As a result of these further considerations, the working party now proposes that animal-to-human transplantation research should be permitted in Australia under a strict regulatory system in which trial protocols are given rigorous scientific and ethical scrutiny against NHMRC guidelines by a designated national committee, as well as further assessment by the Therapeutic Goods Administration through its CTX application process (see paragraphs 11.14–11.16). Community responses to this proposal are now requested (see pages iii–iv for information on the consultation process).

12.7 The remainder of this section summarises the broad principles that the XWP identified as necessary to underpin NHMRC guidelines. These principles were introduced in the Discussion Paper and, as a result of the submissions received, have been further developed in this Response Paper.
Ethical basis for the use of animals as a source of organs and tissues

12.8 The XWP has considered the overarching ethical question of whether live organs and tissues from animals should ever be used for human therapies; that is, whether there are any in-principle objections to the use of animals in this way. The working party considered the broad ethical concepts that influence this issue (respect for humans, respect for animals and so on) in the context of a range of cultural and religious views about the use of animals by human beings to improve or save lives.

XWP conclusion: The view of a majority of people is that, while there are some specific concerns about aspects of the procedures themselves, there are no significant in-principle ethical objections to the use of live organs and tissues from animals for human therapies, that would preclude any further research to develop such therapies.

However, it is important to acknowledge that some people do not share this view. Some find the idea of mixing living animal and human tissues unacceptable. Others think it is not ethical to use animals for medical research at all, and are particularly opposed to raising animals specifically for their parts.

Summary of the principles for ethical animal-to-human transplantation research protocols

12.9 Having determined that there is no inherent ethical reason why animal organs and tissues should not be used for human therapies, the XWP considered some guiding principles that should apply to research aimed at the development of such therapies. These principles were identified in Section 3.3 of the Discussion Paper and summarised in the preamble to the Draft Guidelines, as follows:

- the research must serve the common good;
- the research must be scientifically sound;
- the research must be based on relevant efficacy data from preclinical studies;
- the research must be therapeutic in design;
- the benefits must justify any risks;
- the research should not expose the participants, their contacts or society to any unreasonable risks;
- the research must respect the dignity of participants;
- participants must give adequately informed and voluntary consent;
- arrangements for monitoring and follow-up must take account of the participant’s right to withdraw from the trial;
- the safety and rights of close contacts of the participants must be protected; and
- the research must respect the welfare of animals used in the trials and be conducted according to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC 1997a, 2003a).

12.10 As noted in this Response Paper, the XWP agreed with submissions that animal welfare was not given enough consideration in the Discussion Paper and that the welfare of animals involved in preclinical animal-to-animal studies also needs careful consideration, taking into account the procedures being studied, alternative therapies and the likelihood of success in the research. That is, animal experiments should only be carried out to
support significant, promising lines of investigation where there are no alternative therapies available that do not require the use of animals in this way.

12.11 To provide a stronger emphasis on animal welfare in both animal-to-animal and animal-to-human transplantation research, and for overall simplicity, the principles listed above can be related to the following key issues:

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

12.12 These issues were described in some detail in the Discussion Paper and have each been discussed further in this Response Paper in the light of the submissions received. The conclusions of the XWP about each issue are given below.

**Overall benefit of the research (the common good)**

12.13 As discussed in Chapter 4, when applied to health care, the common good refers to a delivery system that promotes the health of all members of a community. Hence, the assessment of animal-to-human transplantation research proposals should consider the effects of the research on society as a whole as well as the needs of the research participants and the researchers.

12.14 The Draft Guidelines published with the Discussion Paper did not provide specific guidance for researchers concerning ‘serving the common good’ but the ‘Advice regarding application of the proposed guidelines’ indicated that one of the key issues to be considered, along with the overall benefits and risks of the procedure, was whether alternative therapies are being researched with the same or better prospects for treating the disease or condition but without the public health risks associated with animal therapies. If so, the common good may be served by supporting research into the alternative therapies rather than the animal therapies.

12.15 As indicated in paragraph 12.8, some people find research involving animals unacceptable. Therefore, consideration of the common good should include serious consideration of the concerns of people who hold this view, and inclusion of measures to minimise those concerns.

**XWP conclusion:** Animal-to-human transplantation research proposals should only be approved if there are clear potential benefits, both for the individual patients and for the general public, that outweigh any risks to either the patients or the public. Public health risks associated with the procedures should be publicly explained and be acceptable to the general public. Animal welfare concerns should also be taken into consideration.

Protocols for research participant selection should ensure that alternative therapies or approaches that provide an equivalent benefit to participants with less public health risk compared to animal transplantation therapies, either have not been developed or are not available within a clinically useful timeframe.
Animal welfare

12.16 When assessing proposals to use animals in xenotransplantation research, animal ethics committees (AECs) must decide whether any pain and suffering caused to the animals can be justified by the potential benefit of the research to humans or other animals. If so, experimental design should ensure that the animals are cared for in a way that provides for their social and environmental needs and minimises pain and suffering.

12.17 In the case of xenotransplantation research, three areas of animal use have been identified as needing special consideration: use of nonhuman primates, use of pigs as source animals and genetic modification of animals.

12.18 These issues are reflected in the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (NHMRC 1997a; update in progress, NHMRC 2003a), which is referred to in this document as the Code of Practice, and its supplementary policies on the use of nonhuman primates (NHP Policy; NHMRC 2003b) and genetically modified animals (GM Policy; NHMRC 2003c).

12.19 The Code of Practice provides overall guidance and the NHP policy and GM Policy provide additional guidelines for the use of nonhuman primates and GM animals, respectively. To provide further guidance to AECs for xenotransplantation research, the NHMRC Animal Welfare Committee has decided to produce a policy statement on the care and use of animals in xenotransplantation research.

12.20 To further assist AECs and provide improved national oversight of animal use in xenotransplantation research (both in animal-to-animal and animal-to-human transplantation research), the XWP proposes that there should be a national notification system for the use of animals in animal-to-animal (preclinical) studies that are intended to lead to animal-to-human (clinical) studies.

**XWP conclusion:** Animal-to-animal transplantation studies that are required to provide evidence of effectiveness for animal-to-human transplantation trials (eg pig-to-nonhuman primate studies) should only be approved if both the chances of success and the potential benefits of such therapies are high and no other realistic therapeutic advances are available.

All xenotransplantation research proposals involving animals (both preclinical and clinical) must include protocols that comply with the Code of Practice and its supplementary policies and ensure high standards of animal welfare. Protocols should also include measures to minimise the risks of human-to-animal infections.

To provide national oversight and assist decision making, there should be a national register of animal-to-animal (preclinical) studies that are intended to lead to animal-to-human (clinical) studies.

Efficacy

12.21 Some animal-to-human transplantation trials of animal external therapies and animal cell therapies have been carried out or are in progress overseas. The results so far do not show clear benefits of the therapies but there have been improvements in some patients and very few adverse effects for these types of therapies. Further advances in gene technology may allow development of new approaches to improve the outcomes of animal therapies, including animal organ transplants.
12.22 Other approaches, such as human external therapies and human cell therapies (stem cell research), are also being developed and may or may not yield more promising results over the same timeframe as animal transplantation therapies. Meanwhile, people who are suffering from serious diseases and conditions, and their families, want improved medical treatment.

12.23 Because of the wide variety of therapies covered and the severity of different diseases and conditions to be treated, it is not possible to define prospectively the precise point at which evidence from laboratory experiments and animal-to-animal studies is considered sufficient to move to clinical trials of animal transplantation therapies.

12.24 The overall safety considerations associated with animal-to-human transplantation research dictate that only trials that offer a therapeutic benefit to the participants are ethically acceptable, rather than those that are designed only to advance knowledge. Therefore, for each proposed trial, there needs to be a realistic expectation that the therapy will provide some therapeutic benefit to the participants in the trial, based on well-designed preclinical studies in animals.

**XWP conclusion:** Animal-to-human transplantation research proposals should only be approved if animal-to-animal studies have shown a clearly documented therapeutic benefit for the participant. Such proposals should also only be approved if the research sponsors have shown that there are no alternative therapies for which preclinical studies or clinical trials show more chance of benefit.

**Safety**

12.25 There is broad agreement in the scientific community that animal-to-human transplantation carries some risk of transmitting infectious diseases from the source animals to human recipients and, in the worst case, to the wider community. The extent of this risk is the subject of some debate but, as for other uses of biological materials where transmission of infection is a concern (such as blood transfusion and human organ transplants), the medical community has considerable expertise in minimising and managing such risks.

12.26 Although researchers report that the chance of a major infectious disease outbreak occurring as the result of animal-to-human transplantation trials is likely to be very low, the consequences of such an outbreak would be extremely serious. This is reflected in an understandably high level of concern in the community about such risks and considerable tension between the general public and researchers, as well as between groups of scientists who are divided over whether the risks can be managed. This concern and uncertainty must be taken into account when decisions are made about the acceptability of a proposed animal-to-human transplantation trial and, because of the inherent uncertainties about potential infectious agents, an extremely cautious approach will be needed.

12.27 As there are some risks involved with all activities in life, risks need to be balanced against benefits to decide when they are acceptable and when they are not. It is impossible to define a precise point at which a risk becomes acceptable but for each situation a detailed risk analysis can help decision making. Risk analysis involves identifying all the factors involved and what is known and not known about how they may interact to cause an adverse event.
12.28 Therefore, assessment of proposed animal-to-human transplantation trials would need to include a risk analysis, based on all the known characteristics of potential infectious agents, the extent of the interaction between animal and human tissues (in both time and space), and the proposed strategies and tests to be used to monitor patients and close contacts and manage an infection should one occur.

**XWP conclusion:** Animal-to-human transplantation research proposals should be accompanied by a detailed analysis of the risks of infectious disease transmission and spread and a plan for minimising the risks and managing any infection that may occur (including an appropriate policy of containment). Trials that carry an unacceptable level of risk, or do not include appropriate risk management strategies, should not be approved.

**Trial protocols for information sharing and consent**

12.29 As for any clinical trial proposal, proposals for animal-to-human transplantation trials will need to meet all the ethical standards set out in the National Statement (NHMRC 1999), including those for participant selection.

12.30 In addition, the arrangements for information giving will need to be sensitive to the potentially serious health problems of the proposed participants, possible lack of other options, and the ongoing implications both for themselves and for their close contacts of contracting an infectious disease of animal origin.

12.31 Consent forms should clearly separate consent for participation in the trial and consent for long-term monitoring and surveillance as participants will have the right to withdraw from the clinical trial itself (ie to not received further medical treatment) but not from long-term monitoring and surveillance.

**XWP conclusion:** Animal-to-human transplantation research proposals should only be approved if the trial protocol includes clear patient information sheets and procedures to be followed for appropriate information sharing, counselling and consent. These procedures should involve both the research participants and their close contacts and include information and counselling on the need for ongoing and long term follow-up and surveillance. Consent forms for participants, and signed information sheets for close contacts, should set out clearly the conditions of the trial and the potential risks. Consent should also be obtained for long-term follow-up.

**Monitoring and follow-up of participants and contacts**

12.32 However slight the risk of infectious disease spread may be for a particular trial proposal, monitoring and follow-up of participants and contacts will be an essential part of the risk management strategy. To be effective, such a strategy must be based on validated, up-to-date tests and procedures that allow early detection of the emergence of a potential infection in the participant, or its spread to a close contact.

12.33 In this regard, it will also be important that all trial participants are entered in a national register and that all necessary clinical data (including tissue samples) is collected and stored to allow later assessment and tracing of public health risks. Such registers should also be used to ensure that participants in animal transplant procedures do not donate their organs or tissues to others in the future or after their death.
XWP conclusion: Animal-to-human transplantation trial proposals should only be approved if the trial protocol includes validated processes for monitoring and surveillance of research participants and close contacts for public health risks (including overseas movements). Protocols should also include procedures for collection and storage of sufficient clinical data and tissue samples to allow tracing of public health risks and prevention of future organ and tissue donations by recipients of animal transplants.

Alternatives to xenotransplantation

12.34 Organ and tissue donations are required to overcome a large range of diseases and conditions. Xenotransplantation is only one of a number of approaches that might be used to overcome the current shortage of such donations.

12.35 Although vigorous efforts are needed to increase the number of human donations to transplantation programs, it is unlikely that such efforts will overcome the extreme shortfall, especially as further new therapies are developed that use transplanted cells and tissues.

12.36 Although various alternative therapies are currently being researched (human external and cell therapies, artificial organs and so on), the XWP concluded that Australia should be able to opt for the therapy that is considered the most efficacious and safest at the time. If human cells fulfil this role in a given circumstance, they will supplant animal cells for that particular therapy and vice versa. Before agreeing to proceed with a trial of animal-to-human transplantation, the proposed regulatory committee will need to consider all alternative therapeutic options available at the time.

12.37 Attention to preventive strategies is always a worthwhile goal for health care systems, and could remove the need for transplants for some patients. However, many other diseases that are treatable by transplant therapies are not related to lifestyle or preventable by other public health measures (see paragraphs 6.47–6.50).

XWP conclusion: Until we can more accurately identify the best option for treating particular diseases and conditions, it may be best to adopt an integrated research approach, including a range of different options.

Extreme care will be needed, however, to ensure that participants are only enrolled into animal-to-human transplantation trials when either: (a) there are no alternative treatments available that could provide greater therapeutic benefit than the proposed animal therapy; or (b) if there is an alternative therapy (such as a human organ transplant), this option is not available within a clinically useful timeframe.

Resourcing

12.38 As for other new medical technologies, xenotransplantation raises resource use issues. These include the costs of research to develop the technology, access of patients to the therapies through the public and private health systems, and liability for the costs to individual patients or society as a whole of an infectious disease outbreak.

12.39 Funding agencies, such as the NHMRC and the Australian Research Council, set research priorities based on national health priorities and will continue to consider applications case by case basis within that framework. Privately funded research will continue to be based
on the prospects of a commercial return from the technology. The XWP noted that, in either case, research sponsors and funding agencies need to adequately assess all the costs involved in conducting animal-to-human transplantation research in Australia, including long-term monitoring and surveillance activities.

12.40 Participation in animal-to-human transplantation trials would be free to the patients involved (as for all clinical trials), because the costs of such research are borne by the research sponsors. If the technologies become routine clinical practice, appropriate funding arrangements will need to be made through the Medical Benefits Scheme, public hospitals and publicly funded specialist units, to ensure access to the procedures (as for similar procedures, such as human-to-human transplants).

12.41 Under the National Statement and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Note for Guidance on Good Clinical Practice (CPMP/ICH 135/95), research sponsors are required to insure against possible compensation claims for adverse events in both the short and the long term. Legal liability, insurance and compensation issues should therefore all be clearly stated in research protocols. However, appropriate regulations will be required to ensure that mechanisms are in place to minimise the risk of an adverse event occurring.

**XWP conclusion:** Research funding agencies will continue to fund research based on national health priorities (public funding), or commercial viability (private funding). In either case, research sponsors should ensure that all costs of the research are considered, including long-term monitoring and surveillance of transplant recipients and close contacts.

Access to clinical trials will be based on research participant selection criteria (see paragraph 12.29) and participation in the trials, including all monitoring and follow-up, will incur no costs to the participants.

Under Australian and international guidelines, research protocols must include insurance arrangements for compensation in the event of an adverse event in the short or long term, including emergence of an infectious disease.

### Regulation of xenotransplantation research

12.42 The XWP has considered several approaches that could be taken for the regulation of xenotransplantation research, from the most permissive (allow all trials that meet local HREC and AEC approval) to the most restrictive (ban all trials). Taking account of all the issues raised in the Discussion Paper, submissions and this Response Paper, including progress already being made to develop and trial animal therapies overseas, the XWP has concluded that Australia should pursue an intermediate option. That is, animal-to-human transplantation clinical trials should be permitted as long as trial protocols meet rigorous NHMRC guidelines for efficacy, safety, animal welfare and ethical conduct of the trials. This approach would allow the field to develop in a regulated and safe way.

12.43 It is anticipated that, initially, smaller exploratory trials would be carried out, which would need to be extremely well planned and closely monitored. Such trials would provide further evidence of efficacy and safety for human recipients. Larger trials would not be undertaken until there had been a proper and thorough assessment of the results from the smaller studies.
Proposed strict national regulation for animal-to-human transplantation trials

12.44 To provide the rigorous oversight of animal-to-human transplantation clinical trials that would be expected by the Australian community, the XWP has proposed a regulatory process with:

- national oversight of NHMRC ethical guidelines; and
- legislated further approval by the Therapeutic Goods Administration (TGA) in every case.

12.45 The proposed regulatory process is described in detail in Section 11 of this Response Paper. Briefly, it includes an expansion of both the membership and terms of reference of the NHMRC’s Gene and Related Therapies Research Advisory Panel (GTRAP) to allow it to provide national oversight of animal-to-human transplantation trial proposals (ie to become the National Xenotransplantation and Gene Therapy Committee).

12.46 Under this scheme, all animal-to-human transplantation research proposals would be submitted to the new National Xenotransplantation and Gene Therapy Committee, for assessment against NHMRC guidelines. Approved proposals would then have to be submitted to the TGA as CTX applications and the TGA would further assess efficacy and safety (particularly with respect to the manufacture and supply of the xenotransplantation products). Only trials approved by the national xenotransplantation committee and the TGA could be further considered by local HRECs and AECs. Access to xenotransplantation therapies for individual patient use would not be allowed under the Special Access Scheme (SAS) or other similar schemes. This would mean that every use of a xenotransplantation therapy in humans would have to be first approved by the national committee and the TGA.

12.47 These last two conditions (mandatory CTX application to the TGA and prohibition of access through the SAS) would both require changes to the Therapeutic Goods Act 1989. Such changes are already foreshadowed in recent proposals by the TGA to amend its legislation to allow better regulation of a range of biological therapies that are considered to be high risk. The XWP supports these proposals.

12.48 The role of the Office of the Gene Technology Regulator in administering the Gene Technology Act would also form an important part of any regulatory scheme, especially for the development and production of genetically modified xenotransplantation products.

12.49 In setting up this scheme, important issues that will need further consideration by the NHMRC are:

- the funding and legal basis of the proposed national xenotransplantation committee, which would be based on the existing GTRAP (with additional members and broadened terms of reference commensurate with its new role), to allow it to perform its expanded role with respect to xenotransplantation;
- setting up and maintaining a register of all animal-to-human transplantation clinical trials and research participants; and
- setting up and maintaining a register of all animal-to-animal transplantation preclinical studies that are directly related to the development of clinical trial proposals.
Purpose of NHMRC guidelines

12.50 A central element of the proposed regulatory approach for animal-to-human transplantation trials is the assessment of trial proposals against strict NHMRC guidelines. The draft guidelines presented by the XWP for public comment with the Discussion Paper in June 2002 were developed to take into account the principles outlined above. In response to the submissions received and the further issues raised in this Response Paper, the draft guidelines have been revised and are presented at the end of this section for further public comment.

12.51 Once approved, these guidelines would be used by the proposed national committee, TGA and the institutional HRECs and AECs to assess animal-to-human transplantation trial proposals and monitor the progress of trials. The guidelines would help to ensure that only proposals that are deemed safe, provide a real possibility of therapeutic success and have protocols that ensure the highest ethical standards for animal welfare, patient selection, information sharing and consent, and participant protection, would be approved.

12.52 An early task for the national committee in implementing the guidelines would be to develop more detailed instructions for research sponsors in preparing research proposals. The Discussion Paper included some draft material (‘Advice regarding the application of the proposed guidelines’), which may form the starting point for more detailed guidance. This advice is also included with the draft guidelines below.
Revised draft NHMRC guidelines for clinical xenotransplantation research

Introduction

These revised draft guidelines are drawn from the issues raised in the Discussion Paper, in the submissions received and in this Response Paper. They are presented here for public consultation. The draft guidelines draw on the following key principles.

- Preclinical xenotransplantation research (animal-to-animal studies) is already established in Australia. Although translation of that research and research from overseas into clinical (animal-to-human) trials is likely to be slow, especially for solid organ transplantation, a moratorium on such clinical research is not appropriate.

- Clinical (animal-to-human) trials must be based upon relevant efficacy data from preclinical (animal-to-animal) research.

- Translation of animal-to-animal xenotransplantation studies into clinical (animal-to-human) trials raises special issues beyond those encountered in almost all other types of human research, especially issues of safety, efficacy and consent. In particular, at our present state of knowledge, it is acknowledged that xenotransplantation carries a risk of introducing new infectious agents into recipients of xenotransplantation products, with the possibility of infecting close contacts and the wider community.

- Xenotransplantation clinical (animal-to-human) trials must therefore have broad community acceptance and must be subject to guidelines, which, once finalised, will apply to all such trials conducted in Australia.

- Xenotransplantation clinical (animal-to-human) trials must be overseen by a single national committee with the necessary expertise and with community input, in order to reassure the community that any proposed clinical trials are adequately assessed and monitored according to agreed national guidelines.

- Human research ethics committees (HRECs) and animal ethics committees (AECs) must be bound by the advice of the proposed national committee, but should have the power to refuse to authorise any research to be done in their own institution. HRECs and AECs should also be involved in onsite monitoring of the trials.

Use of the (draft) guidelines

These draft guidelines provide direct guidance only on areas that are specific for xenotransplantation and should be read in conjunction with the current edition of the NHMRC National Statement on Conduct in Ethical Research Involving Humans, which provides ethical guidelines for all other aspects of research involving humans.

The (draft) guidelines have been developed to guide the (proposed) National Xenotransplantation and Gene Therapy Committee in its deliberations and to assist investigators wishing to submit proposals for assessment. When finalised, the guidelines will also assist the Therapeutic Goods Administration (TGA) and individual HRECs and AECs in those institutions in which xenotransplantation human trials are conducted.
The (draft) guidelines address the key issues at stake for the participants in this research and the community and are broad in their design. They are accompanied by a draft of a more detailed set of advice detailing how each guideline may be fulfilled. The Xenotransplantation Working Party hopes that such broad guidelines, together with the composition and powers of the national committee and refinement of the accompanying advice to provide more detailed day-to-day working guidelines, will adequately safeguard the community and, at the same time, allow sufficient flexibility for the national committee to respond to emerging knowledge about risks, efficacy and consent in this type of human research.

Animal-to-animal (preclinical) xenotransplantation studies are also subject to existing Australian guidelines, State and Territory legislation and, in relevant situations, oversight by the Office of the Gene Technology Regulator.

**Coverage of the (draft) guidelines**

**National assessment and authorisation**

All animal-to-human xenotransplantation research proposals must be assessed according to these (draft) guidelines and authorised by the (proposed) National Xenotransplantation and Gene Therapy Committee and the Therapeutic Goods Administration (as a CTX application for use of an unregistered therapeutic good) before they can be considered by HRECs and AECs at the institutions where the research will occur. The (proposed) national committee and the TGA must be satisfied that the research proposal conforms with the current edition of the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) *Note for Guidance on Good Clinical Practice* (CPMP/ICH 135/95), as well as with these (draft) guidelines.

The following human research is defined to be xenotransplantation.

(a) Any procedure that involves the transplantation, implantation or infusion into a human recipient of live cells, tissues or organs from a nonhuman animal source (an in vivo transplant), that is:
   - organ transplants (eg heart, kidney, liver)
   - tissue transplants (eg skin)
   - cellular transplants
     - without a semipermeable capsule (eg fetal pig neural cells transplanted into the human brain for treatment of Parkinson’s disease); and
     - enclosed in a semipermeable capsule (eg encapsulated islets of Langerhans cells transplanted into the peritoneal cavity to treat diabetes).

(b) Any procedure that involves the transplantation, implantation or infusion into a human recipient of human body fluids, cells, tissues or organs that have had contact outside the body with live nonhuman animal cells, tissues or organs (an ex vivo procedure), that is:
   - perfusion of human body fluid through animal tissues or cells, which may or may not be separated by a semipermeable membrane (eg perfusion of human blood through a dialysis-like system containing animal liver cells, or perfusion of human blood through a whole pig liver)
– growth of human cells on a feeder layer of animal cells for transplanting back to the same individual (e.g., growth of human skin or human stem cells on a mouse cell feeder layer).

A human xenotransplantation research proposal that has been approved by the national committee and allowed to proceed by the institutional HREC and AEC must be monitored nationally by the national xenotransplantation committee and locally by the HREC/AEC.

**Local approval**

HRECs and AECs must not authorise xenotransplantation human trials without express authorisation in writing from the national xenotransplantation committee. If such authorisation has been granted, HRECs and AECs should use these (draft) guidelines and the current edition of the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* to assess the suitability of xenotransplantation research proposals for their institutions.

**Xenotransplants received overseas**

If a recipient of xenotransplantation (as defined above) returns to or travels to Australia, having received a xenotransplant abroad, the treating medical practitioner in Australia is required to advise the national xenotransplantation committee and follow such aspects of these (draft) guidelines as advised by the national committee. In particular, the treating medical practitioner should obtain consent from the xenotransplant recipient to being entered on the central register (see Guideline 7, below).

**Principles**

The (draft) guidelines are designed to ensure that the following principles are adhered to in the assessment and approval or rejection of proposals for human xenotransplantation clinical research:

- the research must serve the common good;
- the research must be scientifically sound;
- the research must be based on relevant efficacy data from preclinical studies;
- the research must be therapeutic in design;
- the benefits must justify any risks;
- the research should not expose the participants, their contacts or society to any unreasonable risks;
- the research must respect the dignity of participants;
- participants must give adequately informed and voluntary consent;
- arrangements for monitoring and follow-up must take account of the participant’s right to withdraw from the trial;
- the safety and rights of close contacts of the participants must be protected; and
- the research must respect the welfare of animals used in the trial and be conducted according to the NHMRC *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.*
Draft guidelines

Guideline 1 (Animal welfare)
(a) All xenotransplantation studies (preclinical and clinical) involving animals must be conducted with due regard for high standards of animal welfare and in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (the Code of Practice) and other associated policies.
(b) To assist national overview and decision making on animal-to-animal xenotransplantation research in accordance with the Code of Practice, researchers should submit information to a central register about all animal-to-animal studies that are directly related to the development of animal-to-human trials (eg pig-to-nonhuman primate studies).

Guideline 2 (Efficacy)
Any proposed clinical (animal-to-human) transplantation trial must be based on preclinical (animal-to-animal) studies that demonstrate a likely therapeutic benefit to the participants.

Guideline 3 (Safety)
The public health risks of any proposed animal-to-human transplantation trial must be minimal and must be acceptable to the community.

Guideline 4 (Patient selection)
Research protocols must include clear criteria for patient selection and also provide evidence to support the benefit of animal-to-human transplantation therapy for these patients compared to other conventional or experimental therapies available.

Guideline 5 (Information giving)
The research protocol must include:
(a) clear patient information sheets that allow potential research participants to make an informed decision about the proposed procedure; and
(b) procedures which, when followed, ensure that appropriate information and counselling are provided to potential participants and that no coercion is used; and
(c) procedures which, when followed, ensure that appropriate information and counselling are provided to close contacts, including carers, of the xenotransplant recipient; and
(d) procedures which, when followed, ensure that research participants and their close contacts, including carers, are aware of the need for ongoing and long-term follow-up and surveillance for possible emerging personal and public health risks.
Guideline 6 (Consent)

The research protocol must include:

(a) procedures which, when followed, ensure that the consent of potential research participants is obtained after the necessary information is provided (Guideline 5) and which allow the participant to take a reasonable period to think things over and discuss the information provided with their close contacts; and

(b) consent forms that clearly set out what is being consented to, including the need for ongoing and long-term surveillance for possible emerging personal and public health risks; and

(c) procedures for collection of signed information sheets (or equivalent) from close contacts of research participants.

Guideline 7 (Monitoring and surveillance)

The research protocol must include processes for monitoring and surveillance based on the most up-to-date procedures available. It must also show that resources and facilities are available for the timely monitoring and surveillance for public health risks of research participants and, if required, their close contacts.

Guideline 8 (Data and tissue storage)

The research protocol must include procedures which, when followed, ensure that:

(a) all research participants are informed about, and have consented to, their clinical data being entered on a central register maintained by the national committee; and

(b) the necessary clinical data are collected to enable future analysis; and

(c) all necessary tissue samples are collected and securely stored for an appropriate period to allow tracing of public health risks.

Guideline 9 (Management of public health risks)

The research protocol must include procedures for the management of public health risks if they should occur (such as an emerging infectious disease), including an appropriate policy of containment.
Advice regarding the application of the proposed guidelines

The following tables present advice on data requirements and assessment issues for animal-to-human (clinical) transplantation research guidelines. They are an outline of the detail that the proposed national xenotransplantation committee would expect to see addressed in any application for approval and authorisation of a human xenotransplantation trial.

A. THE COMMON GOOD

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<tr>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are the ethical issues associated with this procedure acceptable to the general public?</td>
</tr>
<tr>
<td>What are the public and individual benefits of this procedure?</td>
</tr>
<tr>
<td>What are the public and individual risks of this procedure?</td>
</tr>
<tr>
<td>Are there any alternative procedures available?</td>
</tr>
<tr>
<td>Are the infectious risks associated with this procedure acceptable to the general public?</td>
</tr>
</tbody>
</table>
### B. ANIMAL WELFARE

<table>
<thead>
<tr>
<th>ANIMALS</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonhuman primates</strong></td>
<td>Rationale/justification for use in preclinical animal-to-nonhuman primate study</td>
<td>Is the use of nonhuman primates justified in this study?</td>
</tr>
<tr>
<td></td>
<td>Number to be used</td>
<td>Is the proposed number of animals acceptable for this procedure?</td>
</tr>
<tr>
<td></td>
<td>Source</td>
<td>What is the source of the animals?</td>
</tr>
<tr>
<td></td>
<td>Level of containment</td>
<td>Is the proposed level of containment appropriate for the trial?</td>
</tr>
<tr>
<td></td>
<td>Animal husbandry information:</td>
<td>Do the conditions comply with all aspects of the Code of Practice?</td>
</tr>
<tr>
<td></td>
<td>– housing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– environmental enrichment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– transport requirements</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– pre- and postsurgery care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– appropriate anaesthetic and analgesic regimes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– immunosuppression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– length of time animals would be held in laboratories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– number of experimental and surgical procedures to be conducted on an individual animal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– special dietary needs</td>
<td></td>
</tr>
<tr>
<td><strong>Pigs</strong></td>
<td>Rationale/justification for use</td>
<td>Is the use of pigs justified in this study or trial?</td>
</tr>
<tr>
<td></td>
<td>Number to be used</td>
<td>Is the proposed number of animals acceptable for this procedure?</td>
</tr>
<tr>
<td></td>
<td>Source</td>
<td>What is the source of the animals?</td>
</tr>
<tr>
<td></td>
<td>Genetic modification(s)</td>
<td>Will the proposed genetic modifications alter the essential nature of the pig (ie are they ethically acceptable)?</td>
</tr>
<tr>
<td></td>
<td>– What are the nature and extent of the modification(s)?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Does the modification significantly alter the animal?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level of containment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal husbandry information:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– housing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– socialisation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– appropriate food</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– adequate number and appropriate qualifications of animal technicians involved in routine care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– appropriate use of analgesics and anaesthetics</td>
<td></td>
</tr>
<tr>
<td><strong>Other species</strong></td>
<td>Similar considerations to the above</td>
<td>Compliance with the Code of Practice</td>
</tr>
</tbody>
</table>
### C. EFFICACY

<table>
<thead>
<tr>
<th>RESEARCH</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed trial description/protocol</td>
<td>Rationale</td>
<td>What is the proposed procedure?</td>
</tr>
<tr>
<td></td>
<td>Description of trial</td>
<td>What is the expected therapeutic benefit to the research participants? (Note: nontherapeutic trials will not be permitted)</td>
</tr>
<tr>
<td></td>
<td>Therapeutic benefit to participants</td>
<td>What are the gross physiological issues, biochemical/endocrinological factors and immunological barriers that may affect the outcome of this trial?</td>
</tr>
<tr>
<td></td>
<td>Factors that may affect outcome</td>
<td>Is it a permanent transplant, or a bridging procedure?</td>
</tr>
<tr>
<td></td>
<td>Proposed strategies to ensure success</td>
<td>How does the investigator propose to overcome barriers to success (eg by genetic modification of the source animal)?</td>
</tr>
<tr>
<td></td>
<td>Literature research</td>
<td>What is the evidence that this will succeed (including detailed assessment of preclinical studies)?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Has all the relevant background information from published literature been evaluated?</td>
</tr>
<tr>
<td>Source animal characterisation</td>
<td>Choice and justification of source animal species</td>
<td>What animal species will be used?</td>
</tr>
<tr>
<td></td>
<td>Anatomical, physiological and genetic considerations</td>
<td>What are the reasons for the choice of animal?</td>
</tr>
<tr>
<td></td>
<td>Animal history/herd characterisation</td>
<td>What genetic modifications have been undertaken?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What are the geographic origins, strain and genealogy of the source animal?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Have all necessary measures been taken to ensure the quality of the xenotransplantation product?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[See also advice under C. Safety and E. Animal welfare, below.]</td>
</tr>
<tr>
<td>Xeno-transplantation product characterisation</td>
<td>Type of product</td>
<td>What type of product will be used (eg organ, tissue, cells)?</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>Will the product be treated in any way after harvesting (eg encapsulated, cultured, stored)?</td>
</tr>
<tr>
<td></td>
<td>Quality control/good manufacturing practice (GMP)</td>
<td>Does the protocol take account of all relevant GMP and quality control considerations for the xenotransplantation product?</td>
</tr>
<tr>
<td>Participant selection</td>
<td>Criteria for selection of research participants</td>
<td>How will candidates with the best potential for clinically significant improvement and increased quality of life be identified and selected?</td>
</tr>
<tr>
<td></td>
<td>Alternative therapies</td>
<td>Are there any adequate, safe and effective alternative therapies available?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If so, does the protocol exclude from the trial patients who could benefit from these alternatives?</td>
</tr>
</tbody>
</table>

*contd...*
<table>
<thead>
<tr>
<th>RESEARCH</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence of efficacy/safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal-to-animal (preclinical) studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– experimental (in vitro) studies</td>
<td>In vitro studies of biochemical/endocrine/immunological responses relevant to therapeutic outcomes</td>
<td>Do these studies show the mechanisms involved and how they can be modified to increase the chance of a successful outcome in humans?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Have all aspects of the mechanisms been studied?</td>
</tr>
<tr>
<td></td>
<td>– animal studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Source animal</td>
<td>Was the same source animal used as is proposed for the human trial? (If not, provide justification)</td>
</tr>
<tr>
<td></td>
<td>Recipient animal</td>
<td>Was the recipient animal (preferably baboon) a suitable model for human transplantation?</td>
</tr>
<tr>
<td></td>
<td>Study protocol</td>
<td>Did the preclinical study protocol reflect the proposed clinical trial protocol (e.g. implantation site, duration, immunosuppressive protocol)?</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression used</td>
<td>Were there any clinical toxicological, pharmacological or immunological issues arising from the drug regimen used?</td>
</tr>
<tr>
<td></td>
<td>Rejection of transplant</td>
<td>How well did the xenotransplant survive? (e.g. success of genetic modification in preventing rejection, or in vivo function and durability of encapsulation or other barriers to diminish rejection)</td>
</tr>
<tr>
<td></td>
<td>Functioning of transplant/survival of recipient animal</td>
<td>How well did the xenotransplant perform? Did it sustain life or reverse disease symptoms of the recipient?</td>
</tr>
<tr>
<td></td>
<td>Other considerations</td>
<td>Are there any other considerations arising from the study that might affect efficacy (e.g. the tumourigenic potential of the transplant, migration of xenogenic cells etc)?</td>
</tr>
<tr>
<td>Animal-to-human (clinical) trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– previous trials using the proposed protocol</td>
<td>Source/study protocol/outcomes</td>
<td>As for animal-to-animal studies (Note: this will only apply for phase II or III clinical trial applications where there is already some phase I trial evidence available)</td>
</tr>
<tr>
<td>– trials using a related protocol</td>
<td>Source animal/study protocol/outcomes</td>
<td>Do the results of related clinical trials help to understand the possible outcomes of the proposed trial?</td>
</tr>
</tbody>
</table>
# D. SAFETY (risk analysis for infection risks)

<table>
<thead>
<tr>
<th>RISK ANALYSIS</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk assessment</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard identification</td>
<td>Source animal (and pedigree): – nonhuman primate, pig, other</td>
<td>Infectious agents present (exogenous and endogenous)</td>
</tr>
<tr>
<td>Hazard characterisation</td>
<td>Infectious agent of concern</td>
<td>Infectivity to patient (infectious dose and dose response) Mode of transmission and infectivity for contacts Incubation/window period (ie potential for early diagnosis before it spreads to other people) For PERV, data on gene mapping, secretion and infectivity Type of genetic modification Relationship between genetic modification and infectious agents (could modification increase the potential for infectivity?)</td>
</tr>
<tr>
<td></td>
<td>Genetic modification of source animal</td>
<td></td>
</tr>
<tr>
<td>Exposure assessment</td>
<td>Type of procedure</td>
<td>Vascularised organ or nonvascularised tissue or cells In vivo transplant or ex vivo perfusion Barrier or no barrier Agents used Immunologically protected site (eg brain) or not</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression of recipient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Site of transplant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Length of exposure</td>
<td>Long or short term (eg permanent or bridging transplant) Based on available information</td>
</tr>
<tr>
<td></td>
<td>Estimated exposure</td>
<td></td>
</tr>
<tr>
<td>Impact/consequences</td>
<td>Human infection</td>
<td>Nature of disease (pathogenicity) Potential for transmission (related to mode, incubation period, ‘window’ for diagnosis etc) Potential for treatment</td>
</tr>
<tr>
<td>Risk characterisation</td>
<td>Overall assessment of potential for human infection and spread of infection Disclosure of areas where not enough information is known to assess risk</td>
<td></td>
</tr>
<tr>
<td>Risk management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocols to maintain risk below acceptable levels</td>
<td>Screening for infectious agents (eg PERV)</td>
<td>What test will be used to screen for infectious agent? What is the sensitivity and specificity of the test? How often will participants and contacts be screened? What arrangements are in place for storage of samples?</td>
</tr>
<tr>
<td></td>
<td>Other surveillance measures</td>
<td>What other disease surveillance measures are in place at the local, national and international levels?</td>
</tr>
<tr>
<td></td>
<td>Procedures if infection occurs</td>
<td>What procedures will be followed if a participant becomes infected?</td>
</tr>
<tr>
<td>Risk communication</td>
<td>Have there been discussions with experts, stakeholders and the community about the level and acceptability of risks, including uncertainties?</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on assessment of all relevant experimental and preclinical studies and clinical trials relating to infectious agents of concern
<br>
PERV = porcine endogenous retrovirus
### E. TRIAL PROTOCOL

<table>
<thead>
<tr>
<th>PARTICIPANT</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research participant</td>
<td>Selection</td>
<td>Does the protocol for participant selection comply with guidance in the National Statement? Does the protocol include a process to ensure that all other therapeutic options will be considered for each participant?</td>
</tr>
<tr>
<td></td>
<td>Information</td>
<td>Is the information that will be given to research participants sufficient to help them decide whether to consent to the procedure or not (eg efficacy and safety issues, alternative treatments available, requirement for long-term monitoring, measures that may be required if an infection is detected)?</td>
</tr>
<tr>
<td>Voluntary consent</td>
<td></td>
<td>Is the person who will present the information to the research participant suitable for the task (eg independent of the research team)? Are safeguards in place to ensure that the research participant’s consent to the procedure is obtained voluntarily and without coercion?</td>
</tr>
<tr>
<td>Long-term follow-up (monitoring)</td>
<td></td>
<td>Is the information that will be given to research participants about lifelong monitoring sufficient to encourage them to commit to and comply with these measures (eg tests involved, frequency, measures that may be required if an infection is detected)? Are there any arrangements in place to facilitate compliance with monitoring requirements (eg travel arrangements, home visits)? If a patient withdraws from the trial (ie does not continue with long-term monitoring), how will this affect the overall risk assessment for the trial?</td>
</tr>
<tr>
<td>Confidentiality</td>
<td></td>
<td>Does the protocol include measures to ensure that the confidentiality of the research participant is safeguarded within the constraints of the necessary arrangements for identifying and monitoring close contacts?</td>
</tr>
<tr>
<td>Close contacts of research participant</td>
<td>Risk status</td>
<td>Is the risk status of close contacts of the research participant clearly defined?</td>
</tr>
<tr>
<td></td>
<td>Information</td>
<td>Is the information that will be given to close contacts of the research participant sufficient for their role in the decision process (eg potential outcome for the research participant, their own risk status, requirements for monitoring)? Is the person who will present the information to close contacts suitable for the task?</td>
</tr>
<tr>
<td></td>
<td>Voluntary involvement</td>
<td>Are there safeguards in place to ensure that close contacts (including carers) are completely comfortable with their involvement in the trial?</td>
</tr>
<tr>
<td></td>
<td>Monitoring</td>
<td>Is the information that will be given to close contacts about monitoring requirements sufficient to encourage them to commit to and comply with these measures (eg tests involved, frequency, measures that may be required if an infection is detected)? Are there any arrangements in place to facilitate compliance with monitoring requirements (eg home visits)? If a close contact does not comply with the monitoring requirements, how will this affect the overall risk assessment for the trial?</td>
</tr>
</tbody>
</table>
## OVERALL ASSESSMENT OF PROPOSAL

<table>
<thead>
<tr>
<th>Issue</th>
<th>Criterion</th>
<th>Yes/no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public good</td>
<td>Does the research serve the common good?</td>
<td></td>
</tr>
<tr>
<td>Animal ethics of protocol</td>
<td>Does the research protocol respect the dignity and welfare of animals used in the trial?</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>Is the research based on preclinical (animal-to-animal) studies that show a therapeutic effect?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do the benefits justify the risks?</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>Would the research expose the participants or society to any unreasonable risks?</td>
<td></td>
</tr>
<tr>
<td>Human ethics of protocol</td>
<td>Is the research therapeutic in design?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Does the research protocol respect the dignity of participants?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Does the protocol for participant selection meet all relevant guidelines?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Are there any alternative therapies that would offer a better outcome for participants?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Does the protocol allow research participants to give adequately informed and voluntary consent?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Does the protocol take account of research participants’ right to withdraw from further medical treatment?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Are the safety and rights of close contacts of the research participants adequately protected?</td>
<td></td>
</tr>
</tbody>
</table>

| APPROVAL                     | YES/NO                                                                 |        |

Animal-to-human transplantation research: How should Australia proceed?
Appendix A Committee membership

Xenotransplantation Working Party

Dr Jack Sparrow Chair
Dr Kerry Breen Chair of AHEC
Associate Professor Bernadette Tobin AHEC member (former) with expertise in philosophy and transplantation ethics
Dr Dominic Dwyer Research Committee/GTRAP member with expertise in clinical virology and infectious diseases
Professor Aileen Plant Member with expertise in infectious diseases and public health
Associate Professor Philip O’Connell Research Committee/GTRAP member with expertise in clinical and experimental transplantation
Dr Simone Strasser Clinician with background in transplantation (excluding xenotransplantation)
Ms Elizabeth Grant Chair of NHMRC Animal Welfare Committee
Ms Glenys Oogjes Member with animal welfare background (Animals Australia)
Dr Hugh Wirth Member with animal welfare background (RSPCA)
Ms Michele Kosky Member with expertise in consumer issues (Consumers’ Health Forum)
Mr Twanny Farrugia Member with expertise in consumer issues (Chronic Illness Alliance Inc)
Dr Leonie Hunt Therapeutic Goods Administration
Dr Bruce Scoggins Observer, New Zealand Health Department
To be appointed Member with expertise in clinical and experimental transplantation

Secretariat (Office of NHMRC)

Dr David Abbott Project officer since April 2003

Technical writer
Dr Janet Salisbury Biotext, Canberra
### Animal Issues Subcommittee

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ms Elizabeth Grant</td>
<td>Chair</td>
</tr>
<tr>
<td>Dr Bidda Jones</td>
<td>Member with a demonstrable commitment to, and experience in, furthering the welfare of animals and who is not involved in the care and use of animals for scientific purposes (RSPCA)</td>
</tr>
<tr>
<td>Ms Helen Rosser</td>
<td>Member with a demonstrable commitment to, and experience in, furthering the welfare of animals and who is not involved in the care and use of animals for scientific purposes (Animals Australia)</td>
</tr>
<tr>
<td>Dr Lyndy Scott</td>
<td>Independent member with recent veterinary and animal husbandry experience (The Australian Veterinary Association Ltd)</td>
</tr>
<tr>
<td>Dr Robert Dixon</td>
<td>Member with experience in the regulation of the use of animals in research</td>
</tr>
<tr>
<td>A/Professor Graham Jenkin</td>
<td>Member from the Animal Welfare Committee of NHMRC with expertise in stem cell research</td>
</tr>
</tbody>
</table>
# Appendix B  List of respondents to the Discussion Paper

<table>
<thead>
<tr>
<th>Submission number</th>
<th>Name/organisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>X001</td>
<td>Dr Nicholas Tonti-Filippini</td>
</tr>
<tr>
<td>X002</td>
<td>Ms Sarah McNabb</td>
</tr>
<tr>
<td>X003</td>
<td>Mr Tony Clunies-Ross</td>
</tr>
<tr>
<td>X004</td>
<td>Mr Russell Linfoot</td>
</tr>
<tr>
<td>X005</td>
<td>Mr CA de Jong</td>
</tr>
<tr>
<td>X006</td>
<td>Ms Kerryn Elze</td>
</tr>
<tr>
<td>X007</td>
<td>Ms Lene Martens</td>
</tr>
<tr>
<td>X008</td>
<td>Individual (Confidential)</td>
</tr>
<tr>
<td>X009</td>
<td>South Australian Department of Human Services HREC (Mr Andrew Stanley)</td>
</tr>
<tr>
<td>X010</td>
<td>Ms Eliza Poulton</td>
</tr>
<tr>
<td>X011</td>
<td>Ms Alma S Jackson</td>
</tr>
<tr>
<td>X012</td>
<td>Dr John W Cox</td>
</tr>
<tr>
<td>X013</td>
<td>Mr Michael Mairou</td>
</tr>
<tr>
<td>X014</td>
<td>Queensland Health Department (Dr Gerry FitzGerald, Chief health Officer)</td>
</tr>
<tr>
<td>X015</td>
<td>Mr Trevor Wilson</td>
</tr>
<tr>
<td>X016</td>
<td>Professor Bernie Tuch</td>
</tr>
<tr>
<td>X017</td>
<td>Organisation (Confidential)</td>
</tr>
<tr>
<td>X018</td>
<td>Ms Debbie Blakeney</td>
</tr>
<tr>
<td>X019</td>
<td>Mr Chay Neal</td>
</tr>
<tr>
<td>X020</td>
<td>Ms Sydney Birchall</td>
</tr>
<tr>
<td>X021</td>
<td>Mr Craig Dearth</td>
</tr>
<tr>
<td>X022</td>
<td>Ms Stephanie Tabashneck</td>
</tr>
<tr>
<td>X023</td>
<td>Ms Jenny Moxham</td>
</tr>
<tr>
<td>X024</td>
<td>‘Joraen’</td>
</tr>
<tr>
<td>X025</td>
<td>Ms Maria Armstrong</td>
</tr>
<tr>
<td>X026</td>
<td>Mr Henry Sills</td>
</tr>
<tr>
<td>X027</td>
<td>Ms Carly Cooper</td>
</tr>
<tr>
<td>X028</td>
<td>People for the Ethical Treatment of Animals (USA) (Mr Peter Wood)</td>
</tr>
</tbody>
</table>
Animal-to-human transplantation research: How should Australia proceed?

X029 Thoracic Society of Australia and New Zealand
(Professor Allan Glanville)

X030 Ms Maren E Child

X031 Ms Ambre Hudson

X032 Mr Simon Wood

X033 Humane Charities Australia Inc
(Ms Helen Rosser)

X034 Christchurch School of Medicine and Health Sciences
(New Zealand) (Dr Anthony Raizis)

X035 Salvation Army
(Colonel Ivan B Lang)

X036 Ms Dawn Lowe

X037 Caroline Chisholm Centre for Health Ethics
(Rev Norman Ford)

X038 Ms Elizabeth Pappas

X039 Emeritus Professor David Allbrook

X040 Ratifiers for Democracy
(Toshi Knell)

X041 Gene and Related Therapies Research Advisory Panel

X042 Russell and Lindsey Linfoot (see also X004)

X043 Ms Karen Hudson

X044 Humane Charities Australia
(Helen Rosser)

X045 Ms Erica Lobl

X046 Ms Stella Hondross

X047 Federation of Ethnic Communities Councils of Australia
(Abd Malak, Chair)

X048 Armadale Health Service Ethics and Research Committee,
Department of Health, Western Australia
(Dr Judith Thomson)

X049 Anti-Vivisection Union of South Australia
(Diana Palmer)

X050 RSPCA Australia
(Dr Bidda Jones)

X051 Ms Sylvia Ahern

X052 Ms Bernice Bovenkerk

X053 Transplantation Society of Australia and New Zealand
(Dr Randall Faull; Professor Anthony D’Apice; Professor Ken
Hardy; Professor Mauro Sandrin; Professor Bernie Tuch)

X054 Individual (confidential)
Department of Human Services, South Australia, Human Research Ethics Sub-committee
(Andrew Stanley)

St Vincent’s Hospital Clinical Trials Centre
(Prof Dr Winston Liauw; Prof Richard Day; A/Prof Ken Williams)

Dr Joe Santamaria

Ms Heide Nore

Individual (Confidential)

Humane Society of Western Australia
(Mrs Margaret Regts)

Individual (Confidential)

Mr John Lambeth

A/Prof Peter Collignon

Compassion for Animals
(Julia Carryer)

Animal Defenders Australia
(Claudette Vaughan)

Ms Astrid Herlihy

Campaign for Responsible Transplantation (USA)
(Alex Fano)

National Serology Reference Laboratory Australia
(A/Prof Elizabeth M. Dax)

Catholic Women’s League Aust Inc., Bioethics Working Party
(Mrs Mary Uhlmann)

NSW Agriculture Animal Welfare Unit
(Lynette Chave)

‘Ree’

Science for Health/Doctors and Lawyers for Responsible Medicine
(France) (Claude Reiss)

Bureau of Animal Welfare, Department of Natural Resources and Environment
(Dr Jane Canole)

Ms Nell McNally

Therapeutic Goods Administration
(Terry Slater)

Institute for Judaism and Civilisation
(Rabbi Shimon Cowen)

International Xenotransplantation Association
(Dr Ian FC McKenzie and Megan Sykes)

Dr Judy Carman
Animal-to-human transplantation research: How should Australia proceed?

Animals Australia
(Glenys Oogjes)

Royal Australasian College of Surgeons
(David Scott)

Preterm Foundation
(Stefania Siedlecky)

Susan Conway and family

Diatranz Ltd (New Zealand)
(Professor RB Elliott)

Gene Technology Ethics Committee
(Professor D Chalmers)

World Association for Voice of Animals
(Stephanie Nakata)

Consumers’ Health Forum
(Helen Hopkins)

WA Stem Cell Consultative Group, Health Department of Western Australia
(Dr Peter O’Leary)

Health Research Council of New Zealand
(Bruce Scoggins)

Monash University Animal Welfare Committee
(Professor RH Day)

NSW Health Department
(Dr Greg Stewart)

RSPCA UK
(Penny Hawkins)

Ms Kerrie Donaldson

Australian Infection Control Association
(Di Dreimanis)

Australian Association for Humane Research Inc
(EM Ahlston)

Ms Pam Ahern

RSPCA (South Australia) Inc
(Dr M D Peters)

Integrative Strategies
(James Rose)

Dr Shabbir Ahmed
Appendix C  Analysis of submissions by submitter type

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Animal-to-human transplantation research: How should Australia proceed?


Ivinson AJ and Bach FH. The xenotransplantation question: public consultation is an important part of the answer. Canadian Medical Association Journal 167(1):42.


UK Home Office (no date). Draft home office code of practice for the housing and care of pigs intended for use as xenotransplantation source animals.  


Administration, Center for Biologics Evaluation and Research. 


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ATTACHMENT:

NHMRC procedures for making submissions
PUBLIC CONSULTATION –
PROCEDURES FOR MAKING
SUBMISSIONS
THE NHMRC IN BRIEF

The National Health and Medical Research Council (NHMRC) consolidates within a single national organisation the often independent functions of research funding and development of advice. One of its strengths is that it brings together and draws upon the resources of all components of the health system, including governments, medical practitioners, nurses and allied health professionals, researchers, teaching and research institutions, public and private program managers, service administrators, community health organisations, social health researchers and consumers. The functions of NHMRC come from the statutory obligations conferred by the National Health and Medical Research Council Act 1992 (the Act).

The Act sets down four statutory obligations on the directions taken by NHMRC. These obligations are:
- to raise the standard of individual and public health throughout Australia;
- to foster the development of consistent health standards between the various States and Territories;
- to foster medical research and training and public health research and training throughout Australia; and
- to foster consideration of ethical issues relating to health.

The Council comprises nominees of Commonwealth, 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.

APPROACH TO CONSULTATION BY COUNCIL

The Council undertakes its advisory role with the assistance of an extensive structure of committees, working parties and expert panels. The substantial networks represented in this structure are used both to disseminate information about the Council’s activities and to assist the Council to gain a full appreciation of the range of views in the community. This networking complements the public consultation processes.

The Council is keen to ensure that the Australian community has the best opportunity to participate in developing Council reports. For this reason a consultation strategy is an important part of any recommendation or guideline development process. The strategy will identify individuals and organisations who have a special interest in the topic under consideration and who will receive direct contact from Council. In developing the timetable for consultations the need to allow adequate time for participants to undertake their own processes is taken into account. Other current consultative activities relevant to the issues are also taken into consideration.

Participants involved in consultations will be provided with:
- information about the reasons for the consultation;
- any other available background information; and
- a contact name.

The Act sets out steps to be followed by the Council in consulting people and bodies when it intends to:
- make a regulatory recommendation;
  - that is, a recommendation of the Council that is intended to be given legal effect in a State or Territory by legislation of that State or Territory;
- issue guidelines;
- approve guidelines developed by other organisations; or
- engage in other activity prescribed in regulations to the Act;
  - the Council’s present plans do not include any activities that will need to be prescribed.

THE CONSULTATION PROCESS

Council now has two separate consultation processes as follows.

Regulatory recommendations and prescribed activities

Council follows a two stage consultation process. Firstly, Council will advertise its intention to develop a regulatory recommendation or engage in a prescribed activity. At this stage Council will seek comment on its intentions.

Once comments have been received and considered, Council will draft the regulatory recommendation or refine its prescribed activity and will then publish a second notice asking for comment on the actual draft.

Notices for both these stages of consultation will be published in the Commonwealth Gazette and on the NHMRC website. Copies of draft documents and supporting information will be available free of charge from the Office of NHMRC and on the NHMRC website. In addition, notices may be included in other publications and media such as
newspapers and radio, and will be circulated to bodies that are expected to be interested.

The notices will state:
- that submissions should normally be in writing but would also be acceptable on audio tape;
- details of where, and by when, the submissions are to be lodged; and
- whether it is intended to conduct other forms of consultation.

Development of guidelines

Council undertakes a single stage of consultation. When Council has determined a need for a guideline, undertaken the initial research and developed a draft of the guideline, a notice inviting submissions will be published in the Commonwealth Gazette and on the NHMRC website. The notice will give the same information referred to above.

In addition, notices may be included in other publications and media, such as newspapers, and the draft guideline will be circulated to bodies that are expected to be interested.

Consideration of submissions

All submissions will be acknowledged upon receipt. All submissions will be considered. The committees are obliged to report to Council on the consultation process, including showing how they have addressed the comments that submitters have made.

Variations to standard consultation arrangements

On occasions it is necessary for Council to modify the consultation process, for example in an emergency situation or where proposed recommendations or guidelines are of minor significance. The Act allows Council to take this course of action.

If this happens, Council will advertise its reasons for making such a decision. In the case of an emergency situation, Council will also consult formally with interested individuals and organisations before confirming its original decision. The Act sets out strict timeframes for this type of consultation.

HOW TO WRITE A SUBMISSION

Submissions should be clear and concise, preferably typewritten and submitted as an original by mail or email. Facsimile copies will be accepted, but are sometimes difficult to read. Audio tapes will also be accepted.

Each submission should include:
- the submitter’s name and address;
- names of any additional contributors to the submission who may wish to be acknowledged;
- contact telephone numbers in case Council needs to clarify any points, obtain additional information, or advise if the submission appears incomplete (eg pages missing); and
- fax and email address where possible.

Submissions to Council need to include specific information that will help Council to consider the point(s) being made. Evidence that supports the point(s) being made should include full references and copies of material referred to. If it is not possible to include such references, please include as much detail as possible.

Information in the submission should be in a logical order, preferably following the layout of the consultation document (for instance, use the same chapter headings and subheadings). Quote the page number relevant to the point(s) being made.

There is no set length for a submission and, in fact, the length will vary depending on the complexity of the issue and the number of comments a submitter wants to make. However, submissions should balance the need to provide as much information as possible with a need to be concise. If particular length restrictions are set, they will be specified in the notice inviting submissions.

GENERAL INFORMATION ON COUNCIL'S ACTIVITIES

Information on the activities of the Council can be obtained from its secretariat by phoning (02) 6289 9184, faxing (02) 6289 9197 or writing to:

The Executive Secretary
National Health and Medical Research Council
Office of NHMRC (MDP 100)
GPO Box 9848
Canberra ACT 2601

The Council’s Secretariat circulates periodically a catalogue of Council publications and is able to provide synopses of publications upon request. Most of Council’s publications are available through AusInfo (contact details on back page). There are also many NHMRC publications available on the NHMRC website, including synopses.
How to Contact Us

General
Postal: The Executive Secretary
National Health and Medical Research Council
Office of NHMRC
(MDP 100) GPO Box 9848
Canberra ACT 2601
Physical: The Executive Secretary
National Health and Medical Research Council
Office of NHMRC
32 Corinna Street
Woden ACT 2606
Phone: +61 2 6289 9184
Fax: +61 2 6289 9197
Email: exec.sec@nhmrc.gov.au

Publications
The Publications Officer
Office of NHMRC
(MDP 100) GPO Box 9848
Canberra ACT 2601
Phone: +61 2 6289 9520
Toll-free: 1800 020 103 (inside Australia only)
Fax: +61 2 6289 9197
Email: nhmrc.publications@nhmrc.gov.au

Web Site
The NHMRC Webmaster
Office of NHMRC
(MDP 100) GPO Box 9848
Canberra ACT 2601
Phone: +61 2 6289 9173
Fax: +61 2 6289 9197
Email: nhmrc.webmaster@nhmrc.gov.au
Internet: http://www.nhmrc.gov.au

Research Program
NHMRC Centre for Research Management
Office of NHMRC
(MDP 33) GPO Box 9848
Canberra ACT 2601
Phone: +61 2 6289 9167
Fax: +61 2 6289 9132
Email: nhmrc.research@nhmrc.gov.au

Advisory Program
Health Advisory Section
Office of NHMRC
(MDP 100) GPO Box 9848
Canberra ACT 2601
Phone: +61 2 6289 9188
Fax: +61 2 6289 9180
Email: health.advisory.cttee.nhmrc@nhmrc.gov.au

Ethics Program
Health Ethics Section
Office of NHMRC
(MDP 70) GPO Box 9848
Canberra ACT 2601
Phone: +61 2 6289 9154
Fax: +61 2 6289 9198
Email: ahec.nhmrc@nhmrc.gov.au

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