Australian Government
National Health and Medical Research Council

National Health and Medical Research Council Statement on Animal-to-Human Transplantation (Xenotransplantation) Research

10 March 2005

The Xenotransplantation Working Party was established by the National Health and Medical Research Council (NHMRC) in 2000 to investigate the scientific, ethical and technical issues surrounding animal-to-human transplantation (xenotransplantation). In September 2004, following two rounds of public consultation and a series of public meetings[1], the Xenotransplantation Working Party provided Council with its final advice, recommendations and draft guidelines on xenotransplantation clinical research in Australia.

Council considered this matter in detail at its 154th and 155th meetings in September and December 2004 and after significant discussion, decided not to support all the recommendations of the Working Party nor endorse the draft guidelines. However, because of the significant public involvement in the process, Council decided that both documents would be released to the public. The Working Party's final report *Animal-To-Human Transplantation: Final report and advice to the National Health and Medical Research Council* and draft, unendorsed *Guidelines for Clinical Animal-to-Human Transplantation Research* are provided as attachments to this Statement (Attachments 1 and 2 respectively).

Council concluded that the risks of transmission of animal viruses to transplant recipients and the wider community have not as yet been adequately resolved. In addition, xenotransplantation research is at an early stage and clinical trials in the foreseeable future are unlikely to be of significant benefit to the research participants. In light of these conclusions, the NHMRC:

- Agreed with the Xenotransplantation Working Party's recommendation that there be no clinical trials of animal-to-human whole organ transplants[2] for a period of five years and that non-human primates should not be considered as source animals for clinical trials of animal-to-human transplantation;

[1] The Xenotransplantation Working Party considered all submissions received through public consultation, feedback from the public meetings, advice prepared by its Animal Issues Subcommittee and all relevant technical information on the safety and efficacy of xenotransplantation.

[2] The Xenotransplantation Working Party's definitions of animal to human organ transplants, cellular therapies and animal external therapies, are provided at Appendix A.

- Determined that there should be no clinical trials using animal cellular therapies for five years[3];
- Determined that there should be no clinical trials in Australia using animal external therapies for five years[3]. However, Council noted that there are procedures utilised in current clinical practice in Australia that involve the culturing of human cells on feeder layers of irradiated mouse cells, and are thus defined as animal external therapies[4]. These procedures have well established benefits to patients and carry a low but unquantifiable risk. In light of this, Council requested the NHMRC Gene and related Therapies Research Advisory Panel (GTRAP) to undertake further consultation, including with the Therapeutic Goods Administration, to:
    - Investigate and report back to Council on the feasibility of allowing some clinical research[5] to proceed, based on a case-by-case assessment of the potential benefits in relation to the risks; and
    - Investigate mechanisms through which existing clinical treatments and clinical research (if allowed) could be monitored to allow Council to further quantify the risks of such treatments;
- Referred the Working Party's recommendation relating to the establishment of a central register of animal-to-animal pre-clinical studies to the NHMRC's Animal Welfare Committee (AWC), to report back to Council on the feasibility of this recommendation; and
- Requested that GTRAP monitor developments regarding the risks and efficacy of xenotransplantation and report regularly to Council. Council will reconsider its position, should relevant new information become available during the next five years.

[3] Council did not accept the Xenotransplantation Working Party recommendation.

[4] For example, the culture of human cells on mouse cell feeder layers for the treatment of burns patients.

[5] For example, clinical research to improve the protocols to treat burns victims referred to in footnote 4.

Animal to human transplantation procedures[6]

Procedure	Description	Examples
Animal external therapies (AETs)	A range of procedures involving contact between human and animal cells/tissues outside of the body of the patient, such as:	
	(a) cells or fluids from the patient are perfused through animal cells and returned to the patient; or	Passage of blood from a patient with liver failure through an external device (Hepatassist machine) containing pig liver cells (similar to a kidney dialysis machine).
	(b) human cells or tissue pieces are cultured with animal cells in the laboratory in order to obtain a larger supply of human cells or tissue for transplantation.	Growth of human skin grafts for wound healing (eg for burns) on a feeder layer of animal cells.
Animal cell therapies (ACTs)	Procedures in which animal cells are transplanted or implanted into a human patient to compensate for deficient functioning of the patient's own cells. Transplanted cells can either be enclosed in a semipermeable capsule (encapsulated) or have no such capsule.	Animal pancreatic cells to produce insulin for people with diabetes. Animal brain cells to produce dopamine for people with Parkinson's disease.
Animal organ transplants (AOTs)	Procedures in which whole organs or tissues from an animal are transplanted or implanted into a human patient to replace a diseased or damaged organ or tissue.	Heart, kidney, liver, skin, adrenal glands etc

[6] Source: Table 2.1 'Animal-to-human transplantation procedures', *ANIMAL-TO-HUMAN TRANSPLANTATION: Final report and advice to the National Health and Medical Research Council* (September 2004)

Australian Government

National Health and Medical Research Council

ANIMAL-TO-HUMAN TRANSPLANTATION (xenotransplantation):

Final report and advice to the National Health and Medical Research Council

September 2004

*This document was noted by Council at its 154th Session (September 2004) but not endorsed, and should be read in conjunction with the *NHMRC Statement on Animal-to-Human Transplantation which appears at the front of this document (10 March 2005).*

Xenotransplantation Working Party

To obtain details regarding NHMRC publications contact:

Email: nhmrc.publications@nhmrc.gov.au
Phone: Toll Free 1800 020 103 Extension 9520
Interent: http://www.nhmrc.gov.au

Technical writing and production by Biotext, Canberra

Contents

Tables

Figures

Executive summary

Introduction

The Xenotransplantation Working Party (XWP) was established by the National Health and Medical Research Council (NHMRC) late in 2000 and asked to report to Council through the Australian Health Ethics Committee (AHEC) and Research Committee. The XWP was charged with the task of investigating the scientific, ethical and technical issues surrounding animal-to-human transplantation (xenotransplantation) research. The task also included conducting public consultation on whether animal-to-human transplantation clinical trials should be permitted in Australia and, if so, on possible mechanisms for the oversight of individual research projects.

Since its first meeting early in 2001, the XWP has published two public consultation documents — *Draft Guidelines and Discussion Paper on Xenotransplantation* in July 2002 (Discussion Paper), and *Animal-to-Human Transplantation: How Should Australia Proceed*? in December 2003 (Response Paper). It also prepared a plain English community guide (*Animal-to-Human Transplantation: A Guide for the Community*), which was published in December 2003 (Community Guide), and ran public meetings in all capital cities.

In early 2003, after publication of the Discussion Paper and the first round of public consultation, the membership of the XWP was expanded and a subcommittee — the Animal Issues Subcommittee (AISC) — was established to assist the XWP assess issues relating to animal ethics, animal welfare and regulation of the use of animals in xenotransplantation research for preparation of the Response Paper, the second round of public consultation, and the preparation of advice to the NHMRC.

The XWP has considered all the submissions received during both rounds of the public consultation, the feedback from the public meetings and all other relevant information about animal-to-human transplantation. It has also considered final advice prepared by the AISC after this committee's consideration of the responses to the second round of public consultation.

The XWP has used all this information to prepare this final report and to provide advice to the NHMRC on how Australia should proceed in relation to animal-to-human transplantation research.

NHMRC guidelines

One of the terms of reference of the XWP was to produce guidelines to cover the scientific, ethical and technical aspects of animal-to-human transplantation research. The working party therefore drafted guidelines to inform investigators of NHMRC requirements for this type of research, and to assist national and local agencies responsible for the oversight of animal-to-human transplantation research in their decision about whether or not to approve the research. The first draft of these guidelines was released with the Discussion Paper.

It was clear from the submissions to the first round of public consultation that the community did not fully understand the purpose of the draft guidelines prepared by the XWP. Many respondents thought that inclusion of draft guidelines in the Discussion Paper indicated that the NHMRC had already decided to allow animal-to-human transplantation research to proceed. This was not the case — the XWP's position has always been that the purpose of guidelines would be to provide a basis from which to:

- assess research proposals against the very strict standards set by the NHMRC guidelines;
- prevent unacceptable research proposals from going ahead; and
- ensure that, if animal-to-human transplantation were allowed to go ahead at all, this would occur very cautiously if, and only if, the research met the standards set by the guidelines.

The proposed guidelines for animal-to-human transplantation research are provided in the document, *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research*, which accompanies this advice document.

XWP advice to the NHMRC

Definitions

The public consultation showed that many people are uncomfortable with the use of technical terms, such as 'xenotransplantation', and that many people think that the term only refers to animal organ transplants.

The XWP therefore advises the NHMRC that the term '**animal-to-human transplantation**' and **'animal transplantation products**' should be used to describe human xenotransplantation procedures and products.

The XWP also advises the NHMRC that in all documentation about animal-to-human transplantation, the NHMRC should distinguish three broad groups of procedures —**animal external therapies, animal cell therapies** and **animal organ transplants** — which have different rationales for research and different ethical and technical issues associated with them.

Rationale

The XWP notes that references to the shortage of human organs as the only rationale for animal-to-human transplantation research is misleading for the general public and does not help community understanding about the different types of procedures.

The XWP therefore advises the NHMRC that care should be taken to explain the rationale for specific procedures and their relationship to other developing biotechnology and biological therapies.

Key public concerns

Both rounds of public consultation revealed significant public concerns about animal-to-human transplantation. These included ethical and social concerns about the use and welfare of animals; fear of new infectious diseases transferring from animals to humans; doubts around the efficacy of the procedures; practicalities of conducting clinical trials; and the potentially high level of resource use relative to any benefits (thus diverting funds away from other more potentially beneficial uses).

The XWP therefore advises the NHMRC that Australia should take a very cautious approach to clinical animal-to-human transplantation research, under guidelines that apply strict standards to the above issues.

Animal ethics committees

Some respondents to the public consultation noted concerns about how animal ethics committees function, including the ability of community ethics committee members to contribute to technical discussions and the lack of information available to committees about animal research conducted in other institutions.

The XWP therefore advises the NHMRC that this issue should be referred to the NHMRC Animal Welfare Committee for further investigation.

Resource use

A number of biotechnology and biological therapies are being researched for treatment of the same conditions that animal-to-human transplantation is proposed to treat.

The XWP therefore advises the NHMRC to carefully monitor developments across the spectrum of developing biotechnology and biological therapies to ensure that the research that offers the best chance of individual and society benefits is supported.

Animal-to-human transplantation clinical trials

The public consultation showed that animal-to-human transplantation, in particular animal organ transplantation, is not acceptable to many people.

The XWP therefore advises the NHMRC that:

- research proposals for clinical trials of animal organ transplants should not be considered in Australia (ie no animal-to-human whole organ transplants should be permitted);
- nonhuman primates should not be considered as source animals for clinical trials of animal-to-human transplantation;
- clinical trials of animal cell therapies and animal external therapies can be considered in Australia under strict standards set by NHMRC guidelines **(see *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document)** and oversight arrangements that would not

allow research to proceed unless it is assessed as being safe, potentially offers benefits to the recipients and conducted according to high ethical standards;

- these recommendations and the guidelines should be reviewed in five years; and
  - earlier review of the guidelines should only be permitted if a recommendation from the national animal-to-human transplantation committee indicates that such a review is warranted based on new information on safety and efficacy;
  - the review must include public consultation.

Consultation with the Therapeutic Goods Administration (TGA)

The TGA is currently considering revisions to the *Therapeutic Goods Act 1989* and associated Regulations, to take account of a range of emerging biological therapies, including animal-to-human transplantation.

The XWP advises the NHMRC that, in implementing the recommendations for national oversight of animal-to-human transplantation, it consults closely with the TGA to ensure that the revised therapeutic goods legislation provides the necessary regulatory framework to support the scheme.

Inclusion of animal transplantation products as 'therapeutic goods'

The definitions of a '**therapeutic good**' and of '**therapeutic use**' in the *Therapeutic Goods Act* 1989 appear to be broad enough to include animal cells, organs or tissues when used therapeutically.

The XWP therefore advises the NHMRC to ensure that animal transplantation products *remain within the definition* of therapeutic goods in the Therapeutic Goods Act 1989.

Clinical trial applications

To ensure that any trials of animal-to-human transplantation, including individual use, are assessed by local ethics committees, the proposed national animal-to-human transplantation committee and the TGA, all such uses need to be submitted as a clinical trial application under the CTX (Clinical Trial Exemption) scheme.

The XWP therefore advises the NHMRC that the *Therapeutic Goods Act 1989* and associated Regulations should be amended to:

- ensure that animal-to-human transplantation, including for individual patients, can be undertaken only as part of a clinical trial;
- prevent the use of animal transplantation products under the Authorised Prescriber Scheme, the Personal Use Scheme or the Special Access Scheme; and
- prescribe that animal-to-human transplantation research proposals must be submitted as CTX applications.

National animal-to-human transplantation committee

Because of the ethical and scientific issues associated with animal-to-human transplantation research in Australia, and to ensure adequate community and scientific input, local ethics committees (human and animal) need advice from a national committee with specific expertise in this research.

The XWP therefore advises the NHMRC that animal-to-human transplantation research proposals in Australia should be referred to a national animal-to-human transplantation committee set up by the NHMRC for detailed assessment against NHMRC guidelines.

The XWP also advises the NHMRC that the *Therapeutic Goods Act 1989* should be amended to provide legislative backing for the role of an NHMRC national animal-to-human transplantation committee.

Structure and role of the national animal-to-human transplantation committee

The XWP advises the NHMRC that the national committee should be set up and funded with a broad range of expertise relevant to animal-to-human transplantation, including representatives from the TGA and OGTR, with terms of reference to:

- apply NHMRC guidelines for the assessment of animal-to-human transplantation research proposals;
- provide advice to local ethics committees and the TGA as required;
- authorise and monitor the conduct of animal-to-human transplantation clinical trials with local ethics committees and the TGA;
- maintain a register of trial participants, including those from research conducted overseas;
- establish an animal use and oversighting subcommittee to maintain a register of animal-to-animal transplantation studies of relevance to animal-to-human transplantation and advise on other animal issues;
- monitor developments in animal-to-human transplantation research; and
- conduct ongoing public education.

The XWP advises that the existing Gene and Related Therapies Research Advisory Panel already has considerable expertise in assessing related research proposals. The final appointment and reporting arrangements for the national committee should be determined by the NHMRC, although public consultation indicated public confidence would be increased if the committee was independent of commercial and research interests.

Oversight of animal issues

The Animal Issues Subcommittee (AISC) of the XWP has proposed that a central register of animal-to-animal transplantation studies of relevance to animal-to-human transplantation, together with an associated technical review group should be established to record data relevant to animal welfare considerations of xenotransplantation research and to support animal ethics committees in their assessment of research proposals.

The XWP advises the NHMRC that the AISC-proposed central register of animal-to-animal transplantation studies of relevance to animal-to-human transplantation, should be established. Furthermore, the register and its associated technical review capability could be achieved by setting up an animal use and oversighting subcommittee of the proposed national animal-to-human transplantation committee with the task of managing the proposed register (**see also Guideline 2b in *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document).**

Guidelines

The XWP has prepared guidelines for animal-to-human transplantation. These guidelines provide strict standards against which animal-to-human transplantation research proposals can be assessed and monitored.

The XWP advises the NHMRC to consider and endorse the proposed guidelines for animal-to-human transplantation research (see ***Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document).**

1 Public consultation on animal-to-human transplantation

1.1 Introduction

The Xenotransplantation Working Party (XWP) was established by the National Health and Medical Research Council (NHMRC) late in 2000 and asked to report to Council through the Australian Health Ethics Committee (AHEC) and Research Committee. Since its first meeting early in 2001, the XWP has thoroughly investigated the scientific, ethical and technical issues surrounding clinical animal-to-human transplantation (xenotransplantation) research in terms of whether such research should proceed in Australia and, if so, possible mechanisms for the oversight of individual research projects. The specific terms of reference of the XWP at each stage of the consultation are shown in Sections 1.2 and 1.3.

To fulfil its terms of reference, the XWP has consulted widely with the community on animal-to-human transplantation through two rounds of public consultation involving a range of written materials and public meetings (see Sections 1.2 and 1.3). The purpose of this report is to advise the NHMRC of the findings of the working party with respect to the scientific, ethical and technical aspects of animal-to-human transplantation research in Australia and to provide guidelines for the oversight of such research.

1.2 Discussion Paper and first stage of public consultation (2002)

The specific terms of reference of the XWP when it started its work in 2001 are shown in Box 1. A list of members is shown in Appendix A.

Box 1 Terms of reference of the Xenotransplantation Working Party, 2001–02 (first round of public consultation)

The Xenotransplantation Working Party will:

- report to NHMRC through the Australian Health Ethics Committee and Research Committee;
- provide advice to Council on the scientific, ethical and technical issues related to xenotransplantation research involving humans;
- produce guidelines covering the scientific, ethical and technical aspects of xenotransplantation research involving humans, including consideration of
  - animal issues (including animal husbandry practices)
  - accepted practices (eg use of denatured pig tissues for mitral valve replacement); and
- undertake wide consultation in the preparation of guidelines.

In July 2002, the XWP released a detailed report (NHMRC 2002) — *Draft Guidelines and Discussion Paper on Xenotransplantation* (Discussion Paper). The primary role of the Discussion Paper was to provide sufficient background material about all known ethical and technical aspects of animal-to-human transplantation and to promote informed

community discussion on this issue. The Discussion Paper also included draft guidelines prepared by the XWP to indicate to the community the strict standards that it proposed would need to be met by researchers before any animal-to-human transplantation trials could be considered for approval in Australia. The community was particularly asked to comment on these proposed guidelines. The Discussion Paper was accompanied by a media release that led to extensive media coverage of the issues surrounding animal-to-human transplantation.

From August to October 2002, the NHMRC placed advertisements in major national and metropolitan newspapers and on its website inviting the community to comment on the Discussion Paper. A total of 97 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. Further details of the submissions and public meetings are included in Appendix B.

The submissions received and the discussions at the public meetings 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 clinical animal-to-human transplantation research would be regulated in Australia. In addition, 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.

Also, most respondents only considered animal-to-human transplants of whole organs, rather than the broader range of treatment options involving animal products that are included in the definition of xenotransplantation. For these reasons, the XWP advised Council that, as a result of considering the submissions received and the input from the public meetings, the working party needed to be enlarged and that a second round of public consultation was required.

1.3 Second stage of public consultation (2003–04)

In early 2003, the NHMRC agreed that the XWP should conduct a second round of consultation. The purpose of the second consultation was to consider the issues raised in the first stage in relation to all the types of animal-to-human transplantation procedures covered by the definition of xenotransplantation. To facilitate this process, the membership of the XWP was expanded to include additional members with expertise in animal welfare, infectious disease control, clinical transplantation, experimental transplantation (including animal-to-human transplantation) and the regulation of clinical trials.

The Animal Issues Subcommittee (AISC) was also established to assist the XWP assess issues relating to animal ethics, animal welfare and regulation of the use of animals in xenotransplantation research.

The specific terms of reference of the expanded XWP and the AISC are shown in Box 2. A list of members is shown in Appendix A.

Box 2 Terms of reference of the Xenotransplantation Working Party and Animal Issues Subcommittee, 2003–04 (second round of public consultation)

The Xenotransplantation Working Party will:

- undertake a community education program on xenotransplantation;
- undertake wide consultation to obtain community views on the acceptability of proceeding with clinical xenotransplantation research in Australia and on related issues;
- produce guidelines covering the scientific, ethical and technical aspects of xenotransplantation research involving humans;
- consider the issues that xenotransplantation raises in relation to the use of animals for this purpose;
- undertake wide consultation on proposed guidelines and regulatory mechanisms for clinical xenotransplantation research; and
- 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.

The Animal Issues Subcommittee will:

- provide advice to the XWP on issues associated with animal ethics and welfare in the context of xenotransplantation research, including regulatory issues;
- provide advice to the XWP on relevant issues raised in the public consultation activities; and
- prepare input and provide comments on documents prepared by the XWP, which may include:
  - the second round consultation document;
  - the lay guide to xenotransplantation; and
  - 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.

In December 2003, the XWP released a second paper for public discussion (NHMRC 2003a), *Animal-to-Human Transplantation: How Should Australia Proceed?* (Response Paper). The Response Paper was written to directly respond to issues raised in the first round of public consultation and provide additional information to inform further public debate on the issues. It also included a proposal for a regulatory framework for animal-to-human transplantation research and a revision of the proposed guidelines for the conduct of such research, should it be allowed to proceed.

Finally, to assist community understanding of animal-to-human transplantation research, and in response to criticisms that the Discussion Paper was too technical, the XWP also produced a plain English community guide to animal-to-human transplantation (NHMRC 2003b)— *Animal-to-Human Transplantation: A Guide for the Community* (Community Guide). The Community Guide complemented the Response Paper by providing an overview of animal-to-human transplantation and the proposed regulatory arrangements in concise simple English.

Once again, from December 2003 to March 2004, the NHMRC advertised the public consultation documents widely in major national, metropolitan, local and ethnic

newspapers throughout Australia and on its website, inviting the community to comment on the Response Paper and Community Guide. At the same time, media releases were also used to promote public awareness and knowledge about animal-to-human transplantation. A public relations company was also contracted to assist the XWP, in order to ensure that the community were aware of the debate including the availability of the Response Paper and Community Guide and the public meetings.

In February 2004, the NHMRC also ran a series of public meetings in all Australian state and territory capital cities, which attracted a total of close to 400 attendees. Unlike the first round of public meetings, these meetings were moderated by an independent facilitator in order to further promote open discussion.

The working party received 343 written submissions from individuals and organisations within Australia and overseas. Almost one-third (106) of the submissions were 'form' letters (three different letters) and 43 were from schoolchildren (either from Queensland or Victorian secondary schools). An email petition was also received as an attachment to one submission. This petition contained the names (without signatures) of 435 people (many from overseas).

Further information about the submissions received and public meetings are in Appendix B.

1.4 Advice to the NHMRC

From April to June 2004, the XWP considered the submissions from the second round of public consultation, the feedback from the public meetings and all the other relevant information it had gathered about animal-to-human transplantation. It also considered final advice prepared by the AISC (see Appendix C). Using this information, the XWP has prepared this final report to provide advice to the NHMRC on how Australia should proceed in relation to animal-to-human transplantation research.

The reports published in the two rounds of public consultation have covered the relevant aspects of animal-to-human transplantation in considerable detail. This final report does not attempt to repeat matters already covered by these reports, but highlights the significant areas of public discussion that have informed the final advice provided by the XWP to the NHMRC.

1.5 NHMRC guidelines

It was clear from the first round of submissions that the community did not fully understand the purpose of the draft guidelines prepared by the XWP. Many respondents thought that inclusion of draft guidelines in the Discussion Paper indicated that the NHMRC had already decided to allow animal-to-human transplantation research to proceed. This was not the case — the XWP's position has always been that the purpose of guidelines would be to provide a basis from which to:

- assess research proposals;
- prevent unacceptable research proposals from going ahead; and
- possibly allow some research to proceed if, and only if, it meets the very strict standards set by the guidelines.

The XWP believed that issuing of draft guidelines at the same time as the discussion documents would assist the community to understand the tentative conclusions drawn by the working party and would be an efficient means of undertaking community education and consultation at the same time.

Although an explanation of the position of the XWP was included in the Response Paper and Community Guide, the inclusion of draft guidelines with the Response Paper was again challenged in the second round of public consultation, fuelled by several misleading media reports that the NHMRC had already decided to allow animal-to-human transplantation in Australia.

Again, the XWP took care to explain at the public meetings that the proposed guidelines set a very high bar for efficacy and safety of clinical trials. Indeed, without any guidelines in place, it may prove difficult to *prevent* research from going ahead under current Therapeutic Goods Administration, NHMRC and institutional ethics committee arrangements, which are not specifically designed to deal with this type of research and may not provide the necessary legal barriers to the use of animal-to-human transplantation (eg in individual patients).

Since the second round of public consultation, the XWP has reviewed and updated the proposed guidelines in the light of the submissions received. The finalised guidelines are provided in the document, *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* (which accompanies this advice document) for consideration by the NHMRC.

XWP advice to NHMRC — guidelines

The XWP has prepared guidelines for animal-to-human transplantation. These guidelines provide strict standards against which animal-to-human transplantation research proposals can be assessed and monitored.

The XWP advises the NHMRC to consider and endorse the proposed guidelines for animal-to-human transplantation research (see *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document).

2 Animal-to-human transplantation procedures

2.1 Definitions of animal-to-human transplantation

The Xenotransplantation Working Party (XWP) defined animal-to-human xenotransplantation to include any procedure that involves transplantation, implantation or infusion into a human recipient of cells, tissues or organs from a nonhuman animal source. Furthermore, based on the definition used by the United States Food and Drug Administration (US FDA 2001, 2003), the XWP distinguished two forms of procedures:

- '*in vivo transplants*' involving transplantation, implantation or infusion into a human recipient of live cells, tissues or organs from a nonhuman animal source; and

- '*ex vivo procedures*' involving 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.

Working from this definition, the sections of the Discussion Paper on the scientific basis of animal-to-human transplantation each distinguished three types of transplantation procedures: whole organs, cells and external procedures. Nevertheless, most respondents to the first round of consultation focused only on whole organ transplantation and some noted that grouping such a diverse range of therapies together under the banner of 'xenotransplantation' was not very helpful.

To address this issue, for the second round of consultation, the XWP developed new terminology for the three different types of animal-to-human transplantation procedures under consideration:

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

These three different procedures (which are described in Table 2.1) were considered separately in the Response Paper wherever possible with separate information about the alternatives, efficacy, levels of risk and clinical management associated with each type of procedure.

Table 2.1 Animal-to-human transplantation procedures

Procedure	Description	Examples
Animal external therapies (AETs)	A range of procedures involving contact between human and animal cells/tissues outside of the body of the patient, such as:	
	(a) cells or fluids from the patient are perfused through animal cells and returned to the patient; or	Passage of blood from a patient with liver failure through an external device (Hepatassist machine) containing pig liver cells (similar to a kidney dialysis machine).
	(b) human cells or tissue pieces are cultured with animal cells in the laboratory in order to obtain a larger supply of human cells or tissue for transplantation.	Growth of human skin grafts for wound healing (eg for burns) on a feeder layer of animal cells.
Animal cell therapies (ACTs)	Procedures in which animal cells are transplanted or implanted into a human patient to compensate for deficient functioning of the patient's own cells. Transplanted cells can either be enclosed in a semipermeable capsule (encapsulated) or have no such capsule.	Animal pancreatic cells to produce insulin for people with diabetes. Animal brain cells to produce dopamine for people with Parkinson's disease.
Animal organ transplants (AOTs)	Procedures in which whole organs or tissues from an animal are transplanted or implanted into a human patient to replace a diseased or damaged organ or tissue.	Heart, kidney, liver, skin, adrenal glands etc

Throughout the public consultation process, 'xenotransplantation products' were defined as any live animal cell, tissue or organ that is used in an animal-to-human transplantation procedure (ie not including processed, nonviable products, such as pig heart valves). This exclusion of nonviable products from the definition was accepted by most respondents to the consultation.

However, in hindsight, it may have been preferable to avoid the term 'xenotransplantation' altogether as, during the public consultations, it was frequently remarked that the term was unknown to most members of the public. In the remainder of this advice document, the term 'animal transplantation products' is used to define the live animal materials used in animal-to-human transplantation procedures.

XWP advice to NHMRC — definitions

The public consultation showed that many people are uncomfortable with the use of technical terms, such as 'xenotransplantation', and that many people think that the term only refers to animal organ transplants.

The XWP therefore advises the NHMRC that the term 'animal-to-human transplantation' and 'animal transplantation products' should be used to describe human xenotransplantation procedures and products.

The XWP also advises the NHMRC that in all documentation about animal-to-human transplantation, the NHMRC should distinguish three broad groups of procedures —animal external therapies, animal cell therapies and animal organ transplants — which have different rationales for research and different ethical and technical issues associated with them.

2.2 Focus of public discussion

The XWP hoped that in the second round of public consultation the community would provide opinions on each of the three types of animal-to-human transplantation procedures. However, once again, very few respondents made a distinction between the three categories, although some who did were more supportive of cell and external therapies than of organ transplants.

The working party considered the reasons for this focus on organ transplants, which it felt may have been due to a number of factors, including:

- the emphasis in all the public consultation documents that the rationale for animal-to-human transplantation is the worldwide shortage of human organs for transplant (see Section 2.3 for further information on rationale for each type of therapy);
- continued lack of understanding of the three different types of procedures;
- media coverage emphasising organ transplants; and
- a perception that the two main objections to animal-to-human transplantation (disease risk and animal suffering) are the same for all types of procedures.

2.3 Rationale for animal-to-human transplantation

Worldwide, the scientific literature and popular media reports on animal-to-human transplantation have all stressed the shortage of human organ donors as the rationale for current research on animal-to-human transplantation. In fact, it is rare to see any other reason stated, although the rationale for external and cell transplants is, in reality, much more complex than a shortage of human donors.

In line with this international trend, the Discussion Paper, Response Paper and Community Guide all highlighted the shortage of human organ donors as the rationale for animal-to-human transplantation research. In retrospect, this is seen as unwise by the XWP as there are different rationales for research on AOTs, AETs ACTs, which are summarised below.

Animal organ transplants

The current interest in research on AOTs is in direct response to a worldwide shortage of human organ donors and the increasing number of people waiting for organ transplants. This issue was discussed in both the Discussion Paper and Response Paper and on both occasions many of the submissions received and discussion at the public meetings highlighted the shortage of human organs for transplantation and Australia's poor record in this regard in comparison with a number of European countries.

These submissions highlighted the need for governments to vigorously promote human organ donation in order to reduce the need to consider options such as animal-to-human transplantation. Although a detailed discussion of human organ donation rates was outside its terms of reference, the XWP wishes to draw these community concerns to NHMRC and suggest that this be taken up by Council in some other way.

Animal cell therapies

The development of ACTs has been in response to increasing knowledge about, and technical ability to manipulate, individual cell types. This has opened possibilities for biological therapies for diseases and conditions involving lack or imbalance of biological molecules. Researchers have come to hope that transplantation of suitably stimulated cells that are able to produce the required molecules and correct the deficiency may become a method to treat a range of conditions, providing longer-term and safer 'cures' than life-long drug therapies.

Undoubtedly, if there was an unlimited supply of suitable donated human tissues that could be used to obtain the cells required for cellular therapies, there may have been less reason to consider animal cells as the source of such therapies. However, a supply of different human cell types based on cadaveric donation would never provide a sustainable option for either research or, in the future, for therapeutic use. Hence, researchers have turned to animals as a more readily available and sustainable source of cellular materials for the development of these therapies.

As many respondents pointed out, in recent years, stem cell research has provided the promise of an alternative source of human cellular materials that may ultimately replace the need to use animal cells. However, despite the media enthusiasm about stem cell research, the growth of different cell types from either adult stem cells or embryonic stem cells is, at present, no more than an experimental possibility. It will require many years of painstaking research to further develop the necessary methods for specific cell growth and biological stimulation. It is not yet known whether the technology will ever prove as successful as is hoped.

On the other hand, animal cells of the required types can be readily obtained, and preclinical (animal-to-animal) research has indicated that, with some further refinements, cellular therapies may prove efficacious for some otherwise incurable diseases, such as, Parkinson's disease and type 1 diabetes. However, if alternative approaches to cell therapy, such as human stem cells, prove more effective in future, the rationale for continued work with animal cells may decrease. Therefore, there needs to be ongoing monitoring of developments across the spectrum of biotechnology and biological therapy so that the procedures with the most potential benefit and fewest ethical and safety concerns are developed.

Animal external therapies

AETs cover a wide range of procedures and hence there are also a range of reasons behind their development apart from a shortage of human organ donors. For example, growth of human skin on an external feeder layer of animal cells has been seen as a method to quickly provide a source of skin (eg for a burns victim) and the use of an animal cell feeder layer in this case is due to the ready availability of existing animal cell culture lines. Furthermore, the animal cell lines that can be used as feeder layers have been grown in laboratories for many years, have well-understood growth characteristics and properties, and their continued use does not require the death of any further animals.

External liver perfusion techniques have been developed to assist people with liver failure, either until a suitable human liver donor is found, or until the liver failure is resolved spontaneously. An unlimited supply of human liver donations would reduce the number of people requiring a bridging procedure, while a readily available source of human cells (eg from fragments of liver obtained during liver surgery or by growth of human liver cell lines) may meet the need for short-term perfusion. However, these options are currently either unreliable, not feasible, or at the experimental stage so that researchers have turned to animal liver cells as the only readily available source of viable functioning liver cells for such use.

As with ACTs, alternative approaches to the use of animal products in external therapies, may be developed in future thus reducing the rationale for continued work with animal products. Ongoing monitoring of such developments will therefore be needed to ensure that procedures with the most potential benefit and fewest ethical and safety concerns are developed.

XWP advice to NHMRC — rationale

The XWP notes that references to the shortage of human organs as the only rationale for animal-to-human transplantation research is misleading for the general public and does not help community understanding about the different types of procedures.

The XWP therefore advises the NHMRC that care should be taken to explain the rationale for specific procedures and their relationship to other developing biotechnology and biological therapies.

2.4 Conclusion

'Xenotransplantation' has been defined by the XWP in line with international terminology to include a range of procedures that involve the use of living animal products in human therapies. Unfortunately, the diversity of the therapies covered by this definition, the technical nature of this field of research, and the ethical and psychosocial issues that are raised by it, have made it hard for the community to separate out all the issues involved for each type of therapy. Most public comment has appeared to focus on the procedure that is easiest to understand and which raises the most ethical and psychosocial issues, which is organ transplants.

Although the rationale for animal-to-human transplantation is usually stated as being a shortage of human organs, which is certainly the case of whole organ donations, the reasons for pursuing ACTs and AETs are more complex — relating to a combination of new technological possibilities opening up and difficulties in accessing and working with

human products in the context of these therapies. These conditions may change rapidly over the next few years as progress is made in other areas of biotechnology and biological therapy. Careful monitoring of these developments will be required for some years to ensure that, at any time, only research proposals that offer the best chance of benefit to the recipients and to the community as a whole are supported.

3 Key issues from public consultation

3.1 Overview

The submissions to the second round of public consultation focused on key issues that were presented in the Community Guide, as follows:

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

The majority of the respondents to the public consultation and attendees at the public meetings were opposed to animal-to-human transplantation. Although all of the issues noted above were discussed in the submissions and at the public meetings, the following issues received particular attention:

- ethical and social concerns
- animal welfare
- efficacy and safety
- trial protocol (including consent, follow-up and insurance arrangements)
- allocation of resources.

These concerns are discussed further in Sections 3.2–3.7. Another issue that was frequently raised in submissions and at the pubic meetings was that development of other therapies, most notably human stem cell therapies, which were argued to involve fewer ethical, social and safety issues than animal-to-human transplantation research. This issue is discussed further in Section 2.3.

Some respondents supported the concept of animal-to-human transplantation, feeling that ethical and animal welfare considerations had been adequately addressed. However, many of those who expressed in-principle support were nevertheless concerned about safety issues, particularly the possibility that the living animal transplants might transfer a novel infectious agent to humans, which could then infect other humans causing a possibly deadly new disease epidemic.

The XWP's proposal for regulation of animal-to-human transplantation research proposals and any research that was allowed to proceed are described in Section 5.

Advice to NHMRC — key public concerns

Both rounds of public consultation revealed significant public concerns about animal-to-human transplantation. These included ethical and social concerns about the use and welfare of animals; fear of new infectious diseases transferring from animals to humans; doubts around the efficacy of the procedures; practicalities of conducting clinical trials; and the potentially high level of resource use relative to any benefits (thus diverting funds away from other more potentially beneficial uses).

The XWP therefore advises the NHMRC that Australia should take a very cautious approach to clinical animal-to-human transplantation research, under guidelines that apply strict standards to the above issues.

3.2 Ethical and social concerns

Many respondents expressed their view that the use of live animal parts for human medical therapies is not ethical and should not be countenanced under any circumstances. Many expressed revulsion at the thought of live animal organ transplants. Some of these respondents felt that the public documents had not discussed the ethical issues in sufficient detail and had overstressed the significance of the general social acceptance of using animals for human benefit (such as for food). Many of these respondents felt that the use of animals for animal-to-human transplantation is fundamentally different to their use for food.

Although religious objections were cited by many respondents as reasons why animal-to-human transplantation should not be used, there was disagreement between individual respondents, reflecting a diverse range of views even within a particular religion. For example, some Buddhists who attended the public meetings indicated that most Buddhists would not accept an animal transplant, as they would regard it as against the order of nature, but the XWP has received other advice that Buddhists do accept transplantation indicating, the broad spectrum of views that exist, even within a specific religious group. Overall, the advice received from representatives of major religions has indicated to the XWP that there are no overarching theological objections to animal-to-human transplantation.

Some respondents expressed the view that medicine is becoming too interventionist and that people should be more accepting of the time to die. However, other people, particularly younger people and parents of children who could benefit from a transplant, expressed the opposite view.

Some respondents noted that the public documents lacked analysis of the psychosocial issues relating to animal-to-human transplantation. For example, the attitudes of people towards using animals as medical therapies for humans (compared to attitudes towards using animals for food), and the psychological impact of mixing animal and human tissues, were not explored. The way in which people balance decisions about extending life and the allocation of limited health care resources among increasingly complex and expensive health care technologies, was also not explored in much detail in the reports. The XWP agreed that, in retrospect, a sociologist would have been a useful addition to the group to help understand these issues.

The ethics of genetically modifying animals by the addition of human genes was also questioned by many people who felt that the transfer of human genes into another species carried significant ethical implications in terms of both the definition of 'human-ness', and unknown consequences in future generations if the transferred genes behave in an unexpected way. It was clear that many members of the public are not comfortable with the concept of putting human genes into animals and do not feel that they have been consulted on this issue.

It was felt that the genetic modification of animals for transplantation has not been explained well enough; there are further issues of integrity of species that need to be explored. Issues requiring further consideration include the long-term effect of genetic modification on animals and the effect of using live animal products in humans (particularly products that include human genes).

3.3 Animal welfare

Concerns about animal welfare research and objections to the use of animals for human therapies were expressed by over three-quarters of all the submissions received. These concerns included both the animals that would be reared specifically to derive animal products for human use (mainly pigs) and also the animals that would be used as recipients for animal-to-animal transplantation research to develop the procedures (particularly primates).

The Animal Issues Subcommittee (AISC) considered these issues in detail and prepared a report for consideration by the XWP (see Appendix C). The main animal welfare issues identified by AISC were as follows:

- 'Animal welfare' has not been adequately defined in the documents so far. The AISC suggested that the XWP should refer to the definitions of animal welfare and animal wellbeing given in the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes*, 7th edition, 2004 (the Code of Practice) in further documents (see Appendix C).

- Informed debate can only occur if explicit details of the direct effect on animals in this research are detailed.

- Death must not be used as an endpoint of animal studies. ('Death as an endpoint' is when the death of an animal is the deliberate measure used for evaluating biological or chemical processes, responses or effects, ie where the investigator does not intervene to kill the animal humanely before death occurs in the course of a scientific activity.)

- To facilitate the three Rs from the Code of Practice (replacement, reduction and refinement), and thus reduce animal suffering, more emphasis should be placed on alternative therapies that require less use of animals, increasing the rate of human organ donation in Australia and health education programs.

- Animal ethics committees (AECs) do not always have enough information (such as about what other research has already been done) to make decisions because there is no national oversight of animal research. A register of animal-to-animal preclinical xenotransplantation studies was widely supported as a way of overcoming this problem and providing a central agency to advise AECs.

Other important animal welfare issues, including genetic modification of animals, potential for transfer of infectious agents between species and resource allocation, are discussed in Sections 3.2, 3.4 and 3.7.

AISC stressed that, considering the animal suffering involved, animal use must be very carefully weighed up in terms of potential benefits to humans. If the 'costs' to animals in animal-to-human transplantation research (in terms of animal suffering) are not justified by the potential benefits to humans, such research should not be allowed to proceed. AISC did not consider that the potential benefits to humans of animal-to-human transplantation research currently justify the costs to animals.

Importantly, it was acknowledged that even if no animal-to-human transplantation clinical trials are permitted to go ahead in Australia, there is still likely to be ongoing animal-to-animal transplantation research. AISC therefore proposed that a central register of animal-to-animal preclinical xenotransplantation studies should be set up (as proposed in the Response Paper) and a detailed proposal for this register is included in Appendix C and discussed further in Section 6 of this report.

A further concern expressed by a number of respondents was the functioning of local AECs, as these committees do not always function as they should. For example, community representatives on the committees may feel unable to speak out on technical issues in the face of the greater knowledge of researchers, and committees may not have enough information about what research is occurring elsewhere or that has been tried before, to make decisions that facilitate the three Rs from the Code of Practice. This issue could be reviewed by the NHMRC Animal Welfare Committee.

Advice to NHMRC — animal ethics committees

Some respondents to the public consultation noted concerns about how animal ethics committees function, including the ability of community ethics committee members to contribute to technical discussions and the lack of information available to committees about animal research conducted in other institutions.

The XWP therefore advises the NHMRC that this issue should be referred to the NHMRC Animal Welfare Committee for further investigation.

3.4 Efficacy

In both rounds of public consultation, many respondents highlighted the lack of evidence to date of efficacy of any of the animal-to-human transplantation procedures, with even the more promising animal-to-animal transplantation studies involving organ transplants achieving only very short-term survival of the transplanted organs (mostly less than three months). Although researchers are optimistic that further genetic modification of the source animals will help to overcome rejection and significantly improve outcomes, other significant physiological barriers still need to be overcome.

The efficacy of cellular and external therapies has been more variable in studies to date. The efficacy of these therapies is also less crucial for the wellbeing of the recipient as failure of the animal products to function is not necessarily life-threatening. Therefore, allowing clinical trials of only some of these procedures may be a more feasible option than allowing all animal-to-human transplantation clinical trials. The efficacy of different procedures is discussed further in Section 4.

3.5 Safety

The other issue that received a very large amount of attention in the submissions was the risk that human transplant recipients may be infected with a virus or novel disease agents from animals and that this infection may spread in the community causing a serious epidemic.

Nonhuman primates, such as baboons, are not considered to be a suitable source animal for any of the animal therapies under development because of the risk of infections to the recipient and the wider community (see Section 4). At present, pigs are considered to be the most likely nonhuman source of transplants.

Considering that pigs were proposed as the most likely source of transplantation products, much of the discussion about infection risks centred around porcine endogenous retrovirus (PERV) but respondents also expressed concern that other completely unknown agents could emerge, such as occurred with the transfer of bovine spongiform encephalopathy (BSE) to humans in the United Kingdom.

Although there was disagreement among experts on the extent of this risk, there was agreement that transfer of infection from animals to humans could not be completely ruled out, particularly in circumstances where there was prolonged direct contact between animal and human tissues (such as would be the case for whole organ transplants). Some respondents also highlighted the potential for genetic modification of animals to increase the likelihood of infection (by reducing the antigenic difference between the animal and human cells). The need for a high-level of immunosuppression is also a risk factor, significantly reducing the ability of transplant recipients to fight an infection.

Although some respondents highlighted the HIV/AIDS epidemic as an example of how health authorities have been unable to manage emerging infectious diseases in the past, the XWP noted that since the initial outbreak of HIV/AIDS in the 1980s, international health authorities have become better organised to manage some incidents, as was shown by the response to the recent outbreak of severe acute respiratory syndrome (SARS).

A further concern expressed by respondents was the environmental implications of genetically modified breeding animals escaping (including for wildlife and feral pigs). The additional risk of infections spreading from recipient humans back to animals is a particular concern for animal production industries.

The relative risks of different types of animal-to-human transplantation procedures are discussed further in Section 4.

3.6 Clinical trial protocol

The practicalities of conducting clinical trials of animal-to-human transplantation were also questioned by many respondents. Issues raised include:

- the difficulties of obtaining voluntary and informed consent from people who may be very sick and have few options for survival;
- the difficulties of obtaining a binding commitment from participants to continue in the trial, even if the procedure itself fails;

- the issue of whether close contacts of the transplant recipient should be included in the definition of 'participants' because of the need for long-term monitoring and follow up; and

- the need for clear criteria for closing a trial, if this becomes necessary, and mechanisms for achieving this (see Section 5.3).

These issues were all discussed in some detail in the previous reports and the XWP believe they are covered by the requirements of the proposed NHMRC guidelines (see *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document).

However, the XWP noted that for animal organ transplants, although such a procedure would be experimental, it would be an innovative therapeutic procedure of last resort for the recipient and, as such, issues of information sharing and consent would be very difficult to manage.

The importance of long-term monitoring and inclusion of close contacts would depend on the extent of the risk of infection and would therefore apply differently to each type of procedure (see Section 4.2). Irrespective of the infection risk, however, the need for comprehensive ongoing psychosocial support for patients and their families was stressed by many respondents.

Finally, given the infectious disease risks of animal-to-human transplantation to both transplant recipients and the general community, many respondents to the public consultation raised the issue of the responsibility of researchers to pay for the necessary infection control activities should something go wrong and of compensation arrangements for transplant recipients and contacts. Insurance arrangements for clinical trials are covered by Section 12.7 of the *National Statement on Ethical Conduct in Research Involving Humans,* NHMRC 1999 (National Statement), which requires trial sponsors to ensure adequate compensation to participants for any injury suffered as a result of participation in the trial.

3.7 Resource use

Many respondents expressed concern that the development of high-technology medical solutions, such as animal-to-human transplantation, are resource intensive and therefore (a) may only benefit those who will be able to pay for the procedures, and (b) direct scarce funds — for both research and treatment — away from other more widely applicable areas of health care.

This issue is clearly one that raises a lot of concern in the community but has been largely outside the scope of the XWP's role to investigate in detail. Important considerations in relation to these concerns are:

- for clinical research, the costs should be covered by researchers/sponsors and there will be no cost to transplant recipients;

- all costs associated with the trials, including long-term follow-up and public liability insurance have to be met by the research sponsor, as for other clinical trials;

- most research to date in this field has been sponsored by biotechnology companies;

- if treatments become routine therapy, public funding under Medicare will be reviewed in the same way as it is for other new health technologies, based on safety, efficacy and cost-effectiveness; and

- the need for clear criteria for closing a trial, if this becomes necessary, and mechanisms for achieving this.

AISC identified that little is known about the overall 'cost–benefit' tradeoff for animal-to-human transplantation research at this time. An analysis of the quality of life for both source animals and human recipients; monetary costs of procedures versus benefits to human health and productivity; and projected diversion of human and financial resources within the health budget will be very helpful as more information becomes available.

NSW Health and the South Australian Department of Human Services both noted that alternative approaches to dealing with human organ and tissue shortages should be supported, especially as animal-to-human transplantation is unlikely to become a pre-eminent therapy. The South Australian Department of Human Services further expressed concern that medical research is continually being extended whereas welfare/community service issues fail to receive adequate funding and attention. They noted that allocating resources to animal-to-human transplantation has risks for the whole community but may only benefit a few people. Therefore, support for, and funding of, animal-to-human transplantation research needs careful consideration.

Advice to NHMRC — resource use

A number of biotechnology and biological therapies are being researched for treatment of the same conditions that animal-to-human transplantation is proposed to treat.

The XWP therefore advises the NHMRC to carefully monitor developments across the spectrum of developing biotechnology and biological therapies to ensure that the research that offers the best chance of individual and society benefits is supported.

3.8 Conclusion

Respondents raised many concerns about animal-to-human transplantation covering ethical and social concerns, the efficacy and safety of the procedures, trial design and resource use. These issues had all been previously discussed in the Discussion Paper and Response Paper. However, it was clear that the Response Paper had not allayed most respondents' concerns.

The strongest concerns of the majority of respondents who were opposed to animal-to-human transplantation were about (a) animal welfare, and (b) the risk of a novel infectious disease spreading from animals to humans. Overall, most respondents to the public consultation did not feel that the benefits of animal-to-human transplantation to the community would outweigh the 'costs' in terms of animal suffering, or the risks in terms of a possible human infectious disease epidemic. However, as discussed in Section 2, most of these respondents did not consider the three types of animal-to-human transplantation therapy separately, and appear to have directed their comments towards animal organ transplants. A comparison of these issues across the three different types of therapy is given in Section 4.

The issue of resource use was also a recurrent theme in both rounds of public consultation and reflects broad community concern about a range of modern high-technology health care interventions. It was beyond the scope of the XWP to conduct an in-depth analysis of the cost of animal-to-human transplantation research as this is an issue for research funding bodies to assess against Australia's current research and health care priorities. However, as discussed in Section 2, as biotechnology and biological therapy research advances, there will be a need for careful monitoring of ongoing developments across a range of therapeutic options to ensure that resources are used to support research that has the most potential for benefit both for individuals and society as a whole.

4 Should Australia proceed?

4.1 Introduction

As indicated in Sections 2 and 3, the majority of respondents in both rounds of public consultation and at the public meetings were opposed to animal-to-human transplantation research being allowed in Australia. Many people expressed an overall abhorrence for inserting living animal tissues into human beings and these feelings were discussed in terms of moral and ethical values about the relationship between humans and other animals and the psychosocial implications of crossing the species barrier (see Section 3.2).

On the other hand, a number of people expressed strong support and a willingness to accept animal to human transplants, provided they were assured of safety and efficacy (see Section 3.1). Some of the people who expressed these views identified that they themselves were recipients of human transplants or had relatives on waiting lists for transplants.

Overall, the issues raised by the majority of respondents about the prospect of animal-to-human transplantation trials themselves, reflected strongly held misgivings about three issues:

- animal welfare;
- the possible infectious disease risks associated with such therapies; and
- the limited evidence for efficacy of the procedures.

As already stressed, it appeared from the context of the submissions that most of the concerns were directed towards animal organ transplants (AOTs). Very few respondents specifically addressed animal cell therapies (ACTs) or animal external therapies (AETs), although each of these types of therapy has quite different sets of considerations for the above issues.

The Xenotransplantation Working Party (XWP) therefore considered each type of therapy in the light of the public concerns. The results of this review are discussed below and briefly summarised in Table 4.1.

4.2 Review of issues

Animal welfare

Animal welfare considerations raised in the public consultation are described in detail in the report of AISC (see Appendix C).

Translating public concerns about use of animals for medical therapies and the welfare of the animals concerned, into a policy for animal-to-human transplantation research is a complex matter because there are a number of issues involved for different stages of

research. Respondents to the public consultation who opposed animal-to-human transplantation on animal welfare grounds did not always separate these issues.

Issues that need to be differentiated are:

- the use of animals in preclinical and clinical research;
- the creation and maintenance of source animals for preclinical and clinical research and the use of recipient animals (including primates) for preclinical animal-to-animal transplantation studies; and
- the use of genetically modified (GM) versus unmodified animals.

A summary of animal welfare issues for each type of animal-to-human transplantation therapy is given in Table 4.1.

Preclinical and clinical research

Responses that highlighted animal suffering rarely differentiated between preclinical studies (animal-to-animal transplantation) and clinical trials (animal-to-human transplantation). Particular concern was expressed about the use of primates in animal-to-animal transplantation studies involving high levels of surgical intervention (such as organ transplants), which was not considered acceptable to many people. The terms of reference of the XWP were directed towards considering animal-to-human transplantation research (ie clinical trials) rather than animal-to-animal transplantation research. The XWP assumed initially that the Code of Practice would address concerns about animal-to-animal transplantation research. However, on the advice of AISC (see below), the XWP now advises the NHMRC that there are additional matters that will require attention.

The level of public concern expressed about the use of animals in preclinical animal-to-animal transplantation studies indicates that such studies should be restricted to those where the presumed benefits to human health outweigh the costs to animals in terms of quality of life, pain and suffering.

Creation and maintenance of source animals

Concern was also expressed about the conditions required to breed and raise animals suitable for use in animal-to-human transplantation. Such conditions would need to comply with relevant good laboratory practice requirements, including a specific disease-free environment. However, a completely pathogen-free environment would not be required. Establishment of a breeding colony would involve similar practices to those used in agricultural practice to establish a 'closed herd' (ie birth by caesarean section in the first generation and then normal mating and birthing within the closed herd in subsequent generations).

Genetic modification of animals

Genetic modifications of pigs have involved both gene silencing (ie when specific genes are 'switched off') and insertion of human genes, to increase the immune compatibility between pig and human tissues and to overcome other physiological problems. Many respondents expressed concern about human gene insertions into animals as there has been no public consultation about such research.

Further information about the current regulatory arrangements for genetically modified organisms (GMOs), which is administered by the Gene Technology Regulator, through the Office of the Gene Technology Regulator (OGTR), is given in Section 5.4.

The OGTR arrangements take account of the potential risk to human health and the environment of the release of the genetically modified animal but do not include an ethical assessment of the effects of the modification. As for all other ethical considerations of medical research, an ethical assessment of GM research is carried out by the animal ethics committee at the institution, in line with the Code of Practice, but there is no mechanism for wider community discussion.

Position of the Animal Issues Subcommittee

AISC concluded that it could not support Australia proceeding with any animal-to-human transplantation research at this time. The subcommittee has therefore recommended that XWP amend the proposed guidelines that appeared in the Response Paper to include a moratorium on all animal-to-human transplantation research. AISC members were unanimous in this position, which they stressed was not based solely on animal welfare issues but on consideration of the overall balance of all issues raised by respondents (see Appendix C for the full report of AISC).

Efficacy

Evidence for the potential efficacy of animal-to-human transplantation therapies was summarised in detail in the Discussion Paper and the Response Paper and the lack of evidence of efficacy was highlighted by many respondents. Table 4.1 provides a summary of this information.

Despite the emphasis on research (ie clinical trials) throughout the public consultation, most respondents did not distinguish between research and therapy. This reflected the focus in the submissions on AOTs. Indeed, for an organ transplant, there would be little, if any, distinction between a clinical trial and an innovative therapy.

Animal organ transplants

For AOTs there are clearly major immunological and physiological barriers to achieving successful outcomes. In animal-to-animal organ transplantation studies to date, transplanted organs always fail within a short timeframe. However, successful genetic modification of pigs over the past couple of years has improved outcomes in pig-to-primate studies and further studies are currently being undertaken in the United States using the most recently created genetically modified pigs.

For a clinical trial of an AOT to be considered, there would need to be data that showed the transplanted organs will function fully outside the laboratory (ie be physiologically competent and compatible with the recipient), which is not currently the case. The aim for current pig-to-primate studies is to answer further biological questions about the compatibility and physiological competence of organ transplants between species rather than to provide direct evidence in support of ethical approval of clinical trials.

In these studies, either the organs fail or there is a secondary complication, such as coagulation. These conditions are identified by routine blood tests and the animals are killed humanely (ie death is not used as an endpoint of the studies).

Animal cell therapies

For ACTs, immune rejection may be a less significant problem than for AOTs and longer-term survival of the transplanted material has been achieved in both animal-to-animal and animal-to-human transplantation procedures.

Cellular transplants have been shown to function therapeutically in some animal-to-animal cell transplantation studies. However, although animal-to-human ACT trials carried out overseas have not shown any major adverse effects of the procedures, the transplanted cells have not provided any therapeutic benefit to the recipient.

Because immune rejection is a less significant issue for ACTs than for AOTs, there is less requirement for immunosuppression and researchers are investigating ways to reduce this requirement further (in the hope that no immunosuppression will be required).

Animal external therapies

Trials of AETs have been more successful than AOTs or ACTs, with both human skin cells grown on an animal feeder layer and liver perfusion methods suggesting positive outcomes in animal-to-human AET trials overseas.

These procedures do not have the same rejection problems associated with AOTs as the animal tissues or cells are not implanted into the recipient and there is less need for immunosuppression of the recipients.

Safety

Fear that animal-to-human transplantation using other animals would initiate another serious disease epidemic like HIV/AIDS, severe acute respiratory syndrome (SARS) or Creutzfeldt–Jakob disease (CJD: the human equivalent of bovine spongiform encephalopathy, or BSE) was expressed by many respondents. Researchers agree that nonhuman primates would not be suitable source animals for animal-to-human transplantation because of the risk of infections to the transplant recipient and the wider community.

The level of risk of such an event occurring when other source animals are used (eg pigs) is the subject of some debate amongst experts, but all agree that such a possibility cannot be completely ruled out when animal and human tissues are mixed together.

Further assessment of the risks in individual trials would be a task for a committee with considerable expertise in such matters, but a number of important factors can be identified that are likely to affect the level of infectious disease risk associated with each type of procedure:

- the amount of live animal tissue transplanted;
- the extent of the direct contact between live animal and human products;
- the length of time the contact is maintained;
- how much immunosuppression the transplant recipient receives;
- whether or not the animal products are genetically modified; and
- the characteristics of the potential pathogen in the source animal.

The risk factors associated with AOTs, ACTs and AETs are shown in Table 4.1.

Table 4.1 Animal-to-human transplantation therapies and their implications for efficacy, safety and animal welfare

Note: This table is a general guide to the major issues only, and is included here to provide an at-a-glance overview of the issues that have informed the XWP's overall advice in which types of research proposal should be allowed to move forward to a more detailed assessment. Assessment of individual research proposals against the proposed NHMRC guidelines would involve an indepth consideration of these and other issues relating to the research, including other existing and potential therapies for the condition in question.

Therapy	Example	Current stage of development	Risk factors	Animal welfare consideration
Animal organ transplants (AOTs)	Heart, kidney	A few animal-to-human organ transplants were attempted overseas from 1960–1993 — all unsuccessful In some animal-to-animal studies, organs have survived for about 3 months (maximum 5 months). However, there are still major unsolved immunological and physiological barriers to long-term survival of whole organ xenotransplants. There are therefore no proposals for clinical trials anywhere in the world; and none are likely in next few years (because no benefit has been shown and risks are too high).	Direct vascular connection + long term + high levels of immunosuppression. Animals are GM. Work to create GM pigs (by both gene silencing and gene insertion) is happening in Australia under regulation from OGTR. [Highest risk]	Animal-to-human transplantation trials Organs obtained from anaesthetised animals, which are killed immediately afterwards. Animals raised in clean environment/closed herds according to GMP requirements (ie specific disease free rather than completely pathogen free). Source animals would need to be GM. Animal-to-animal transplantation studies For preclinical studies, transplant recipient animals undergo major surgery. Whole organ transplants currently being done using GM pigs (source) and cynomolgus monkeys (recipient) at Harvard medical school, US (which is an open facility, unlike UK where facilities were closed). Death is not used as endpoint for the research but some animals have died from complications.
Animal cell therapies (ACTs)	Pancreatic islets (diabetes) Brain cells (Parkinson's disease)	Preclinical studies have shown some efficacy. Some clinical trials have been carried out or are in progress overseas and have shown techniques to be safe in the short term but not efficacious. Further trials applications are expected.	Long-term exposure but small volume and not in direct vascular contact + less need for immunosuppression. Some therapies may have capsule separating cells. Cell types are characterised rather than mixture found in whole organs. [Intermediate risk]	Animal-to-human transplantation trials Tissue obtained from anaesthetised animal (eg pancreas) and disaggregated to obtain cells. Animals then immediately killed. Animals raised in clean environment/closed herds according to GMP requirements (ie specific disease free rather than completely pathogen free). Animals may be GM (but not necessarily) Animal-to-animal transplantation studies For preclinical studies, transplant recipient animals

Therapy	Example	Current stage of development	Risk factors	Animal welfare consideration
				undergo less invasive surgery than for AOTs. Death is not used as endpoint for the research.
Animal external therapies (AETs)	Hepatassist (liver perfusion) Skin grafts	Ongoing active trials overseas with some claims of efficacy. Hepatassist currently used as a bridge to transplant for people with liver failure. Skin grafts currently used for severe burns, including in Australia (but in future could be for all skin grafting).	No direct contact, very short-term exposure and no immunosuppression drugs used. May also be physical barrier (such as in the hepatassist device). [Lowest risk]	Animal-to-human transplantation trials Skin grafting mainly uses established animal cell lines (ie no live animals used) or sometimes irradiated fresh cells (eg mouse thymus cells). Hepatassist uses liver cells extracted as per cell therapies above (see also Response Paper, para 5.36). Animals raised in clean environment/closed herds according to GMP requirements (ie specific disease free rather than completely pathogen free). No need for GM of animals. Animal-to-animal transplantation studies Various procedures involved reflecting the different types of procedures in this category. Some involve no live animal use, some involve invasive procedures.

4.3 XWP recommendations and rationale

In debating and carefully considering what it had learned from its own research and inquiry, from the public consultation process, and from scientific and regulatory material available from other countries, the XWP needed to weigh up a large number of sometimes competing factors including:

- the risks of new infections being transmitted to human recipients and to the wider community;
- the likelihood, or otherwise, of animal-to-human transplantation being effective in the short or long term;
- community concern over the care and use of animals for this purpose;
- the shortage of human organs and tissues for transplantation;
- the hopes of those persons who might benefit from this research;
- the additional broad scientific knowledge and understanding that is likely to come from continuing to undertake animal-to-animal research, which is already making significant progress here and overseas; and
- the fact that clinical trials are already taking place overseas and that Australians may seek such treatment abroad.

Recommendations

After weighing all these considerations, the XWP recommends to the NHMRC an extremely cautious 'green light' to the possibility that strictly overseen and limited animal-to-human trials may be undertaken in Australia.

The XWP first recommends that AOT trials should not be considered for at least the next five years, on the basis that theoretical concerns suggest that this type of transplant carries the greatest risk of infection, current evidence indicates that this risk is not outweighed by likely prospects of success, and there is a high level of public concern about animal welfare for the animals involved in this type of research.

For the two other types of transplant procedures (ACTs and AETs), the XWP recommends a very strict national oversight system for research proposals, involving a broadly representative national committee, the Therapeutic Goods Administration (TGA), the Office of the Gene Technology Regulator and institutional HRECs and AECs, and applying new guidelines for this type of research (see *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document). The guidelines will not permit any animal-to-human trials to proceed until the national committee (on behalf of the Australian community) and the TGA are satisfied that:

- animal welfare concerns have been adequately addressed;
- there is a high level of probability that the procedure will provide significant benefit to the recipient and there are no other current or alternative experimental therapies that would provide more benefit;

- the risk of cross-species infection is minimal and acceptable to the community based on the potential benefit of the proposed procedure; and
- the trial protocol meets all the requirements in the guidelines for information sharing, consent, monitoring, indemnity insurance and follow-up.

The XWP also recommends that, for safety reasons, nonhuman primates (such as baboons) should not be used as the source animals for animal-to-human transplantation (see Section 3).

A summary of the XWP's recommendations and rationale is shown in Table 4.2.

Proposed review of recommendations

As conditions may change in the future, the recommendations shown in Table 4.2 should be reviewed after five years unless a recommendation from the national animal-to-human transplantation committee (see Section 5) indicates that an earlier review is warranted based on new information on safety and efficacy. Any such review must include public consultation.

Table 4.2 Working party recommendations for clinical animal-to-human transplantation research

Therapy	Recommendation	Basis for recommendation
Animal organ transplants (AOTs)	Clinical trials of AOTs should not be permitted in Australia	AOTs are not acceptable because: • the use of animals in this way is not acceptable to the public, with a high level of public concern regarding animal welfare and safety • there is currently no evidence of efficacy • they carry an unknown risk of infection.
Animal cell therapies (ACTs)	Applications for clinical trials of ACTs can be considered in Australia under strict standards set by NHMRC guidelines[a]	Although public consultation did not sufficiently reveal specific information about the acceptability of ACTs, the XWP considered that some clinical research may be considered because: • the level of intervention involved for the procedures is less than for AOTs and therefore may be more acceptable to the public • there is some evidence of efficacy for a range of otherwise incurable conditions • they appear to carry a lower potential risk of infection than AOTs.
Animal external therapies (AETs)	Applications for clinical trials of AETs can be considered in Australia under strict standards set by NHMRC guidelines[a]	Although public consultation did not sufficiently reveal specific information about the acceptability of AETs, the working party considered that clinical research can be considered because: • some procedures involve no use of live animals; others involve similar levels of suffering and intervention to AOTs and ACTs • there is evidence of efficacy for some procedures • they appear to carry a minimal risk of infection.

[a] See *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document

4.4 Conclusion

The XWP has considered AOTs, ACTs and AETs in the light of the high level of community opposition to animal-to-human transplantation revealed via public consultations, noting that this opposition was mainly directed towards animal organ transplantation. Understandably, because of the complexity of the issues involved, most respondents did not distinguish between the three types of animal-to-human transplantation.

The three main areas of concern expressed by respondents about animal-to-human transplantation were animal welfare, efficacy and safety (particularly in respect of the spread of infectious diseases).

The XWP considered how these issues relate to each type of therapy and framed its advice to NHMRC based on its findings against these issues, and on further consideration of the overall concerns expressed by respondents.

Advice to NHMRC — animal-to-human transplantation clinical trials

The public consultation showed that animal-to-human transplantation, in particular animal organ transplantation, is not acceptable to many people.

The XWP therefore advises the NHMRC that:

- research proposals for clinical trials of animal organ transplants should not be considered in Australia (ie no animal-to-human whole organ transplants should be permitted);
- nonhuman primates should not be considered as source animals for clinical trials of animal-to-human transplantation;
- clinical trials of animal cell therapies and animal external therapies can be considered in Australia under strict standards set by NHMRC guidelines (see *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document) and oversight arrangements that would not allow research to proceed unless it is assessed as being safe, potentially offers benefits to the recipients and conducted according to high ethical standards;
- these recommendations and the guidelines should be reviewed in five years, and
  - earlier review of the guidelines should only be permitted if a recommendation from the national animal-to-human transplantation committee indicates that such a review is warranted based on new information on safety and efficacy;
  - the review must include public consultation.

5 National oversight of animal-to-human transplantation research

5.1 Introduction

In the Discussion Paper and Response Paper, the Xenotransplantation Working Party (XWP) described in detail the current regulatory arrangements for clinical trials and how they would relate to proposed animal-to-human transplantation research. This discussion included a detailed description of the role of the Therapeutic Goods Administration (TGA), National Health and Medical Research Council (NHMRC) and Office of the Gene Technology Regulator (OGTR) and the relevant legislation underpinning the activities of these agencies. In the Response Paper, particular attention was also paid to the role of the NHMRC and institutional animal ethics committees (AECs) in the oversight of research involving animals.

From the outset, there appeared to be two options for the future of animal-to-human transplantation in Australia:

- a complete ban of all such research (ie no proposals could be considered at all); or
- a national system for careful consideration of research proposals on a case-by-case basis and oversight of any approved trials.

As discussed in Section 4, animal-to-human transplantation includes a variety of procedures. These are being attempted for a variety of different reasons and have differing potentials for success and associated risks. The XWP has recommended a very cautious approach to animal-to-human transplantation research that does not allow consideration of any research proposals for animal organ transplantation (AOTs) for at least the next five years. However, it does allow proposals for animal external therapies (AETs) and animal cell therapies (ACTs) to be submitted for consideration by a national animal-to-human transplantation committee, the TGA and local institutional animal and human ethics committees, against strict standards set out in the proposed NHMRC guidelines (see *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document). Only if approval is obtained from all these organisations would the research be able to go ahead.

It is important to note that the XWP does not consider that proposing a national system to allow consideration of animal-to-human transplantation research proposals is the same as allowing such research to proceed, as has been implied by some press reports. Under the scheme proposed by the XWP (see below), proposals will be assessed against NHMRC guidelines, with only those that meet the high standards required being permitted to proceed.

The supply of therapeutic goods in Australia is administered by the TGA under the *Therapeutic Goods Act 1989* (TG Act) and Regulations. The legislation establishes a uniform, national system of regulatory controls to ensure the quality, safety, efficacy and timely availability of therapeutic goods for human use. In the Response Paper (paragraphs 11.40 –11.43), the XWP noted that in March 2003 the TGA released a discussion paper on *The Regulation of Human Tissues and Emerging Biological Therapies*. As a result of the responses received to this discussion paper, the TGA is now considering amendments

to the TG Act and associated regulations to cover a range of emerging biological therapies, including animal-to-human transplantation.

The XWP's proposal for national oversight and regulation is described in detail in Section 5.7. Implementation of this scheme will require careful review and possible amendment of the TG Act and associated Regulations in the following important areas:

- To confirm that live animal cells, tissues or organs to be used in animal-to-human transplantation therapies (animal transplantation products) are 'therapeutic goods' for 'therapeutic use' (see Section 5.2).

- To require that any use of animal transplantation products, including for individual patients, can only occur in the context of a clinical trial and that no other avenues for exemption, including use under the Special Access Scheme, can be accessed for animal transplantation products (see Section 5.3).

- To require that all clinical trial applications must be submitted to the TGA as CTX (Clinical Trial Exemption) applications (see Section 5.3).

- To prohibit by legislation access to animal transplantation products under any schemes for individual use of unregistered therapeutic goods or by any route other than by a clinical trial.

- To recognise the role of a national animal-to-human transplantation committee, set up by the NHMRC, in the approval of animal-to-human transplantation research proposals, as an integral part of the assessment of any proposal (see Section 5.7).

In implementing the recommendations for national oversight of animal-to-human transplantation outlined in Section 5.7, it will therefore be necessary for the NHMRC to consult closely with the TGA to ensure that the revised TG Act takes account of these issues.

> Advice to NHMRC — consultation with the Therapeutic Goods Administration (TGA)
>
> The TGA is currently considering revisions to the *Therapeutic Goods Act 1989* and associated Regulations, to take account of a range of emerging biological therapies, including animal-to-human transplantation.
>
> The XWP advises the NHMRC that, in implementing the recommendations for national oversight of animal-to-human transplantation, it consults closely with the TGA to ensure that the revised therapeutic goods legislation provides the necessary regulatory framework to support the scheme.

5.2 Regulation of therapeutic goods

The therapeutic goods legislation (TG Act and Regulations) requires that therapeutic products are included in the Australian Register of Therapeutic Goods before they may be imported into, manufactured in, supplied in, or exported from, Australia.

The TG Act defines therapeutic goods as goods that are for therapeutic use, whether as the active component or as a component or ingredient in the manufacture of the goods or of the container or part of the container for the goods. The definitions of a 'therapeutic good' and of 'therapeutic use' in the TG Act appear to be broad enough to include animal cells, organs or tissues when used therapeutically and, indeed, this is the interpretation

that is currently enforced by the TGA. The only specific exemption is in relation to organ transplantation and relates to human whole organ transplantations from human to human without further manipulation of the organ.

> Advice to NHMRC — inclusion of animal transplantation products as 'therapeutic goods'
>
> The definitions of a 'therapeutic good' and of 'therapeutic use' in the *Therapeutic Goods Act 1989* appear to be broad enough to include animal cells, organs or tissues when used therapeutically.
>
> The XWP therefore advises the NHMRC to ensure that animal transplantation products remain within the definition of therapeutic goods in the *Therapeutic Goods Act 1989*.

5.3 Regulation of clinical trials

The TG Act allows for the supply of unregistered therapeutic goods under some circumstances, including for use in clinical trials. There are also provisions under the legislation to allow the use of unregistered goods in individual patients. These include the Special Access Scheme, Authorised Prescriber Scheme and personal import arrangements. In addition, there are exemptions for goods that are extemporaneously compounded for use in individual patients.

Human research ethics committees (HRECs) would normally be expected to endorse use in the case of Special Access Scheme and Authorised Prescriber Scheme but they do not normally have a major role in personal importation arrangements or in extemporaneously compounded product usage. These are systems which have been set up to give medical practitioners and individuals access to therapeutic goods that are not yet registered in Australia but which may provide the treatment of choice in some circumstances.

For effective regulation of animal-to-human transplantation, it is important that all uses of unregistered animal transplantation products are regulated as clinical trials, even for single patient use, and that there is no access to the other exemptions from the requirement for registration.

Applications for clinical trials can be submitted under either the CTN (Clinical Trial Notification) or CTX schemes. CTN notifications are dealt with by the HREC, the institution, and the TGA. The TGA accepts a notification from the sponsor of the trial, provided that the chair of the HREC, the head of the institution and chief investigator provide certain undertakings concerning the conduct and monitoring of the trial and their agreement to monitor the trial and to allow the TGA access in the future, if required. In this case, the HREC is responsible for reviewing the trial protocol.

CTX applications are reviewed by the TGA, which provides comment to the HREC and may also raise objections with the sponsor of the trial. The major area for review by the TGA in the case of a CTX application is the safety of the clinical trial and defined packages of data must be submitted to justify use. These are based on international clinical trial approval processes. For clinical trials and medicines, this would include review of information relating to overseas status and usage guidelines, and details of the available preclinical and quality data. For medical device trials, it involves examination of design specifications and any available preclinical animal data.

Clinical trial protocols are not approved by the TGA specifically, but a document called the Usage Guideline is approved. If usage is to go beyond the limits of the Usage Guideline, then a further CTX must be lodged with TGA. TGA delegates decide whether or not they have objections to the trial under the CTX system. If any objections are raised, they must be addressed before the trial can proceed.

Under both the CTX and CTN systems, the HREC is responsible for considering the scientific and ethical issues of the proposed trial and the clinical trial protocol. The institution must also give approval for conduct of the trial at its site. Applications can be lodged simultaneously with the TGA and the institution(s) at which studies are proposed to be conducted. However, if the application is lodged simultaneously with the TGA and any HREC involved, the sponsor is required to convey any TGA comments or revisions on the application and/or objections to all HRECs involved.

Under current arrangements, the choice of which scheme to follow (CTN or CTX) lies with the sponsor and the institutional HREC. HRECs usually prefer phase I clinical trial applications to be CTX because they do not have access to the scientific expertise to assess participant safety. In the case of animal-to-human transplantation trials, both the HREC and animal ethics committee (AEC) at the local institution will be involved in the assessment of the trial protocol and these committees may not have access to appropriate scientific and technical expertise for animal-to-human transplantation research, which involves new and rapidly evolving technologies and critical emerging infectious disease safety issues. The XWP therefore recommends that all animal-to-human transplantation trial proposals should be submitted as CTX applications. Furthermore, because of the importance of national oversight for such trials, the CTN application route should be barred through legislation.

Current arrangements under the TG Act and the National Statement provide the TGA and HRECs, respectively, with the power to close down clinical trials if participants are perceived to be at greater risk than was anticipated when the protocol was approved. These powers do not need to be strengthened but local HRECs will have a responsibility to keep the national animal-to-human transplantation committee informed about any emerging safety issues (see Section 5.7).

Advice to NHMRC — clinical trial applications

To ensure that any trials of animal-to-human transplantation, including individual use, are assessed by local ethics committees, the proposed national animal-to-human transplantation committee and the TGA, all such uses need to be submitted as a clinical trial application under the CTX (Clinical Trial Exemption) scheme.

The XWP therefore advises the NHMRC that the *Therapeutic Goods Act 1989* and associated Regulations should be amended to:

- ensure that animal-to-human transplantation, including for individual patients, can be undertaken only as part of a clinical trial;
- prevent the use of animal transplantation products under the Authorised Prescriber Scheme, the Personal Use Scheme or the Special Access Scheme; and
- prescribe that animal-to-human transplantation research proposals must be submitted as CTX applications.

5.4 Regulation of genetically modified animals

The Discussion Paper included a very detailed account of the current regulatory arrangements for use of genetically modified (GM) animals and how these may apply to animal-to-human transplantation research. Under current regulatory arrangements for GM organisms (GMOs), research involving genetic modification of animals must be notified to the Office of the Gene Technology Regulator (OGTR). If a GMO is going to be 'released' into the environment, the OGTR conducts a detailed risk assessment. If there is not going to be any environmental release, however, such research is classified as low risk and a detailed risk assessment by the Gene Technology Regulator is not required. This latter situation is the case for both animal-to-animal studies and potential animal-to-human transplantation trials because the GM animals are held in contained facilities (ie are not 'released').

Products produced from GMOs are called GM products. The difference between a GMO and a GM product is that GMOs are viable, capable of reproduction or capable of transferring genetic material to other organisms, while GM products are derived from GMOs but are not viable. Animal transplantation products from GM animals are GM products.

Both GMOs and GM products are generally regulated by the agencies related to their use (ie the Australian Pesticides and Veterinary Medicines Authority for agricultural and veterinary chemicals, Food Standards Australia New Zealand for foods, and the TGA for therapeutic products). GMOs are also reviewed by the Gene Technology Regulator in terms of their environmental impact, as described above.

The *Gene Technology (Consequential Amendments) Act 2000* amended the legislation of these other regulators to require that:

- when the relevant regulatory agency receives an application for approval of a GM product, the agency must seek and take into account the advice of the GT Regulator; and

- the relevant authority must notify the OGTR of the decision regarding the GM product, so that the Gene Technology Regulator can include the information on the 'Record of GMO and GM Product Dealings'.

However, the requirements for regulatory agencies, when approving GM products, to seek and take into account the advice of the Gene Technology Regulator, do not apply to the conduct of clinical trials. Therefore, the TGA would not need to take account of any advice from OGTR before approval of a GM animal transplantation product. However, the TGA would need to notify OGTR of any decision regarding use of a GM product, for recording in the record of GM product dealings.

In addition, as animal transplantation products are unusual products under the current definitions of the GT Act and the technologies used and types of modifications attempted are rapidly developing, it is possible that, in future, some further assessment by the Gene Technology Regulator may be required on a case-by-case basis for animal-to-animal or animal-to-human research, depending on the exact nature of the product and the genetic modification involved.

5.5 Gene and Related Therapies Research Advisory Panel

The Gene and Related Therapies Research Advisory Panel (GTRAP) was established by the NHMRC Research Committee in the early 1990s to provide advice to HRECs on individual research applications involving gene therapy. More recently the terms of reference of this committee were expanded to include animal-to-human transplantation (until formal Australian guidelines to cover animal-to-human transplantation research are implemented). HRECs have been advised by the NHMRC that proposals for human research in either gene therapy or animal-to-human transplantation must be referred to GTRAP for advice. GTRAP is an expert committee with a relatively broad membership (see http://www.nhmrc.gov.au/research/gtrap.htm).

5.6 Key regulatory issues raised in the public consultation

Although most respondents to the public consultation focused on the animal-to-human transplantation procedures themselves rather than the proposed regulatory processes, some respondents, particularly government agencies and other organisations involved in the current arrangements, commented on regulatory aspects. These responses highlighted the following issues:

- The need for national oversight of research through a national animal-to-human transplantation committee.

- The need for the national committee to be independent from either commercial or other conflicts of interest.

- The need for regulatory control of animal-to-human transplantation clinical trials with proposals only allowed via the CTX application route and no use allowed under the Special Access Scheme or any other similar scheme for individual use.

- The independence of institutional ethics committees (human and animal), which should not feel pressured to approve a research proposal if it has been approved by the national committee.

- The need for all studies involving animals to comply with state and territory animal welfare legislation and the Code of Practice. Therefore, the primary importance of the institutional animal ethics committees in the decision to use animals in animal-to-human transplantation trials was stressed.

- The need for clear mutual relationships between the national committee, TGA, NHMRC and OGTR.

Some respondents were concerned that compliance by institutions not funded by the NHMRC may not be assured and some proposed uniform transplantation-specific legislation at the federal level (eg an Australian Medical Transplant Act, or similar) to overcome this. However, the XWP considers that the proposed arrangements (see Section 5.7), with relevant amendments to the TG Act as indicated, would be sufficient to assure compliance in Australia.

5.7 XWP proposal for national oversight of animal-to-human transplantation

The XWP recommends that the oversight of animal-to-human transplantation research in Australia should have the following characteristics:

- adequate community input;
- adequate scientific input;
- efficient and cost-effective operation without jeopardising patient or community safety;
- the capability for a rapid response to emerging knowledge;
- effective liaison with similar oversighting bodies in other countries; and
- the ability to regulate all animal-to-human transplantation research in the public and private sector.

The XWP therefore proposes that animal-to-human transplantation research proposals in Australia should be referred to a national animal-to-human transplantation committee for detailed assessment against NHMRC guidelines. Only proposals that are approved by this expert committee should be considered further by the TGA and the institutional ethics committees.

The constitution and role of the national animal-to-human transplantation committee, and the roles of institutional ethics committees and the TGA in approval of animal-to-human transplantation research proposals are described below.

Advice to NHMRC — national animal-to-human transplantation committee

Because of the ethical and scientific issues associated with animal-to-human transplantation research in Australia, and to ensure adequate community and scientific input, local ethics committees (human and animal) need advice from a national committee with specific expertise in this research.

The XWP therefore advises the NHMRC that animal-to-human transplantation research proposals in Australia should be referred to a national animal-to-human transplantation committee set up by the NHMRC for detailed assessment against NHMRC guidelines.

The XWP also advises the NHMRC that the *Therapeutic Goods Act 1989* should be amended to provide legislative backing for the role of an NHMRC national animal-to-human transplantation committee.

Role of the national animal-to-human transplantation committee

Terms of reference

Proposed terms of reference and membership of the proposed national committee are:

- advise on the data required to assess safety and efficacy in animal-to-human transplantation procedures;
- assess the safety, efficacy and any other preconditions for proceeding with animal-to-human transplantation procedures as set out in the NHMRC guidelines for such research;
- assess the acceptability of specific applications to proceed with animal-to-human transplantation trials in humans;
- authorise and monitor with the local ethics committees and TGA ,the conduct of animal-to-human transplantation clinical trials, including the imposition of any conditions deemed necessary for their safe conduct;
- provide advice to institutional ethics committees (HRECs and AECs) and the TGA;
- undertake ongoing community consultation and education on animal-to-human transplantation, including the results of animal-to-animal transplantation studies and overseas clinical trials, and monitor public attitudes;
- provide an annual report to the NHMRC, which should be a public report, on developments in the field and any emerging issues;
- maintain a register of all trials and all participants;
- monitor overseas developments in animal-to-human transplantation; and
- establish an animals issues subcommittee to (a) advise the national committee and institutional animal ethics committees on animal welfare issues; and (b) maintain a register of animal-to-animal transplantation studies of relevance to animal-to-human transplantation (see Sections 6.3 and 6.4).

Membership

A number of areas of expertise required to assess animal-to-human transplantation research proposals were identified in the Discussion Paper, including:

- transplantation (clinical practice and research);
- infectious diseases (clinical and laboratory);
- ethical, regulatory and legal issues relating to research, clinical trials and community interests;
- community concerns and public opinion;
- ethical, regulatory and legal issues relating to animal welfare and the use of animals in research; and
- veterinary considerations and animal husbandry.

The XWP envisages the national committee to be an expert committee with a broad range of expertise about relevant technical, safety, ethical, animal welfare, legal and consumer issues relating to animal-to-human transplantation research. The following membership is proposed:

- a chairperson;
- member(s) with knowledge of research in or related to xenotransplantation;
- a member in common with the NHMRC Animal Welfare Committee;
- a member with knowledge of animal ethics and welfare issues;
- a member in common with the Australian Health Ethics Committee (AHEC);
- a member with knowledge of ethics and related issues associated with animal-to-human transplantation;
- 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.

Because of the limited number of transplantation experts in Australia and the consequent potential for a conflict of interest for a specific research proposal, at least two experts may be needed so that one can withdraw from discussion of the proposals, if necessary.

Appointment and reporting arrangements

In the Response Paper, the XWP proposed that a national animal-to-human transplantation committee could be formed by expanding the existing GTRAP. An advantage of using an expanded GTRAP as the national committee is that GTRAP already handles a range of issues relating to gene therapy and has had interim responsibility for animal-to-human transplantation research. Also, GTRAP includes experts in a number of biotechnology areas (gene therapy, stem cells, xenotransplantation). The panel also has representatives from the TGA and OGTR, as well as members with legal and ethical expertise.

However, concern was raised in both rounds of consultation about the need for the national committee to be independent of the interests of researchers. This may not be the case for GTRAP under its current constitution as a subcommittee of the NHMRC Research Committee. GTRAP members are currently appointed by the Research Committee and the chairperson of GTRAP is a member of the Research Committee and reports directly to that committee.

It was suggested in the Response Paper that a solution to this issue may be to reconstitute GTRAP as a committee directly appointed by, and reporting to, the NHMRC. This already happens for the other issues of national concern (eg Special Expert Committee on Transmissible Spongiform Encephalopathies).

An alternative would be to set up a new national animal-to-human transplantation committee with specific responsibility for animal-to-human transplantation (ie in addition to GTRAP) appointed by, and reporting directly to, the NHMRC. However, this would have the disadvantage of requiring additional resources for support.

Research Committee has indicated that it supports the proposal that GTRAP undertake the oversight of animal-to-human transplantation trials, but opposes the reconstitution of GTRAP as a direct committee of the NHMRC. The XWP was therefore unable to reach a consensus on this issue and concluded that the final constitution and composition of the national committee should be decided by the NHMRC after consideration of all the documentation from this public consultation. There are two main options:

- an expanded GTRAP with current reporting arrangements (ie appointed by and reporting to Research Committee); or

- an expanded and renamed GTRAP reconstituted as a committee appointed by and reporting directly to the NHMRC.

Ongoing community consultation, education and review

The XWP recommends that animal organ transplantation trials should not be allowed in Australia at this time under the NHMRC guidelines prepared by the XWP. They also recommend that this decision should be reviewed in five years when the guidelines are next updated (as per the NHMRC publication policy) and that this review of the guidelines should be accompanied by further public consultation (see Section 4.3).

To ensure that the public continue to be well-informed about developments in animal-to-human transplantation research, the XWP recommends that the national animal-to-human transplantation committee should take steps to continue the public debate on this issue using various approaches to community education and debate, such as regular community updates, focus groups, and an annual review of developments in xenotransplantation research.

Funding arrangements

The costs of the national committee and community education activities could be covered by the NHMRC initially but, once established, sponsors should contribute to the costs (cost recovery) as occurs in other areas of regulation.

Advice to NHMRC — structure and role of the national animal-to-human transplantation committee

The XWP advises the NHMRC that the national committee should be set up and funded with a broad range of expertise relevant to animal-to-human transplantation, including representatives from the TGA and OGTR, with terms of reference to:

- apply NHMRC guidelines for the assessment of animal-to-human transplantation research proposals;
- provide advice to local ethics committees and the TGA as required;
- authorise and monitor the conduct of animal-to-human transplantation clinical trials with local ethics committees and the TGA;
- maintain a register of trial participants, including those from research conducted overseas;
- establish an animal use and oversighting subcommittee to maintain a register of animal-to-animal transplantation studies of relevance to animal-to-human transplantation and advise on other animal issues;
- monitor developments in animal-to-human transplantation research; and
- conduct ongoing public education.

The XWP advises that the existing Gene and Related Therapies Research Advisory Panel already has considerable expertise in assessing related research proposals. The final appointment and reporting arrangements for the national committee should be determined by the NHMRC, although public consultation indicated public confidence would be increased if the committee was independent of commercial and research interests.

Role of the TGA

As already indicated in Section 5.3, the XWP recommends that it should be made mandatory for all animal-to-human transplantation research proposals to be submitted as CTX applications. This is in line with previous recommendations from GTRAP that all human gene therapy research proposals should be submitted under the CTX scheme.

This means that the research proposal would have to be submitted to the TGA for assessment of the safety and efficacy of the proposed animal transplant product. Strict timelines apply to TGA assessment of CTX applications so it would be preferable for the assessment by the national committee and any preliminary discussions with the institutional ethics committees to occur before formal submission to the TGA is made.

It is also important that the therapeutic goods legislation continues to permit the exchange of information between the TGA and relevant public health bodies, both at national and state or territory government level, and between the TGA and HREC, as required.

As noted in Section 5.4, current arrangements for approval of a GM product require the TGA to notify OGTR of any decision regarding use of a GM product, for recording in the record of GM product dealings.

Role of the OGTR

Although the OGTR does not currently have a direct role in the approval of the use of GM products in clinical trials, on the advice of the TGA, it would have to record any decisions for the use of GM products in the record of GM product dealings. In addition, as noted in Section 5.4, with further developments in the research in future, it is possible that, some further assessment by the Gene Technology Regulator may be required on a case-by-case basis, depending on the exact nature of the product and the genetic modification involved (see Section 5.4).

The XWP therefore proposes that the NHMRC, TGA and OGTR should maintain very close contact during national oversight of animal-to-human transplantation research.

Advice to NHMRC — role of the Office of the Gene Technology Regulator (OGTR)

Some animal-to-human transplantation research includes genetic modification of the source animal.

The XWP therefore advises the NHMRC that the OGTR should be included in all national arrangements for the oversight of animal-to-human transplantation and that close communication channels should be established between TGA and OGTR personnel responsible for approval and recording of animal transplantation products.

Role of local ethics committees

In proposing a national animal-to-human transplantation committee, the XWP does not intend to withdraw primary responsibility for the assessment of animal-to-human transplantation proposals from AECs and HRECs at the institution where the research is proposed to take place. Initially, the ethics committees at the institution will consider whether the proposed research is suitable for that institution (eg the research may require specialist facilities that may or may not be available). If the research is feasible, under the proposed arrangements, AECs/HRECs will be required to obtain scientific and ethical advice from the national animal-to-human transplantation committee.

If the advice is that the trial can proceed, the local ethics committees would be free to process the application in the usual way for a CTX application (see Section 5.3) and make their own decision about whether to accept or reject the proposal for their institution.

If the national committee advises that the trial should not proceed, the local ethics committees will not be able to consider the proposal further.

Role of research sponsors

Under the proposed arrangements, research sponsors would need to submit their research proposal to the national animal-to-human transplantation committee and the AEC/HREC at the proposed institution for the research.

If the national committee advises the local ethics committees that the trial can proceed, researchers will also need to submit the proposal to the TGA as a CTX application.

Thus, a sponsor will not be able to commence a CTX trial until:

- written advice has been received from the national committee that the trial can proceed;
- written advice has been received from the TGA regarding the application; and
- approval for the conduct of the trial has been obtained from the AEC and HREC at the institution at which the trial will be conducted.

5.8 Long-term monitoring of participants

Until more is known about infection risks, there will need to be extreme caution in following up all people who receive animal-to-human transplants. Therefore, every participant in an ACT or AET trial will need to be recorded on a register. However, if trial is minimal risk, there would be less need for additional mandatory monitoring. If the trial has some risks (even if felt to be low), there would need to be long-term monitoring.

Many people who receive an animal-to-human transplantation would be under constant medical care but this would not always be the case, particularly for recipients who do not require immunosuppression. Provisions for long-term follow up and monitoring are included in the guidelines. The XWP proposes that the national animal-to-human transplantation committee should administer the central register of trial participants and also monitor the progress of research through annual progress reports from research sites.

Irrespective of any animal-to-human transplantation clinical trials approved and/or conducted in Australia, people who receive an animal-to-human transplant overseas and then return to Australia will also need to be included in a register. These may include people in approved Australian trials who receive their treatment overseas, people who go overseas to take part in trials that do not involve Australian researchers but are nevertheless in countries with similar oversight and registration procedures to Australia, and people who take part in trials in countries with less rigorous oversight of trials.

5.9 Proposed NHMRC guidelines

To assist the national animal-to-human transplantation committee, local ethics committees and the TGA in reaching decisions about the acceptability of animal-to-human transplantation research proposals and to monitor the progress of approved research, the XWP has drafted a set of guidelines that take account of the key ethical and technical issues identified as being important for animal-to-human transplantation research (see Section 3). Draft guidelines were released with both the first and second

round consultation documents and respondents to the public consultation commented on several issues relating to them.

Taking these comments into account, the XWP has updated the guidelines and the final proposed version is included as an attachment to this document (see *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document).

6 National oversight of animal-to-animal transplantation research

6.1 Introduction

The Animal Issues Subcommittee (AISC) met in early May 2004 and reviewed the submissions received in response to the second round of public consultation

The report of AISC to the Xenotransplantation Working Party (XWP) is included in full in Appendix C.

Whether or not animal-to-human transplantation clinical trials are approved in Australia, it is likely that researchers currently involved in animal-to-animal studies will continue their research to further elucidate the possible efficacy of animal-to-human transplantation, so that any future review of the proposed NHMRC guidelines is based on sound evidence. In addition, animal-to-animal xenotransplantation research is carried out for many reasons, not all of which relate to animal-to-human transplantation (eg research may be to test the rejection processes to improve allotransplants, research immune function in general, or for veterinary research). Finally, stem cell research also requires animal-to-animal and also human-to-animal research.

In each case, the decision on whether or not a particular research study involving animals can proceed will still be in the hands of the institutional animal ethics committee (AEC).

6.2 National oversight of animal research related to animal-to-human transplantation

A common concern raised in the submissions was in relation to animal-to-animal transplantation studies that are carried out to obtain evidence for animal-to-human transplantation research (particularly when that research involves the use of primates). Currently, there is no system by which individual AECs can obtain an overview of such research or find out what animals have already been used elsewhere, possibly in failed experiments that are not worth repeating. With increasing use of biotechnology, AECs also may not always have sufficient expertise or experience to handle proposals.

In response to these concerns, AISC has recommended that in order to monitor the use of animals in this type of research, an NHMRC register of animal-to-animal xenotransplantation research should be established as indicated in the Response Paper. The register should also have an associated technical review group to help AECs resolve technical issues in research proposals. A proposal for how this register should be set up and run is included in the report of AISC (Appendix C) and the concept was supported by the XWP. The proposal is summarised below.

6.3 Register of preclinical (animal-to-animal) research of relevance to animal-to-human transplantation

Purpose of register

The purpose of a register of preclinical animal-to-animal transplantation studies of relevance to animal-to-human transplantation would be to:

- record data relevant to animal welfare considerations in relation to preclinical animal-to-animal transplantation studies of relevance to animal-to-human transplantation (working in close collaboration with the relevant state/territory agency and the NHMRC Animal Welfare Committee);
- support and advise AECs in their assessment of animal-to-animal and animal-to-human transplantation research proposals;
- provide information for AECs about previous preclinical studies and those in progress in order to reduce duplication and thus the number of animals used in such research;
- advise the national animal-to-human transplantation committee on animal matters; and
- provide a database of information to inform future revisions of the NHMRC animal-to-human transplantation guidelines (in terms of costs to animals versus potential human benefits and so on).

To achieve these functions, the register would need to be supported by a technical committee (see Section 6.4).

What studies would be included?

The issue of which studies should be included in the register poses some difficulty. If it is broadly based on the definition of xenotransplantation (ie that it involves transplantation of cells, organs, tissues between different species), it will capture a great deal of basic biological research where cells are transferred from one species to another (particularly to mice). However, if the definition is narrowly focused around the purpose of the research (ie that it is related to the development of an animal-to-human transplantation therapy), it would be easy for researchers to redefine the research in other terms and not submit it to the register.

AISC has proposed a two-stage process to help AECs define what research should be submitted to the register.

- Stage 1: 'Does the research involve transplantation of cells, organs, tissues between different species?' If the answer is 'yes', go to stage 2.
- Stage 2: 'Is the research directly related to the development of animal-to-human transplantation trials?' If the answer to this question is clearly 'yes', then it must be submitted to the register, irrespective of the species used or specifics of research (this would also include human-to-animal work).

If there is any question over the relevance of the proposal (for example, if it is likely that the ultimate objective of the research is to lead to clinical trials, even though this aim is not explicitly stated in the proposal) then the AEC should seek the advice of the registrar (see below).

Further subcategories (if required) could be based on animal involvement (eg mice or primates) or other risk categories to be determined (ie similar to the current system used by the Office of the Gene Technology Regulator (OGTR) with 'low-risk dealings', 'licensed dealings' etc).

There may be an incentive for researchers to have their studies registered in order to have their research included in any future assessment of the efficacy of animal-to-human transplantation (eg when the guidelines are reviewed).

Information to be submitted/published on register

The simplest and most effective arrangement would be for AECs to have responsibility for forwarding on to the register those proposals that they consider meet the criteria for inclusion. This would require an AEC to forward the register copies of the paperwork they receive from researchers seeking review, together with copies of annual and final reports on approved research.

Confidentiality issues need to be taken into account and published details would be similar to those currently used by the OGTR (titles of projects).

Registrar

The register should be more than just be a simple database; it would need to be overseen by a registrar who is knowledgeable about relevant issues and able to give advice to researchers and AECs, if necessary, about what type of research must be notified to the register etc.

The registrar could also summarise proposals for a technical review group, as outlined below.

Funding of register

Funding would need to be made available for the establishment and ongoing resource needs of the Register (and associated technical review group).

Role of AECs

Institutional AECs would continue their role of deciding whether or not to allow a proposal to go ahead. Advice from a technical review group (see Section 6.4) would assist them in this decision, but would not be binding.

As discussed above, AECs would also have responsibility for determining whether or not a research proposal needs to be forwarded to the register. AECs would then notify the registrar whether or not the proposal is approved. For approved proposals, AECs would also be required to forward to the register copies of annual reports submitted to the AEC

by the researcher (to show that research is still going on, if appropriate) and final reports with the overall results of research (including published papers, etc).

If no report is received from the AEC, the registrar would need to follow up on this.

Enforcement of scheme

Attention needs to be given to how such a system of national oversight of preclinical research involving xenotransplantation should be enforced. One possible means of enforcement would be to make it a requirement of the Code of Practice that AECs reviewing xenotransplantation research forward relevant proposal to the registrar and indicate to the researcher that they have done so. The NHMRC Animal Welfare Committee (AWC) could include this requirement in correspondence with institutions and their AECs.

Review of register

The register should be re-evaluated in 3–5 years.

6.4 Technical review group (animal use and oversighting subcommittee)

As indicated in Sections 6.2 and 6.3, above, the register would need to be supported by a technical review group (TRG).

While some proposals may be 'noted' on the register without further review; more involved proposals would be forwarded to the TRG, which would assess the proposal against a series of criteria (see Appendix C). The TRG would then prepare advice for the AEC and also report its findings to the registrar.

AISC recommended that the TRG should be an independent expert panel with scientific, research and statistical expertise. It would not need ethics expertise as ethical review will be by the AEC.

After consideration of AISC's report, the XWP concluded that an appropriate structure for the TRG may be for an animal issues subcommittee under the new national animal-to-human transplantation committee to assume this role. This subcommittee would then have the dual role of:

- acting as the TRG for the register of animal-to-animal transplantation studies of relevance to animal-to-human transplantation; and
- advising the national animal-to-human transplantation committee on animal issues relating to both animal-to-animal transplantation and animal-to-human transplantation research.

6.5 Conclusion

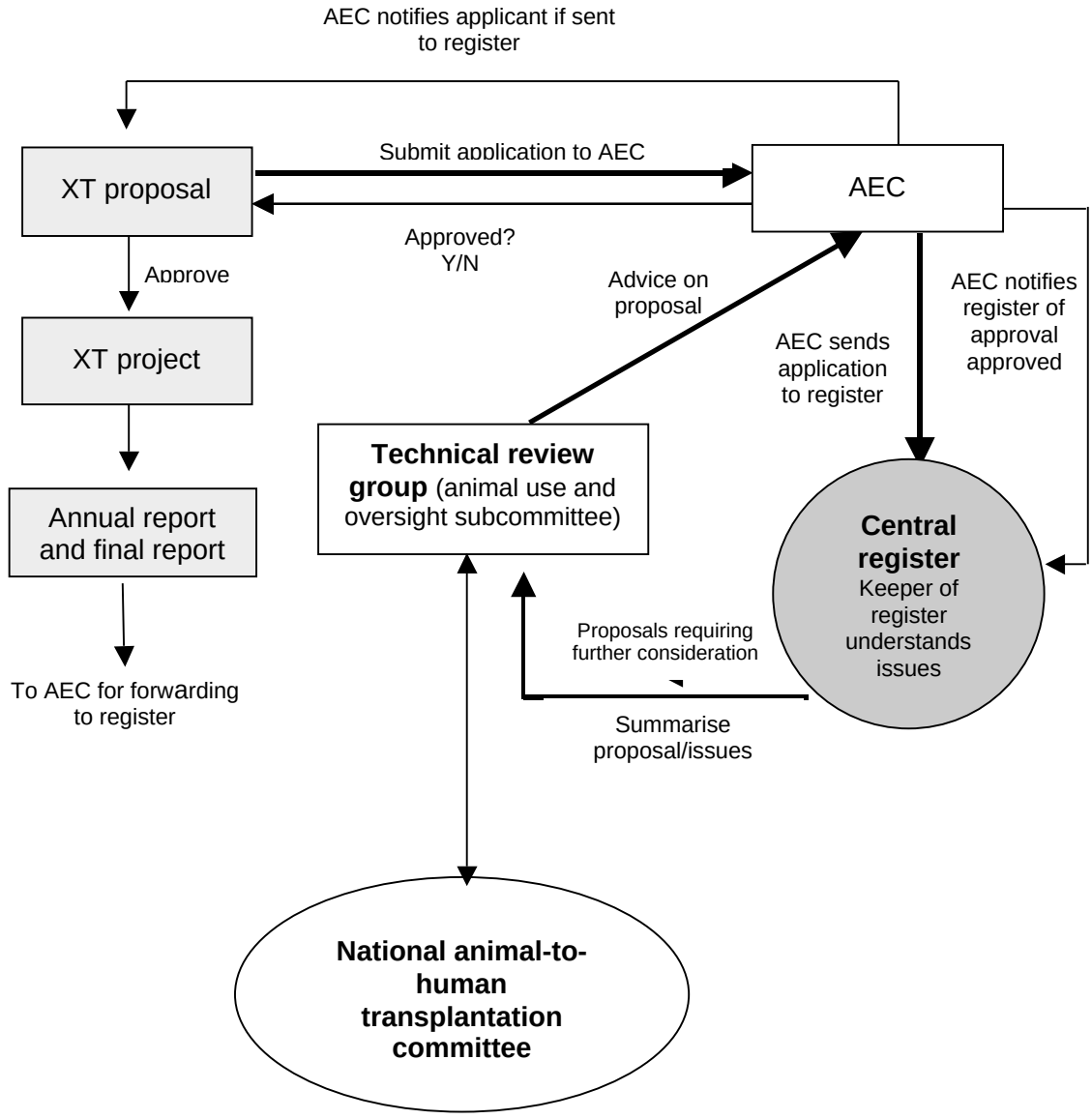
The numerous submissions on the use of animals in xenotransplantation research and the report of AISC indicated that a mechanism for oversight of animal use in both preclinical animal-to-animal transplantation studies, and in any animal-to-human transplantation trials that may be permitted in Australia in the future, needs further consideration. However, it will be important that the mechanism adopted to achieve this does not interfere with the existing regulation and ethical oversight of the use of animals in all other areas of research.

The XWP concluded that the necessary oversight might be best achieved by an animal issues and oversighting subcommittee linked to the national animal-to-human transplantation committee. This subcommittee could also take on the registry roles outlined in Section 6.2 and Figure 6.1. Guideline 2(b) in the proposed NHMRC *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* requires that all research proposals for animal-to-animal studies that are directly related to the development of animal-to-human trials should be forwarded to the proposed register (see proposed guidelines submitted with this document).

Advice to NHMRC — oversight of animal issues

The Animal Issues Subcommittee (AISC) of the XWP has proposed that a central register of animal-to-animal transplantation studies of relevance to animal-to-human transplantation, together with an associated technical review group should be established to record data relevant to animal welfare considerations of xenotransplantation research and to support animal ethics committees in their assessment of research proposals.

The XWP advises the NHMRC that the AISC-proposed central register of animal-to-animal transplantation studies of relevance to animal-to-human transplantation, should be established. Furthermore, the register and its associated technical review capability could be achieved by setting up an animal use and oversighting subcommittee of the proposed national animal-to-human transplantation committee with the task of managing the proposed register (see also Guideline 2b in *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* accompanying this advice document).



XT = animal-to-animal transplantation research involving xenotransplantation; AEC = animal ethics committee

Figure 6.1 Summary of proposed register and technical review group arrangements

Appendix A Committee membership

Xenotransplantation Working Party

2001 – 2002 (first public consultation)

Membership category	Member	Expertise/affiliation
2 members from the Australian Health Ethics Committee*	Dr Kerry Breen (Chair) Associate Professor Bernadette Tobin	Clinical medicine and medical ethics Philosophy and transplantation ethics
2 members from Research Committee* or the Gene and Related Therapies Research Advisory Panel (GTRAP)	Dr Dominic Dwyer (GTRAP) Professor Philip O'Connell (GTRAP)	Clinical virology and infectious disease Clinical and experimental transplantation
2 members representing community views	Ms Michele Kosky Mr Twanny Farrugia	NHMRC member with expertise in consumer issues Counsellor (general, loss and grief)
1 member from the Animal Welfare Committee (a working committee of Research Committee*)	Ms Elizabeth Grant AM	Pharmacist Research Committee Member Chair, Animal Welfare Committee

*The Australian Health Ethics Committee and Research Committee are principal committees of the National Health and Medical Research Council; GTRAP is a working committee of Research Committee

2003 – 2004 (second public consultation)

Membership category	**Member**	**Expertise/affiliation**
Chair	Dr Jack Sparrow	Medical administration
2 members from the Australian Health Ethics Committee*	Dr Kerry Breen Associate Professor Bernadette Tobin (former AHEC member)	Clinical medicine and medical ethics Philosophy and transplantation ethics
2 members from Research Committee* or the Gene and Related Therapies Research Advisory Panel (GTRAP)	Dr Dominic Dwyer (former GTRAP member) Professor Philip O'Connell (GTRAP)	Clinical virology and infectious disease Clinical and experimental transplantation
1 Therapeutic Goods Administration nominee	Dr Leonie Hunt	Assistant Secretary, Drug Safety and Evaluation Branch, Therapeutic Goods Administration

1 clinician with background in transplantation (excluding xenotransplantation)	Dr Simone Strasser	Clinical transplantation
1 member with expertise in clinical and experimental transplantation	Professor Mauro Sandrin	Experimental transplantation (including xenotransplantation) and clinical transplantation
1 member with infectious diseases/public health background	Professor Aileen Plant	Medical epidemiology and international health
2 members representing community views	Ms Michele Kosky Mr Twanny Farrugia	NHMRC member with expertise in consumer issues Counsellor (general, loss and grief)
1 member from the Animal Welfare Committee (a working committee of Research Committee*)	Ms Elizabeth Grant AM	Pharmacist Research Committee Member Chair, Animal Welfare Committee
2 members with animal welfare background	Dr Bidda Jones Ms Glenys Oogjes	Scientific Officer, RSPCA Australia with expertise in animal welfare issues Executive Director, Animals Australia
Observer	Dr Bruce Scoggins	Health Research Council of New Zealand

*The Australian Health Ethics Committee and Research Committee are principal committees of the National Health and Medical Research Council; GTRAP is a working committee of Research Committee

Secretariat

Ms Milly Betteridge	Project Officer from February 2002 to March 2003
Dr David Abbott	Project Officer from April to December 2003
Ms Tamara Shanley	Project Officer from January 2004

Consultant (technical writer)

Dr Janet Salisbury	Biotext, Canberra

Animals Issues Subcommittee

Membership category	Member	Expertise/affiliation
Chair	Ms Elizabeth Grant AM	Pharmacist, Research Committee Member Chair, Animal Welfare Committee
1 member from the Animal Welfare Committee (a working committee of Research Committee*)	Associate Professor Graham Jenkin	Stem cell research
2 members with a demonstrable commitment to, and experience in, furthering the welfare of animals and who are not involved in the care and use of animals for scientific purposes	Dr Bidda Jones Ms Helen Rosser	Scientific Officer, RSPCA Australia with expertise in animal welfare issues Assistant to Executive Director, Animals Australia Co-founder and National Coordinator, Humane Charities Australia Inc.
1 person with experience in the regulation of the use of animals in research	Dr Robert Dixon	Faculty of Veterinary Science, University of Sydney, Subdean Animal Welfare, member of several research institutional animal ethics committees
1 independent person with recent veterinary and animal husbandry experience	Dr Lyndy Scott	The Australian Veterinary Association

*Research Committee is a principal committee of the National Health and Medical Research Council

Appendix B Numbers and types of respondents to public consultation

Written submissions

A total of 97 written submissions were received in the first round of consultation on animal-to-human transplantation research, which was conducted by the NHMRC between August and October 2002. The second round of consultation (December 2003 – March 2004) attracted 343 written submissions. One-third (33) of those who made a submission in the first round also made a submission in the second round.

A breakdown of submissions received in both rounds of consultation is provided below.

Number of submissions received by submitter type

Organisations

The first round of public consultation saw 45 written submissions from organisations compared to 51 in the second round. The organisation type most represented in the first round was government agencies (13). In contrast, the organisation type most represented in the second round was animal welfare organisations (19). Submissions from organisations represented 46% of all submissions received in the first round and 15% of all submissions received in the second round.

Type of organisation	Number of submissions FIRST ROUND	Number of submissions SECOND ROUND
Government agencies	13	8
Hospitals	1	2
Medical associations	5	5
Universities	2	3
Animal welfare organisations	12	19
Religious organisations and individuals	4	4
Consumer organisations	1	2
Biotechnology companies	1	0
Other organisations	6	8
SUBTOTAL	45	51

Individuals

The first round of public consultation saw 52 written submissions from individuals compared to 292 in the second round. The majority of submissions from individuals in both the first and second rounds came from private individuals. In each case, the majority of these individuals did not identify themselves a belonging to a relevant profession (eg medical professional, ethicist). Submissions from individuals represented 54% of all submissions received in the first round and 85% of all submissions received in the second round.

Type of individual	Number of submissions FIRST ROUND	Number of submissions SECOND ROUND
Transplant researcher	1	0
Medical professionals	4	7
Ethicists	3	2
Other	44	283
SUBTOTAL	52	292

TOTAL SUBMISSIONS

	Number of submissions FIRST ROUND	Number of submissions SECOND ROUND
TOTAL	97	343

Number of submissions by state/territory/international

In the first round of consultation, submissions came from respondents in all Australian states and territories except for Tasmania. Submissions also came from international respondents (9). The state from which most submissions came in the first round was Victoria (22), followed by New South Wales (18) and Western Australia (16). This is consistent with the location of the public meetings held in the first round, these being in Melbourne, Sydney and Perth. The origin of six email submissions in the first round could not be determined as these submissions gave no contact details for the respondent.

In the second round of consultation, submissions came from people in all Australian states and territories and again from international respondents (4). The state from which most submissions came in the second round was Western Australia (118), followed by New South Wales (61) and Victoria (56). The origin of 25 submissions could not be determined as these were email or letter submissions that gave no contact details for the respondent.

Region	Number of submissions FIRST ROUND	Number of submissions SECOND ROUND
ACT	10	16
NSW	18	61
NT	1	2
QLD	10	36
SA	5	21
TAS	0	4
VIC	22	56
WA	16	118
International	9	4
Unknown	6	25
TOTAL	97	343

Public meetings

First round of consultation

During the first round of public consultation, public meetings were held in Sydney, Melbourne and Perth, with targeted meetings also being held in Adelaide and Perth. These meetings attracted a total of 116 participants, as follows:

City, state/territory	Date	Number of attendees
Perth, WA	12 August 2002	21 (targeted meeting) 30 (public meeting)
Melbourne, VIC	19 August 2002	20
Sydney, NSW	21 August 2002	15
Adelaide, SA	12 September 2002	30 (targeted meeting)
TOTAL		116

Second round of consultation

As part of the second round of public consultation, public meetings were held in all Australian State and Territory capital cities, and attracted a total of 377 participants (see below). These meetings were moderated by an independent facilitator in order to further promote open discussion. No targeted meetings were conducted in this second round.

City, State/Territory	Date	Number of attendees
Brisbane, QLD	9 February 2004	80
Sydney, NSW	10 February 2004	85
Canberra, ACT	11 February 2004	40
Perth, WA	16 February 2004	50
Adelaide, SA	17 February 2004	45
Darwin, NT	18 February 2004	10
Melbourne, VIC	23 February 2004	50
Hobart, TAS	24 February 2004	17
TOTAL		377

Appendix C Report of Animal Issues Subcommittee, June 2004

Report to the Xenotransplantation Working Party on animal ethics and welfare

Issues raised in second public consultation

The discussions at the February 2004 public consultation meetings and the approximately 340 submissions received in the second round of public consultation have confirmed the concerns expressed during the first round of consultation and have raised a number of new issues.

More than 80% of respondents to the second round of consultation were either explicitly opposed to, were inferred to be opposed to, or expressed serious concern about animal-to-human transplantation (xenotransplantation). Some respondents were unclear, undecided or had no opinion, while others were either explicitly supportive, or were inferred to be supportive of animal-to-human transplantation.

All submissions were considered by members of the Animal Issues Subcommittee (AISC) in the light of the following questions:

- Are there animal issues already examined by the Xenotransplantation Working Party (XWP) that need to be re-visited?
- Are any new animal issues raised that require XWP consideration?
- Are there animal issues that require the XWP to seek external advice or additional information?
- Are there animal issues that require the XWP to re-think/re-phrase the draft guidelines or regulatory framework?

As a result of these considerations, the following were identified by AISC as the main concerns relating to animal ethics and welfare stemming from the second consultation process. Unless otherwise stated below, the subcommittee supports these concerns. Many of these are raised in the document *Animal-to-Human Transplantation Research: How Should Australia Proceed?* [Response Paper] but now have added emphasis or indicate a need for more in-depth consideration.

Animal welfare

'Animal welfare' has not been adequately defined in the XWP documents so far. AISC suggests that the working party refer to the definitions of animal welfare and animal wellbeing in the *Australian Code of Practice for the Care and Use of Animals for Scientific Purpose,* 7th edition, 2004 (Code of Practice) in further documents. These definitions are as follows:

- Animal welfare — an animal's quality of life based on an assessment of an animal's physical and psychological state as an indication of how the animal is coping with the ongoing situation as well as a judgment about how the animal feels.

- Animal wellbeing — an animal's present state with regard to its relationship with all aspects of its environment, both internal and external. It implies a positive mental state, successful biological function, positive experiences and freedom from adverse conditions.

Suffering of animals will be a consequence of animal-to-animal or animal-to-human transplantation research and the XWP should be more explicit about this. The three 'Rs' from the Code of Practice (replacement, reduction and refinement) were not applied to the assessment of issues or development of the draft guidelines on clinical animal-to-human transplantation research (see below).

Further explanation and assurance is needed that death must not be used as an endpoint of animal studies. ('Death as an endpoint' is when the death of an animal is the deliberate measure used for evaluating biological or chemical processes, responses or effects, ie where the investigator does not intervene to kill the animal humanely before death occurs in the course of a scientific activity.)

Alternatives to animal use

To facilitate the three Rs (see above), more emphasis should be placed on:

- human stem cell alternatives to animal-to-human transplantation that do not require the use of animals (although current stem cell technologies do require animal-to-animal and also human-to-animal research) and other alternatives (such as artificial organs);

- increasing the rate of human organ donation in Australia (eg by including an 'opt-out' policy for human organ donation); and

- health education programs.

In terms of stem cells as an alternative, an AISC member who is a stem cell researcher stated that stem cells are not likely to provide an alternative to whole organ transplants in the foreseeable future. It is noted that animal-to-human transplantation of whole organs is also considered highly unlikely in the foreseeable future. Stem cells may be used in the shorter term to solve problems where cell therapies can be used (eg haematopoietic cell diseases, diabetes, Parkinson's disease) but would probably require testing using animal-to-animal xenotransplantation techniques before their clinical use.

Ethics of animal use

To date, discussion in XWP documents of ethical issues relating to the use of animals has not been rigorous enough. The documents are over-simplistic and the ethics of animal welfare and rights are dismissed (there were many comments about this in submissions). The use of animals for animal-to-human transplantation is fundamentally different to their use for food. Informed debate can only occur if explicit details of the direct effect on animals in this research are detailed.

Animal use needs to be considered in terms of potential benefits to humans. Overall, the 'costs' to animals in animal-to-human transplantation research (in terms of animal suffering) are too high to justify the limited potential benefits to humans.

Very few respondents made a distinction between animal external therapies (AETs), animal cell therapies (ACTs) and animal organ transplants (AOTs or whole organ transplants), but those who did were most concerned about whole organ transplants. The lack of comment on AETs and ACTs suggests that, despite attempts by the XWP to explain in the documents that there were three distinct types of therapies involving animal-to-human transplantation, the differences between them were not fully understood. Thus, some respondents appear to have directed their concerns at whole organ transplants. Alternatively, other respondents may have felt that all animal-to-human transplantation procedures involve disease risk and animal suffering and so there was no need to differentiate between them.

A few respondents felt there could be some justification for the use of animals if they were going to enter the food chain anyway. This is clearly not the case and it should be stated that animals will be purpose bred for animal-to-human transplantation and will not, under any circumstances, go into the food chain.

Cross-species infections

The majority of submissions opposed to animal-to-human transplantation research raised concerns about the possibility of infections spreading from animals to humans and to a lesser extent within species. Respondents were greatly concerned that the whole community could be put at risk for the sake of a few individuals.

Concerns also included risks of genetically modified, immune compromised research or breeding animals escaping, environmental implications (including wildlife and feral pigs) and risks of infections spreading from recipient humans back to pigs (animal industries expressed this latter concern).

XWP documents so far have focused on porcine endogenous retrovirus (PERV) but respondents were concerned that there may be other unknown infectious agents.

Genetically modified pigs

Genetic modification (GM) of animals has not been explained well enough; there are further issues of integrity of species that need to be explored.

Issues requiring explanation include the long-term effect of GM on animals or of using live animal products in humans (particularly products that include human genes).

Animal ethics committees

Many submissions raised concerns about the effectiveness of the current animal ethics committee (AEC) system. Others stated that, generally, AECs are very effective but do not always have enough information to make decisions (eg about what other research has already been done) because there is no national oversight of animal research. A register of animal-to-animal studies was widely supported as a way of overcoming this problem (see

discussion of register below), although this was not supported by the NHMRC Research Committee.

The Response Paper (Figure 11.1) indicated that if a research protocol is not accepted by one AEC or human research ethics committee (HREC), sponsors could submit it to a different institution. This is not current practice with AECs. Several respondents stated that such 'shopping' for ethics committee approval must not be permitted.

Definitions

Very few respondents raised concerns about the definition of animal-to-human transplantation (xenotransplantation) included in the Response Paper. Those who did suggested that the transplantation of *nonliving* animal products into humans raised the same ethical and animal welfare concerns as procedures under the current definition and that these products should therefore be considered in this debate. AISC did not express an opinion on this concern.

Suggestions for further investigation

Any cost–benefit analysis for animal use would be assisted by further information on the extent to which animal research improves human health. Such an analysis may include alternative means of measurement, such as assessment of: the quality of life for both source animals and human recipients; monetary costs of procedures versus benefits to human health and productivity; and projected diversion of human and financial resources within the health budget.

An independent assessment of whether human physiology will ever be able to successfully assimilate animal organs would be helpful.

Overall conclusion from issues raised

There was strong agreement within AISC that the opinions expressed in the second round of public consultation must be reflected in the XWP's recommendations to the NHMRC.

The vast majority of respondents did not believe that Australia should proceed with animal-to-human transplantation research at this time. Most respondents did not, however, distinguish between whole organ transplants and other therapies. The underlying argument in these submissions was that animal-to-human transplantation research does not pass the basic test of ethical approval: 'Do the potential benefits outweigh the costs involved?' It is clear that the majority of respondents do not believe that the benefits of animal-to-human transplantation research are significantly clear, achievable or sufficient to justify the cost to animal welfare or potential risk to human and animal health.

In these circumstances, AISC concluded that it could not support Australia proceeding with any animal-to-human transplantation research at this time. AISC therefore recommends that the XWP amend the proposed guidelines to include a moratorium on all animal-to-human transplantation research. The XWP should note that there was no dissent expressed by AISC members to this position, which is not based solely on animal welfare issues (since these cannot be separated out) but on consideration of the overall balance of all issues raised by respondents.

This leads to the question of the continuation of animal-to-animal research.

If animal-to-human trials are not allowed to proceed at this time, it might be argued that animal-to-animal studies which are relevant to animal-to-human transplantation research should also be scaled down to reduce suffering to animals.

When the guidelines are reviewed at a future point in time, other alternatives to animal-to-human transplantation may have advanced sufficiently to reduce or even eliminate the need for animal-to-human transplantation.

On the other hand, it is likely that researchers currently involved in animal-to-animal studies will continue their research to further elucidate the possible efficacy of animal-to-human transplantation, so that any future review of the guidelines is based on sound evidence. In addition, animal-to-animal transplantation research is carried out for many reasons, not all of which relate to animal-to-human transplantation (eg research may be to test the rejection processes to improve allotransplants, research immune function in general, or for veterinary research). Finally, stem cell research also requires animal-to-animal and also human-to-animal research. For these reasons, it is not feasible to recommend a moratorium on specific animal-to-animal studies.

In each case, the decision on whether or not a particular research study involving animals can proceed will still be in the hands of the institutional AEC.

AISC agreed that in order to monitor the use of animals in this type of research, an NHMRC register of animal-to-animal research should be established as indicated in the Response Paper. A proposal for how this register should be set up and run should form part of the final report from the XWP to the NHMRC. A draft proposal from the AISC is provided below.

Register of preclinical research involving xenotransplantation

Purpose of register

The purpose of a register of preclinical research involving xenotransplantation would be to support AECs in their implementation of the Code of Practice, to record data relevant to animal welfare considerations in relation to this research, and to provide information for AECs about previous studies and those in progress in order to reduce duplication and thus the number of animals used in such research. It will also provide a database of information to inform future revisions of the guidelines (in terms of costs to animals versus potential human benefits and so on).

What studies would be included?

The first criterion that would be used by AECs to decide whether or not a study should be included on the register is to base it on the definition of xenotransplantation adopted by the XWP (ie that it involves transplantation of cells, organs or tissues between different species).

Under this criterion, researchers would need to ask, 'Does the research involve transplantation of cells, organs or tissues between different species'?

If the answer is 'yes', then a second question applies: 'Is the research directly related to the development of animal-to-human transplantation trials?'. If the answer to this question is clearly 'yes', then it must be submitted to the register, irrespective of the species used or specifics of research (this would also include human-to-animal work). If there is any question over the relevance of the proposal (for example, if it is likely that the ultimate objective of the research is to lead to clinical trials, even though this aim is not explicitly stated in the proposal) then the AEC should seek the advice of the registrar (see below).

Further subcategories (if required) could be based on animal involvement (eg mice or primates) or other risk categories to be determined (ie similar to the current system used by the Office of the Gene Technology Regulator (OGTR) with 'low-risk dealings', 'licensed dealings' etc).

AISC noted that there may be an incentive for researchers to have their studies registered in order to have their research included in any future assessment of the efficacy of animal-to-human transplantation (eg when guidelines are reviewed).

Information to be submitted/published on register

The simplest and most effective arrangement would be for AECs to have responsibility for forwarding on to the register those proposals that they consider meet the criteria for inclusion. This would require an AEC to forward the register copies of the paperwork they receive from researchers seeking review, together with copies of annual and final reports on approved research.

Confidentiality issues need to be taken into account and published details would be similar to those currently used by the OGTR (titles of projects).

Registrar

The register should not just be a simple database; it would need to be overseen by a registrar who is knowledgeable about relevant issues and able to give advice to researchers and AECs, if necessary, about what type of research must be notified to the register etc.

The registrar could also summarise proposals for a technical review group, as outlined below.

Technical review group

Function

Some proposals may be 'noted' on the register without further review; more involved proposals would be forwarded to a technical review group (TRG) which would assess the proposal against a series of criteria, for example:

1. Is this proposal a repeat of previous experiments; if so is a repeat needed?

2. Is this proposal scientifically valid (however, the TRG must not do the job of the AEC)?

3. Has this proposal been peer-reviewed?

To support question 1, the registrar could conduct a literature review to identify similar studies that have already been done, and check existing entries in the register. This would occur before the proposal is forwarded to the TRG.

The TRG would prepare advice for the AEC and also report its findings to the registrar.

Membership and structure

The TRG should be an independent expert panel with scientific, research and statistical expertise. It would not need ethics expertise as ethical review will be by the AEC.

The NHMRC Gene and Related Therapies Research Advisory Panel (GTRAP) would not be able to take on this role, but an appropriate structure may be for the TRG to be a subcommittee under GTRAP or the NHMRC Animal Welfare Committee (AWC).

Funding of register

Funding would need to be made available for the establishment and ongoing resource needs of the Register and TRG.

Role of AECs

Institutional AECs would continue their role of deciding whether or not to allow a proposal to go ahead. Advice from the TRG would assist them in making this decision, but would not be binding.

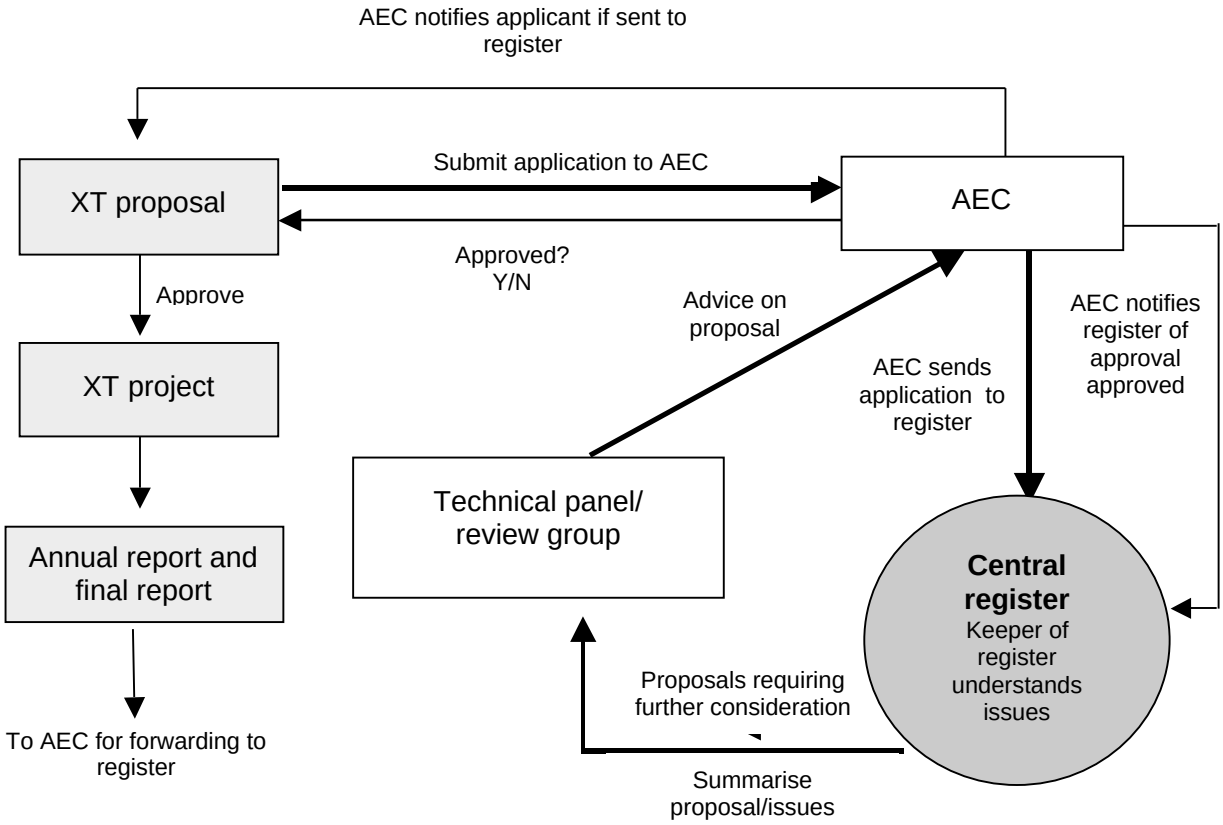
As discussed above, AECs would also have responsibility for determining whether or not a research proposal needs to be forwarded to the register. AECs would then notify the registrar whether or not the proposal is approved. For approved proposals, AECs would also be required to forward to the register copies of annual reports submitted to the AEC by the researcher (to show that research is still going on, if appropriate) and final reports with the overall results of research (including published papers, etc).

If no report is received from the AEC, the registrar would need to follow up on this.

Enforcement of scheme

Attention needs to be given to how such a system of national oversight of preclinical research involving xenotransplantation should be enforced. One possible means of enforcement would be to make it a requirement of the Code of Practice that AECs reviewing xenotransplantation research forward relevant proposals to the registrar and indicate to the researcher that they have done so. The AWC could include this requirement in correspondence with institutions and their AECs.

Summary of proposed national register of preclinical xenotransplantation research



XT = animal-to-animal transplantation research involving xenotransplantation; AEC = animal ethics committee

Abbreviations

ACT	animal cell therapy
AEC	animal ethics committee
AET	animal external therapy
AHEC	Australian Health Ethics Committee (NHMRC)
AISC	Animal Issues Subcommittee
AOT	animal organ transplant
AWC	Animal Welfare Committee (NHMRC)
BSE	bovine spongiform encephalopathy
Code of Practice	*Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, 7th edition*, 2004 (see 'References')
Community Guide	*Animal-to-Human Transplantation: A Guide for the Community* (NHMRC 2003b)
CTN	Clinical Trial Notification (scheme of the TGA)
CTX	Clinical Trial Exemption (scheme of the TGA)
Discussion Paper	*Draft Guidelines and Discussion Paper on Xenotransplantation* (NHMRC 2002)
GM	genetically modified
GMO	genetically modified organism
GTRAP	Gene and Related Therapies Research Advisory Panel (NHMRC)
HIV/AIDS	human immunodeficiency virus /acquired immunodeficiency syndrome
HREC	human research ethics committee
National Statement	*National Statement on Ethical Conduct in Research Involving Humans.* (NHMRC 1999, see 'References')
NHMRC	National Health and Medical Research Council
OGTR	Office of the Gene Technology Regulator
PERV	porcine endog!nous retrovirus
Response Paper	*Animal-to-Human Transplantation: How Should Australia Proceed?* (NHMRC 2003a)
SARS	severe acute respiratory syndrome
TGA	Therapeutic Goods Administration
TG Act	*Therapeutic Goods Act 1989*
TRG	technical review group
XWP	Xenotransplantation Working Party (NHMRC)

References

National Health and Medical Research Council (NHMRC) (1999). *National Statement on Ethical Conduct in Research Involving Humans.*

NHMRC (2002). *Draft Guidelines and Discussion Paper on Xenotransplantation,* Public consultation 2002, Xenotransplantation Working Party, NHMRC, Canberra.

NHMRC (2003a). *Animal-to-Human Transplantation: How Should Australia Proceed?* Response to the 2002 public consultation on *Draft Guidelines and Discussion Paper on Xenotransplantation,* Public consultation on xenotransplantation 2003–04, Xenotransplantation Working Party, NHMRC, Canberra .

NHMRC (2003b). *Animal-to-Human Transplantation: A Guide for the Community,* Public consultation on xenotransplantation 2003–04, Xenotransplantation Working Party, NHMRC, Canberra.

NHMRC (2004). *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes,* 7th edition, NHMRC, Canberra.

Therapeutic Goods Administration (2003). *Discussion Paper: The Regulation of Human Tissues and Emerging Biological Therapies*, TGA, Canberra. http://www.tga.gov.au/docs/html/humantiss.htm (accessed 31 August 2004)

US FDA (2001). *Xenotransplantation Action Plan: FDA Approach to the Regulation of Xenotransplantation*. United States Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. http://www.fda.gov/cber/xap/xap.htm#back (accessed 31 August 2004)

US FDA (2003). *Guidance for Industry: Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans. Final Guidance,* United States Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. http://www.fda.gov/cber/gdlns/clinxeno.htm (accessed 31 August 2004)

Australian Government
National Health and Medical Research Council

Guidelines for clinical animal-to-human transplantation (xenotransplantation) research

DRAFT for NHMRC consideration
(September 2004)

*This document was noted by Council at its 154th Session (September 2004) but not endorsed, and should be read in conjunction with the *NHMRC Statement on Animal-to-Human Transplantation which appears at the front of this document (10 March 2005).*

To obtain details regarding NHMRC publications contact:

Email: nhmrc.publications@nhmrc.gov.au
Phone: Toll Free 1800 020 103 Extension 9520
Interent: http://www.nhmrc.gov.au

Technical writing and production by Biotext, Canberra

Contents

1 Background information

Introduction

In 2004, the National Health and Medical Research Council (NHMRC) approved the recommendation of its Xenotransplantation Working Party (XWP) that a national committee be established to oversee animal-to-human transplantation (xenotransplantation) research proposals in Australia. This committee is called National Committee for <FULL NAME>.

At the same time, Council also endorsed these *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research*, which were developed by the XWP to guide the National Committee <FULL NAME> in overseeing animal-to-human transplantation research, and to assist investigators wishing to submit proposals for assessment. These guidelines also assist the Therapeutic Goods Administration (TGA) in the assessment of clinical trial applications, as well as the individual human research ethics committees (HRECs) and animal ethics committees (AECs) in those institutions in which animal-to-human transplantation trials may be conducted. Appendixes A and B include further information on the XWP and the development of these guidelines.

These guidelines provide direct guidance only on areas that are specific for clinical trials of animal-to-human transplantation and should therefore be read in conjunction with the current edition of the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* (the National Statement; see 'Key information'), which provides ethical guidelines for all other aspects of research involving humans.

Section 2 addresses the key issues at stake for the participants in this research and the community with 10 guidelines that are broad in their design. Section 3 contains a more detailed set of advice detailing how each guideline may be fulfilled. The purpose of the national committee, and these guidelines, is to adequately safeguard the community and, at the same time, allow sufficient flexibility 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.

Key issues

These guidelines have been developed taking into account the following key issues.

- Preclinical xenotransplantation research (including 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 trials of animal-to-human transplantation must be based upon relevant efficacy data from preclinical (including animal-to-animal) research.

- Translation of animal-to-animal transplantation studies into clinical trials of animal-to-human transplantation 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 animal-to-human transplantation carries a risk of introducing new infectious agents into recipients of animal transplantation products, with the possibility of infecting close contacts and the wider community.

- Animal-to-human transplantation trials must therefore have broad community acceptance and must be subject to guidelines, which will apply to all such trials conducted in Australia.

- Animal-to-human transplantation trials must be overseen by a 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.

- HRECs and AECs must seek advice from the national committee. The local committees have the right to authorise research for inclusion in the research program at their institution but must not authorise research that has not been approved by the national committee. HRECs and AECs should also be involved in onsite monitoring of the trials.

Coverage of the guidelines

Definition of xenotransplantation

In keeping with the definition developed by the United States Food and Drug Administration (US FDA) in 2001, the following human research is defined as animal-to-human transplantation (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); and

(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).

The XWP further classified these procedures under three broad categories as follows:

"Not endorsed*"

Procedure	Description	Examples
Animal external therapies (AETs)	A range of procedures involving contact between human and animal cells/ tissues outside of the body of the patient, such as:	
	(a) cells or fluids from the patient are perfused through animal cells and returned to the patient; or	Passage of blood from a patient with liver failure through an external device (Hepatassist machine) containing pig liver cells (similar to a kidney dialysis machine).
	(b) human cells or tissue pieces are cultured with animal cells in the laboratory in order to obtain a larger supply of human cells or tissue for transplantation.	Growth of human skin grafts for wound healing (eg for burns) on a feeder layer of animal cells.
Animal cell therapies (ACTs)	Procedures in which animal cells are transplanted or implanted into a human patient to compensate for deficient functioning of the patient's own cells. Transplanted cells can either be enclosed in a semipermeable capsule (encapsulated) or have no such capsule.	Animal pancreatic cells to produce insulin for people with diabetes. Animal brain cells to produce dopamine for people with Parkinson's disease.
Animal organ transplants (AOTs)	Procedures in which whole organs or tissues from an animal are transplanted or implanted into a human patient to replace a diseased or damaged organ or tissue.	Heart, kidney, liver, skin, adrenal glands etc

'Animal transplantation products' are defined as any live animal cell, tissue or organ that is used in an animal-to-human transplantation procedure (ie not including processed, nonviable products, such as pig heart valves). Animal transplantation products derived from genetically modified animals are classified as GM products and their use must be notified to the Office of the Gene Technology Regulator for entry in the Record of GMO and GM Product Dealings.

National assessment and authorisation

Clinical (animal-to-human) trials of animal organ transplants (AOTs) are not permitted under these guidelines.

Clinical ACT and AET research proposals must be assessed according to these guidelines and authorised by the National Committee <FULL NAME>. Such applications must also be submitted to the TGA as CTX (Clinical Trial Exemption) Scheme applications for use of an unregistered therapeutic good and considered by HRECs and AECs at the institutions where the research will occur. The National Committee <FULL NAME>, TGA and HREC must be satisfied that the research proposal conforms with these guidelines and the current edition of the National Statement. The TGA must also ensure compliance with 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).

An animal-to-human transplantation research proposal that has been approved by the national committee and the TGA and allowed to proceed by the institutional HREC and AEC must be monitored nationally by the national committee and locally by the HREC/AEC. The TGA must also report the use of animal transplantation products from genetically modified animals (GM products) to the Office of the Gene Technology Regulator for entry in the Record of GMO and GM Product Dealings.

Local approval

HRECs and AECs may authorise animal-to-human transplantation trials within their institution but must not do so without approval in writing from the national committee.

If such approval has been granted, HRECs should use these guidelines and the current edition of the National Statement assess the suitability of animal-to-human transplantation research proposals for their institutions.

Likewise, AECs should use these guidelines and the current edition of the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (see 'Key information') to assess the animal welfare aspects of animal-to-human transplantation research proposals for their institutions.

Animal transplants received overseas

If a recipient of an animal transplant (as defined above) returns to or travels to Australia, having received the transplant abroad, the treating medical practitioner in Australia is required to advise the national committee and follow such aspects of these guidelines as advised by the committee. In particular, the treating medical practitioner should obtain consent from the animal transplant recipient to their clinical data being entered on the central register (see Guideline 8, below).

Principles

The guidelines are designed to ensure that the following principles are adhered to in the assessment and approval or rejection of proposals for clinical trials of animal-to-human transplantation:

- 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 be balanced against 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.

2 The guidelines

Guideline 1 (Ethical overview)

(a) All clinical trials of animal-to-human transplantation must be conducted in accordance with the NHMRC *National Statement on Ethical Conduct in Research Involving Humans.*

(b) As for all research applications, the research proposal must identify and address ethical issues specific to the proposal.

Guideline 2 (Animal welfare)

(a) All transplantation 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* (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, animal ethics committees should forward to a central register all research proposals for animal-to-animal studies that are directly related to the development of animal-to-human trials.

Guideline 3 (Efficacy)

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

Guideline 4 (Safety)

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

Guideline 5 (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 6 (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 animal transplant 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 7 (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 6) 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 8 (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, including arrangements in the event that the trial is discontinued.

Guideline 9 (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 10 (Management of public health risks)

The research protocol must include:

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

(b) documentary evidence that shows adequate insurance cover for risks of injuries suffered by participants or members of the public as a result of the trial.

The National Committee <FULL NAME> must give consideration prospectively to criteria that would lead to a clinical research program being halted.

3 Advice regarding the application of the guidelines

The following tables present advice on data requirements and assessment issues for the clinical animal-to-human transplantation research guidelines. They are an outline of the detail that the National Committee <FULL NAME> would expect to see addressed in any application for approval and authorisation of an animal-to-human transplantation trial. This advice will be updated from time to time by the national committee.

A. Ethical overview

ASSESSMENT
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?
Does the institutional research team have sufficient expertise, experience and the resources to ensure safe conduct of the research (see the National Statement, paragraph 1.15)?

B. Animal welfare

DATA REQUIREMENT	ASSESSMENT
Rationale/justification for use	Is the use of animals and choice of species justified in this study or trial?
Number to be used	Is the proposed number of animals acceptable for this procedure?
Source	What is the source of the animals?
Genetic modification(s) – What are the nature and extent of the modification(s)? – Does the modification significantly alter the animal?	Will the proposed genetic modifications alter the essential nature of the animal (ie are they ethically acceptable)?
Level of containment	Is the proposed level of containment appropriate for the trial?
Animal husbandry information: – housing – environmental enrichment – transport requirements – socialisation – appropriate food – adequate number and appropriate qualifications of animal technicians involved in routine care – number of experimental and surgical procedures to be conducted on an individual animal – appropriate use of analgesics and anaesthetics – special dietary needs	Do the conditions comply with all aspects of the Code of Practice?

C. Efficacy

RESEARCH	DATA REQUIREMENT	ASSESSMENT
Proposed trial description/protocol		
Rationale	Description of trial	What is the proposed procedure?
	Therapeutic benefit to participants	What is the expected therapeutic benefit to the research participants? (Note: nontherapeutic trials will not be permitted)
	Factors that may affect outcome	What are the gross physiological issues, biochemical/endocrinological factors and immunological barriers that may affect the outcome of this trial?
		Is it a permanent transplant, or a bridging procedure?
	Proposed strategies to ensure success	How does the investigator propose to overcome barriers to success (eg by genetic modification of the source animal)?
		What is the evidence that this will succeed (including detailed assessment of preclinical studies)?
	Literature research	Has all the relevant background information from published literature been evaluated?
Source animal characterisation	Choice and justification of source animal species	What animal species will be used?
	Anatomical, physiological and genetic considerations	What are the reasons for the choice of animal? What genetic modifications have been undertaken?
	Animal history/herd characterisation	What are the geographic origins, strain and genealogy of the source animal? Have all necessary measures been taken to ensure the quality of the xenotransplantation product?
		[See also advice under D. Safety and B. Animal welfare.]
Xeno-transplantation product characterisation	Type of product	What type of product will be used (eg organ, tissue, cells)?
	Treatment	Will the product be treated in any way after harvesting (eg encapsulated, cultured, stored)?
	Quality control/good manufacturing practice (GMP)	Does the protocol take account of all relevant GMP and quality control considerations for the xenotransplantation product?
Participant selection	Criteria for selection of research participants	How will candidates with the best potential for clinically significant improvement and increased quality of life be identified and selected?
	Alternative therapies	Are there any adequate, safe and effective alternative therapies available?
		If so, does the protocol exclude from the trial patients who could benefit from these alternatives?

contd…

RESEARCH	DATA REQUIREMENT	ASSESSMENT
Evidence of efficacy/safety		
Preclinical studies		
– experimental (in vitro) studies and animal studies	Studies of biochemical/endocrine/ immunological responses relevant to therapeutic outcomes	Do these studies show the mechanisms involved and how they can be modified to increase the chance of a successful outcome in humans? Have all aspects of the mechanisms been studied?
– animal-to-animal transplantation studies	Source animal	Was the same source animal used as is proposed for the human trial? (If not, provide justification)
	Recipient animal	Was the recipient animal (preferably baboon) a suitable model for human transplantation?
	Study protocol	Did the preclinical study protocol reflect the proposed clinical trial protocol (eg implantation site, duration, immunosuppressive protocol)?
	Immunosuppression used	Were there any clinical toxicological, pharmacological or immunological issues arising from the drug regimen used?
	Rejection of transplant	How well did the xenotransplant survive? (eg success of genetic modification in preventing rejection, or in vivo function and durability of encapsulation or other barriers to diminish rejection)
	Functioning of transplant/survival of recipient animal	How well did the xenotransplant perform? Did it sustain life or reverse disease symptoms of the recipient?
	Other considerations	Are there any other considerations arising from the study that might affect efficacy (eg the tumourigenic potential of the transplant, migration of xenogenic cells etc)?
Clinical trials		
– previous trials using the proposed animal-to-human transplantation protocol	Source/study protocol/outcomes	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)
– trials using a related protocol	Source animal/study protocol/outcomes	Do the results of related clinical trials help to understand the possible outcomes of the proposed trial?

D. Safety (risk analysis for infection risks)

RISK ANALYSIS	DATA REQUIREMENT	ASSESSMENT
Risk assessment[a]		
Hazard identification	Source animal (and pedigree): — nonhuman primate, pig, other	Infectious agents present (exogenous and endogenous)
Hazard characterisation	Infectious agent of concern	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
	Genetic modification of source animal	Type of genetic modification Relationship between genetic modification and infectious agents (could modification increase the potential for infectivity?)
Exposure assessment	Type of procedure	Vascularised organ or nonvascularised tissue or cells In vivo transplant or ex vivo perfusion Barrier or no barrier
	Immunosuppression of recipient	Agents used
	Site of transplant	Immunologically protected site (eg brain) or not
	Length of exposure	Long or short term (eg permanent or bridging transplant)
	Estimated dose of agent	Based on available information
Impact/consequences	Human infection	Nature of disease (pathogenicity) Potential for transmission (related to mode, incubation period, 'window' for diagnosis etc) Potential for treatment
Risk characterisation	Overall assessment of potential for human infection and spread of infection Disclosure of areas where not enough information is known to assess risk	
Risk management		
Protocols to maintain risk below acceptable levels	Screening for infectious agents (eg PERV)	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?
	Other surveillance measures	What other disease surveillance measures are in place at the local, national and international levels?
	Procedures if infection occurs	What procedures will be followed if a participant becomes infected?
Risk communication	Have there been discussions with experts, stakeholders and the community about the level and acceptability of risks, including uncertainties?	

a Based on assessment of all relevant experimental and preclinical studies and clinical trials relating to infectious agents of concern

PERV = porcine endogenous retrovirus

E. Trial protocol

PARTICIPANT	DATA REQUIREMENT	ASSESSMENT
Research participant	Selection	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?
	Information	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)?
	Voluntary consent	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?
	Long-term follow-up (monitoring)	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? Are there arrangements for long-term psychosocial monitoring of transplant recipients?
	Confidentiality	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?
Close contacts of research participant	Risk status	Is the risk status of close contacts of the research participant clearly defined?
	Information	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?
	Voluntary involvement	Are there safeguards in place to ensure that close contacts (including carers) are completely comfortable with their involvement in the trial?
	Monitoring	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?

Overall assessment of proposal

Issue	Criterion	Yes/no
Ethical overview	Does the research serve the common good?	
Animal welfare	Does the research protocol respect the dignity and welfare of animals used in the trial?	
Efficacy	Is the research based on preclinical (animal-to-animal) studies that show a therapeutic effect ? Do the benefits justify the risks?	
Safety	Would the research expose the participants or society to any unreasonable risks?	
Trial protocol	Is the research therapeutic in design? Does the research protocol respect the dignity of participants? Does the protocol for participant selection meet all relevant guidelines? Are there any alternative therapies that would offer a better outcome for participants? Does the protocol allow research participants to give adequately informed and voluntary consent? Does the protocol take account of research participants' right to withdraw from further medical treatment? Are the safety and rights of close contacts of the research participants adequately protected?	
APPROVAL		YES/NO

Appendix A Process report

Guidelines development

In 2000, the Xenotransplantation Working Party (XWP) was established by the National Health and Medical Research Council (NHMRC) and asked to report to Council through the Australian Health Ethics Committee and Research Committee. The XWP, which first met in early 2001, was charged with the task of investigating the scientific, ethical and technical issues surrounding animal-to-human transplantation (xenotransplantation) and of conducting public consultation on whether or not clinical trials of animal-to-human transplantation should be permitted in Australia and, if so, on possible mechanisms for the oversight of individual research projects.

Since its formation, the XWP has published two public consultation documents — *Draft Guidelines and Discussion Paper on Xenotransplantation* in July 2002, and *Animal-to-Human Transplantation: How Should Australia Proceed*? in December 2003. It also prepared a plain English community guide (*Animal-to-Human Transplantation: A Guide for the Community*), which was published in December 2003, and conducted public meetings in all capital cities.

In early 2003, after the first round of public consultation, the membership of the XWP was expanded and a subcommittee — the Animal Issues Subcommittee (AISC) — was established to assist the XWP assess issues relating to animal ethics, animal welfare and regulation of the use of animals in xenotransplantation research.

The XWP considered all the submissions received during both rounds of the public consultation, the feedback from the public meetings and all the other relevant information about animal-to-human transplantation. It has also considered final advice prepared by the AISC after this Subcommittee's consideration of the responses to the second round of public consultation.

The XWP used all of this information to prepare its final advice to the NHMRC on how Australia should proceed in relation to animal-to-human transplantation research. This advice included guidelines for a proposed national committee to assist in its oversight of such research, and to assist investigators wishing to submit proposals for assessment. These guidelines will also assist the Therapeutic Goods Administration and individual Human Research Ethics Committees and Animal Ethics Committees in those institutions in which animal-to-human trials may be conducted.

~~These *Guidelines for Clinical Animal-to-Human Transplantation Research* were endorsed by Council at its 154th Session on 16–17 September 2004 [to be confirmed].~~

Public consultation submissions

A total of 97 written submissions were received in the first round of consultation on animal-to-human transplantation research, which was conducted by the NHMRC between August and October 2002. The second round of consultation, conducted between December 2003 and March 2004, attracted 343 written submissions. One-third (33) of those who made a submission in the first round also made a submission in the second round.

Public meetings

During the first round of public consultation, public meetings were held in Sydney, Melbourne and Perth, with targeted meetings also being held in Adelaide and Perth. These meetings attracted a total of 116 participants, as follows:

City, state/territory	Date	Number of attendees
Perth, WA	12 August 2002	21 (targeted meeting) 30 (public meeting)
Melbourne, VIC	19 August 2002	20
Sydney, NSW	21 August 2002	15
Adelaide, SA	12 September 2002	30 (targeted meeting)
TOTAL		116

As part of the second round of public consultation, public meetings were held in all Australian State and Territory capital cities, and attracted a total of 377 participants (see below). These meetings were moderated by an independent facilitator in order to further promote open discussion. No targeted meetings were conducted in this second round.

City, state/territory	Date	Number of attendees
Brisbane, QLD	9 February 2004	80
Sydney, NSW	10 February 2004	85
Canberra, ACT	11 February 2004	40
Perth, WA	16 February 2004	50
Adelaide, SA	17 February 2004	45
Darwin, NT	18 February 2004	10
Melbourne, VIC	23 February 2004	50
Hobart, TAS	24 February 2004	17
TOTAL		377

Guidelines dissemination plan

The XWP recommended that the NHMRC *Guidelines for Clinical Animal-to-Human Transplantation (Xenotransplantation) Research* be distributed to a wide range of stakeholders, including:

- respondents to the first and second rounds of public consultation;
- human research ethics committees registered with the Australian Health Ethics Committee;
- animal ethics committees;
- heads of research institutes and tertiary institutions;
- recipients of NHMRC grants, awards and fellowships;
- research, foundation and patient support groups; and
- relevant Australian, and state and territory, government departments and agencies.

~~These guidelines are also available on the NHMRC website, www.nhmrc.gov.au, and hard copies are available through the NHMRC's publication distribution mechanism (see the NHMRC website for further information).~~

Appendix B Working group membership for development of guidelines

Xenotransplantation Working Party

2001 – 2002 (first public consultation)

Membership category	Member	Expertise/affiliation
2 members from the Australian Health Ethics Committee*	Dr Kerry Breen **(Chair)**	Clinical medicine and medical ethics
	Associate Professor Bernadette Tobin	Philosophy and transplantation ethics
2 members from Research Committee* or the Gene and Related Therapies Research Advisory Panel (GTRAP)	Dr Dominic Dwyer (GTRAP)	Clinical virology and infectious disease
	Professor Philip O'Connell (GTRAP)	Clinical and experimental transplantation
2 members representing community views	Ms Michele Kosky	NHMRC member with expertise in consumer issues
	Mr Twanny Farrugia	Counsellor (general, loss and grief)
1 member from the Animal Welfare Committee (a working committee of Research Committee*)	Ms Elizabeth Grant AM	Pharmacist Research Committee Member Chair, Animal Welfare Committee

*The Australian Health Ethics Committee and Research Committee are principal committees of the National Health and Medical Research Council; GTRAP is a working committee of Research Committee

2003 – 2004 (second public consultation)

Membership category	Member	Expertise/affiliation
Chair	Dr Jack Sparrow	Medical administration
2 members from the Australian Health Ethics Committee*	Dr Kerry Breen	Clinical medicine and medical ethics
	Associate Professor Bernadette Tobin (former AHEC member)	Philosophy and transplantation ethics
2 members from Research Committee* or the Gene and Related Therapies Research Advisory Panel (GTRAP)	Dr Dominic Dwyer (former GTRAP member)	Clinical virology and infectious disease
	Professor Philip O'Connell (GTRAP)	Clinical and experimental transplantation
1 Therapeutic Goods Administration nominee	Dr Leonie Hunt	Assistant Secretary, Drug Safety and Evaluation Branch, Therapeutic Goods Administration

1 clinician with background in transplantation (excluding xenotransplantation)	Dr Simone Strasser	Clinical transplantation
1 member with expertise in clinical and experimental transplantation	Professor Mauro Sandrin	Experimental transplantation (including xenotransplantation), and clinical transplantation
1 member with infectious diseases/public health background	Professor Aileen Plant	Medical epidemiology and international health
2 members representing community views	Ms Michele Kosky Mr Twanny Farrugia	NHMRC member with expertise in consumer issues Counsellor (general, loss and grief)
1 member from the Animal Welfare Committee (a working committee of Research Committee*)	Ms Elizabeth Grant AM	Pharmacist Research Committee Member Chair, Animal Welfare Committee
2 members with animal welfare background	Dr Bidda Jones Ms Glenys Oogjes	Scientific Officer, RSPCA Australia with expertise in animal welfare issues Executive Director, Animals Australia
Observer	Dr Bruce Scoggins	Health Research Council of New Zealand

*The Australian Health Ethics Committee and Research Committee are principal committees of the National Health and Medical Research Council; GTRAP is a working committee of Research Committee

Secretariat

Ms Milly Betteridge	Project Officer from February 2002 to March 2003
Dr David Abbott	Project Officer from April to December 2003
Ms Tamara Shanley	Project Officer from January 2004

Consultant (technical writer)

Dr Janet Salisbury	Biotext, Canberra

Animals Issues Subcommittee

Membership category	Member	Expertise/affiliation
Chair	Ms Elizabeth Grant AM	Pharmacist, Research Committee Member Chair, Animal Welfare Committee
1 member from the Animal Welfare Committee (a working committee of Research Committee*)	Associate Professor Graham Jenkin	Stem cell research
2 members with a demonstrable commitment to, and experience in, furthering the welfare of animals and who are not involved in the care and use of animals for scientific purposes	Dr Bidda Jones Ms Helen Rosser	Scientific Officer, RSPCA Australia with expertise in animal welfare issues Assistant to Executive Director, Animals Australia Co-founder and National Coordinator, Humane Charities Australia Inc.
1 person with experience in the regulation of the use of animals in research	Dr Robert Dixon	Faculty of Veterinary Science, University of Sydney, Subdean Animal Welfare, member of several research institutional animal ethics committees
1 independent person with recent veterinary and animal husbandry experience	Dr Lyndy Scott	The Australian Veterinary Association

*Research Committee is a principal committee of the National Health and Medical Research Council

Abbreviations

ACT	animal cell therapy
AEC	animal ethics committee
AET	animal external therapy
AHEC	Australian Health Ethics Committee (NHMRC)
AISC	Animal Issues Subcommittee
AOT	animal organ transplant
AWC	Animal Welfare Committee (NHMRC)
Code of Practice	*Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (see 'Key information')
CTX	Clinical Trial Exemption (scheme of the TGA)
GM	genetically modified
GTRAP	Gene and Related Therapies Research Advisory Panel (NHMRC)
HREC	human research ethics committee
National Statement	*National Statement on Ethical Conduct in Research Involving Humans.* (see 'Key information')
NHMRC	National Health and Medical Research Council
OGTR	Office of the Gene Technology Regulator
TGA	Therapeutic Goods Administration
XWP	Xenotransplantation Working Party (NHMRC)

Key information

CPMP/ICH 135/95. *Note for Guidance on Good Clinical Practice, Annotated with TGA comments,* Committee for Proprietary Medicinal Products/International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. http://www.tga.gov.au/docs/pdf/euguide/ich/ich13595.pdf (accessed 1 September 2004)

US FDA (2001). *Xenotransplantation Action Plan: FDA Approach to the Regulation of Xenotransplantation.* United States Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. http://www.fda.gov/cber/xap/xap.htm#back (accessed 31 August 2004)

National Health and Medical Research Council (NHMRC) (1999). *National Statement on Ethical Conduct in Research Involving Humans.*

NHMRC (2002). *Draft Guidelines and Discussion Paper on Xenotransplantation,* Public consultation 2002, Xenotransplantation Working Party, NHMRC, Canberra.

NHMRC (2003). *Animal-to-Human Transplantation: How Should Australia Proceed?* Response to the 2002 public consultation on *Draft Guidelines and Discussion Paper on Xenotransplantation,* Public consultation on xenotransplantation 2003–04, Xenotransplantation Working Party, NHMRC, Canberra.

NHMRC (2003). *Animal-to-Human Transplantation: A Guide for the Community,* Public consultation on xenotransplantation 2003–04, Xenotransplantation Working Party, NHMRC, Canberra.

NHMRC (2004). *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes,* 7th edition, NHMRC, Canberra.