Draft guidelines and discussion paper on xenotransplantation

Xenotransplantation Working Party

Public consultation 2002
The strategic intent of the NHMRC is to provide leadership and work with other relevant organisations to improve the health of all Australians by:

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

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

DRAFT GUIDELINES FOR CLINICAL XENOTRANSPLANTATION RESEARCH

You are invited under paragraph 13(1)(b) of the National Health and Medical Research Council Act 1992 to make a submission to the NHMRC about the draft guidelines for clinical xenotransplantation research detailed in the attached document titled Draft Guidelines and Discussion Paper on Xenotransplantation.

In addition, your attention is drawn to the discussion paper as it contains draft advice to the NHMRC regarding options for regulating xenotransplantation and poses many questions upon which public comment is sought.

The draft guidelines and discussion paper were prepared by the NHMRC Working Party on Xenotransplantation and have been approved for release for public consultation by the Australian Health Ethics Committee (AHEC) and the Research Committee.

The working party is proposing seven guidelines for the conduct of clinical xenotransplantation research in the following areas: efficacy; safety; information giving; consent; monitoring and surveillance; data and tissue storage; and management of public health risks. Specific questions in relation to the issues raised by these guidelines are posed in the discussion paper. Responses to these questions in addition to comment on the seven guidelines would be welcome.

Your submission should include your name and address, or a telephone number at which we can contact you, and can be forwarded in writing, by email or on audiotape to:

Project Officer – Xenotransplantation
Health Ethics Section
NHMRC (MDP 100)
GPO Box 9848
CANBERRA ACT 2601
Email ahec.nhmrc@nhmrc.gov.au
Telephone: (02) 6289 9806

To assist you in preparing your submission, a copy of the NHMRC document Public Consultation – Procedures for Making Submissions is included as an attachment to the Draft Guidelines and Discussion Paper on Xenotransplantation.

The closing date for submissions is Friday 6 September 2002.

Additional copies of the document are available from the NHMRC at the above address. The document is also available in PDF format on the NHMRC website at http://www.nhmrc.gov.au/issues/xeno.htm.

contd…
You are also invited to attend public meetings to be held in Sydney, Melbourne and Perth at which members of the working party will provide a short presentation on the draft guidelines and seek views on their appropriateness. Dates and venues for these meetings will be advertised in the local press and will also be available from the NHMRC website or by contacting the Project Officer at the above address.

I look forward to receiving your comments.

Yours faithfully

[Signature]

Dr Kerry Breen
Chairperson
Australian Health Ethics Committee
National Health and Medical Research Council

8 July 2002
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Important information about xenotransplantation and this document

What is this document about?

This document was prepared by a working party of the National Health and Medical Research Council (NHMRC). There are two parts to the document:

1. draft guidelines on xenotransplantation research; and
2. a discussion paper on the ethical, scientific, technical and regulatory aspects of xenotransplantation.

The draft guidelines, and the draft advice regarding a regulatory framework, take a preliminary view on the matter of whether xenotransplantation clinical research should cautiously proceed in Australia. This view is not fixed.

Following the public consultation period, the Working Party is required by the NHMRC Act 1992 to pay due regard to submissions received. Thus the final guidelines and advice that will be presented to Council for approval may differ from these draft guidelines as a result of the consultation process. If the difference is significant, the Council may request a further round of public consultation.

What is xenotransplantation and why is it being considered?

Xenotransplantation is the transplantation of living cells, tissues or organs from one species to another (for example, from pigs to humans). This includes transplantation of solid organs (such as kidney or heart); tissues (such as skin); and clusters of specialised cells (such as brain cells to treat Parkinson’s disease or pancreatic cells to treat diabetes). The term also covers the infusion or transplantation of body fluids, tissues or cells that have had contact with animal tissues or cells outside of the transplant recipient’s body (for example, the infusion of blood through an artificial liver containing pig liver cells). Xenotransplants perform the same functions as the organ, tissue or cells that they replace.

Allotransplantation (transplantation of organs, cells and tissues between members of the same species) is a successful way to treat a variety of human illnesses. However, many patients who could benefit from a transplant wait in vain because of a shortage of human donors.

Transplant specialists are therefore considering animals, particularly pigs, as a possible source of organs, cells and tissues for human transplantation. Recent advances in technology have increased the possibility of successful xenotransplantation and stimulated research in this area.

What does xenotransplantation research involve?

Before xenotransplantation can become an option for human therapy, research is needed that includes:

- animal-to-animal studies — in which xenotransplantation procedures are tested on animals (for example, pig-to-baboon kidney transplant); and
• animal-to-human trials — in which animal products are used for xenotransplantation procedures on human beings (for example, pig-to-human brain cell transplants).

The draft guidelines included in this document are about animal-to-human trials. These have not been carried out in Australia so far. The only trials that would be permitted under these draft guidelines are therapeutic trials (that is, trials intended to provide a direct benefit to the trial participants).

What are the key issues?
Xenotransplantation raises ethical, social and scientific issues that need to be considered by the Australian community before animal-to-human clinical trials are allowed to proceed. These include:

• the implications of mixing human and animal tissues;
• whether it is ethical to use animals in this way;
• the selection of transplant recipients;
• whether xenotransplantation works (efficacy);
• whether it is safe;
• arrangements for information giving, consent, monitoring and follow-up; and
• considerations of animal welfare.

Does xenotransplantation work?
Strong rejection reactions occur when solid organs are transplanted from one species to another (for example, from pig to baboon). Further work is therefore needed to overcome this response and develop procedures that can be shown in animal-to-animal studies to have a comparable chance of success to allotransplantation. The most promising approach at this stage is to genetically modify the source animals so that they do not cause such a strong immune reaction. Scientists have already produced several genetically modified pig strains that show promising properties.

Cellular transplants and external infusion of body fluids cause less immune rejection than solid organ transplants and are the subject of the few clinical trials that are currently under way overseas. These types of procedures, rather than solid organ transplants, are likely to be the subject of the initial research proposals considered in Australia.

Is xenotransplantation safe?
The main safety concern associated with xenotransplantation is that an agent from animal tissue used might infect humans. An animal disease agent that has raised particular concern is the porcine endogenous retrovirus (PERV). This virus is dormant in pigs but it can infect human cells in the laboratory and may infect xenotransplant recipients (although this has not occurred in any xenotransplant recipient to date). The level of risk varies from one procedure to another and depends on a number of factors. These include the type of xenotransplantation product used and the extent of the exposure by the recipient.

Under the draft guidelines, only trials that present a very low, or negligible, risk would be approved. The hospital where the transplant is managed would have appropriate infection control policies and adequate, workable arrangements for long-term surveillance and monitoring of xenotransplant recipients would be in place.
Why are guidelines needed?
If clinical trials of xenotransplantation are undertaken in Australia, guidelines will be
needed to help regulatory agencies and human research ethics committees assess research
proposals against ethical and scientific principles.

How is this document structured?
This document has the following components.

*Draft guidelines and advice*
The draft guidelines proposed by the working party for regulation of clinical
xenotransplantation research.

Draft advice for researchers and the proposed regulatory agency on the application of the
draft guidelines.

*Summary of the discussion paper*
A plain English summary of the discussion paper giving an overview of all the issues
considered by the working party in preparing the draft guidelines and the proposed
regulatory arrangements.

*Invitation to comment*
Questions for consideration by readers of the document.

*Discussion paper*
Detailed information on the issues considered by the working party in preparing the
guidelines (Parts 1 and 2) and about the proposed regulatory arrangements for oversight
of the research in Australia (Part 3). A further plain English overview is provided at the
start of each chapter.

What should you do now?
Readers are asked to review the information contained in the discussion document, with
particular emphasis on the questions raised at various points throughout the document.
Readers are then asked to prepare a submission to the working party that presents their
response to the issues raised.

The working party is particularly seeking comment on the draft guidelines and the
proposed regulatory controls (Chapter 11). However, responses to all questions and issues
raised in the discussion paper are welcome and will inform the working party in the
preparation of its final recommendations to the National Health and Medical Research
Council.

Guidance for preparing submissions is included as an attachment at the end of this
document.
DRAFT GUIDELINES AND ADVICE
Draft guidelines for clinical xenotransplantation research

Introduction

These draft guidelines are drawn from the issues raised in this discussion paper and are presented here for public consultation. The draft guidelines draw on the following key principles.

- Preclinical xenotransplantation research (animal-to-animal studies) is already established in Australia. Although translation of that research and research from overseas into clinical (animal-to-human) trials is likely to be slow, especially for solid organ transplantation, a moratorium on such clinical research is not appropriate.

- Clinical (animal-to-human) trials must be based upon relevant efficacy data from preclinical (animal-to-animal) research.

- Translation of animal-to-animal xenotransplantation studies into clinical (animal-to-human) trials raises special issues beyond those encountered in almost all other types of human research, especially issues of safety, efficacy and consent. In particular, at our present state of knowledge, it is acknowledged that xenotransplantation carries a risk of introducing new infectious agents into recipients of xenotransplant products, with the possibility of infecting close contacts and the wider community generally.

- Xenotransplantation clinical (animal-to-human) trials must therefore have broad community acceptance and must be subject to guidelines, which, once finalised, will apply to all xenotransplantation clinical trials conducted in Australia.

- Xenotransplantation clinical (animal-to-human) trials must be overseen by a single national committee with both the necessary expertise and community input, in order to reassure the community that any proposed clinical trials are adequately assessed and monitored according to agreed national guidelines.

- Human research ethics committees (HRECs) must be bound by the advice of the proposed national committee but should have the power to refuse to authorise any research to be done in their own institution. HRECs should also be involved in onsite monitoring of the trials.

Use of the (draft) guidelines

These (draft) guidelines only provide direct guidance on areas that are specific for xenotransplantation and should be read in conjunction with the current edition of the NHMRC National Statement on Ethical Research Involving Humans, which provides ethical guidelines for all other aspects of research involving humans.
These (draft) guidelines have been developed to guide the (proposed) national xenotransplantation committee in its deliberations and to assist investigators wishing to submit proposals for assessment. When finalised, the guidelines will also assist individual HRECs in those institutions in which xenotransplantation human trials are conducted. The (draft) guidelines address the key issues at stake for the participants in this research and the community and are broad in their design. They are accompanied by a more detailed set of advice detailing how each draft guideline may be fulfilled. The working party hopes that such broad guidelines, together with the composition and powers of the national committee and the existence of the accompanying advice, will adequately safeguard the community and, at the same time, allow sufficient flexibility for the national committee to respond to emerging knowledge in regard to risks, efficacy and consent in this type of human research.

These (draft) guidelines do not address research involving animal-to-animal (preclinical) xenotransplantation studies because such studies are subject to existing NHMRC guidelines, State and Territory legislation and, in relevant situations, oversight by the Office of the Gene Technology Regulator.

Coverage of the (draft) guidelines

National assessment and authorisation

All animal-to-human xenotransplantation research proposals must be assessed according to these (draft) guidelines and authorised by the (proposed) national xenotransplantation committee, before they can be considered by HRECs at the institution where the research will occur. The (proposed) national xenotransplantation committee must be satisfied that the research proposal conforms with the current edition of the NHMRC National Statement on Ethical Conduct in Research Involving Humans as well as with these (draft) guidelines.

The following human research is defined to be xenotransplantation.

(a) Any procedure that involves the transplantation, implantation or infusion into a human recipient of live cells, tissues or organs from a nonhuman animal source (an in vivo transplant), that is:
   – organ transplants (eg heart, kidney, liver);
   – tissue transplants (eg skin);
   – cellular transplants
     - without a semipermeable capsule (eg fetal pig neural cells transplanted into the human brain for treatment of Parkinson’s disease); and
     - enclosed in a semipermeable capsule (eg encapsulated islets of Langerhans cells transplanted into the peritoneal cavity to treat diabetes).

(b) Any procedure that involves the transplantation, implantation or infusion into a human recipient of human body fluids, cells, tissues or organs that have had contact

1 The term ‘national xenotransplantation committee’ is the term used to refer to whatever government body may ultimately be established to oversight xenotransplantation.
outside the body with live nonhuman animal cells, tissues or organs (an ex vivo procedure), that is:

- perfusion of human body fluid through animal tissues or cells, which may or may not be separated by a semipermeable membrane (eg perfusion of human blood through a dialysis-like system containing animal liver cells, or perfusion of human blood through a whole pig liver); and

- growth of human cells on a feeder layer of animal cells for transplanting back to the same individual (eg growth of human skin or human stem cells on mouse cell feeder layer).

A human xenotransplantation research proposal that has been approved by the national committee and allowed to proceed by the HREC must be monitored nationally by the national xenotransplantation committee and by the HREC.

**Local approval**

HRECs must not authorise xenotransplantation human trials without express authorisation in writing from the national xenotransplantation committee. If such authorisation has been granted, HRECs should use these (draft) guidelines and the current edition of the NHMRC *National Statement on Ethical Research Involving Humans* to assess the suitability of xenotransplantation research proposals for their institutions.

**Xenotransplants received overseas**

If a recipient of xenotransplantation (as defined above) returns to or travels to Australia, having received a xenotransplant abroad, the treating medical practitioner in Australia is required to advise the national xenotransplantation committee and follow such aspects of these (draft) guidelines as advised by the national committee. In particular, the treating medical practitioner should obtain consent from the xenotransplant recipient to being entered on the central register (see Guideline 6).

**Principles**

The (draft) guidelines are designed to ensure that the following principles are adhered to in the assessment and approval or rejection of proposals for human clinical xenotransplantation research:

- the research must serve the common good;
- the research must be scientifically sound;
- the research must be based on relevant efficacy data from preclinical studies;
- the research must be therapeutic in design;
- the benefits must justify any risks;
- the research should not expose the participants, their contacts or society to any unreasonable risks;
- the research must respect the dignity of participants;
- participants must give adequately informed and voluntary consent;
- arrangements for monitoring and follow-up must take account of the participant’s right to withdraw from the trial;
- the safety and rights of close contacts of the participants must be protected; and
the research must respect the welfare of animals used in the trial and be conducted according to the NHMRC Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.
Draft guidelines

Guideline 1 (Efficacy)

Any proposed clinical (animal-to-human) xenotransplantation trial must be based on preclinical (animal-to-animal) studies that demonstrate a likely therapeutic benefit to the participants (and are conducted in accordance with the NHMRC Code of Practice for the Use of Animals in Medical Research).

Guideline 2 (Safety)

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

Guideline 3 (Information giving)

The research protocol must include:

(a) clear patient information sheets that allow potential research participants to make an informed decision about the proposed procedure; and

(b) procedures which, when followed, ensure that appropriate information and counselling are provided to potential participants and that no coercion is used; and

(c) procedures which, when followed, ensure that appropriate information and counselling are provided to close contacts, including carers, of the xenotransplant recipient; and

(d) procedures which, when followed, ensure that research participants and their close contacts, including carers, are aware of the need for ongoing and long-term follow-up and surveillance for possible emerging personal and public health risks.

Guideline 4 (Consent)

The research protocol must include:

(a) procedures which, when followed, ensure that the consent of potential research participants is obtained after the necessary information is provided (Guideline 3) and which allow the participant to take a reasonable period to think things over and discuss the information provided with their close contacts; and

(b) consent forms that clearly set out what is being consented to, including the need for ongoing and long-term surveillance for possible emerging personal and public health risks; and

(c) procedures for collection of signed information sheets (or equivalent) from close contacts of research participants.
Guideline 5 (Monitoring and surveillance)

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

Guideline 6 (Data and tissue storage)

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

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

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

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

Guideline 7 (Management of public health risks)

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

The following tables present advice on data requirements and assessment issues for animal-to-human (clinical) xenotransplantation research guidelines. They represent an outline of the detail that the proposed national xenotransplantation committee would expect to see addressed in any application for approval and authorisation of a human xenotransplantation trial.

A. THE COMMON GOOD

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are the ethical issues associated with this procedure acceptable to the general public?</td>
</tr>
<tr>
<td>What are the public and individual benefits of this procedure?</td>
</tr>
<tr>
<td>What are the public and individual risks of this procedure?</td>
</tr>
<tr>
<td>Are there any alternative procedures available?</td>
</tr>
<tr>
<td>Are the infectious risks associated with this procedure acceptable to the general public?</td>
</tr>
</tbody>
</table>

B. EFFICACY

<table>
<thead>
<tr>
<th>RESEARCH</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed trial description/protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>Description of trial</td>
<td>What is the proposed procedure?</td>
</tr>
<tr>
<td></td>
<td>Therapeutic benefit to participants</td>
<td>What is the expected therapeutic benefit to the research participants? (Note: nontherapeutic trials will not be permitted)</td>
</tr>
<tr>
<td></td>
<td>Factors that may affect outcome</td>
<td>What are the gross physiological issues, biochemical/endocrinological factors and immunological barriers that may affect the outcome of this trial?</td>
</tr>
<tr>
<td></td>
<td>Proposed strategies to ensure success</td>
<td>Is it a permanent transplant, or a bridging procedure?</td>
</tr>
<tr>
<td></td>
<td>Literature research</td>
<td>How does the investigator propose to overcome barriers to success (e.g., by genetic modification of the source animal)?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What is the evidence that this will succeed (including detailed assessment of preclinical studies)?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Has all the relevant background information from published literature been evaluated?</td>
</tr>
<tr>
<td>Source animal characterisation</td>
<td>Choice and justification of source animal species</td>
<td>What animal species will be used?</td>
</tr>
<tr>
<td></td>
<td>Anatomical, physiological and genetic considerations</td>
<td>What are the reasons for the choice of animal?</td>
</tr>
<tr>
<td></td>
<td>Animal history/herd characterisation</td>
<td>What genetic modifications have been undertaken?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What are the geographic origins, strain and genealogy of the source animal?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Have all necessary measures been taken to ensure the quality of the xenotransplantation product?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[See also advice under C. Safety and E. Animal welfare, below.]</td>
</tr>
</tbody>
</table>

contd...
<table>
<thead>
<tr>
<th>RESEARCH</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeno-&lt;br&gt;transplantation&lt;br&gt;product&lt;br&gt;characterisation</td>
<td>Type of product&lt;br&gt;Treatment&lt;br&gt;Quality control/good manufacturing&lt;br&gt;practice (GMP)</td>
<td>What type of product will be used (eg organ, tissue, cells)?&lt;br&gt;Will the product be treated in any way after harvesting (eg encapsulated, cultured, stored)?&lt;br&gt;Does the protocol take account of all relevant GMP and quality control considerations for the xenotransplantation product?</td>
</tr>
<tr>
<td>Participant&lt;br&gt;selection</td>
<td>Criteria for selection of research&lt;br&gt;participants&lt;br&gt;Alternative therapies</td>
<td>How will candidates with the best potential for clinically significant improvement and increased quality of life be identified and selected?&lt;br&gt;Are there any adequate, safe and effective alternative therapies available?&lt;br&gt;If so, does the protocol exclude from the trial patients who could benefit from these alternatives?</td>
</tr>
<tr>
<td>Evidence of efficacy/safety</td>
<td>Animal-to-animal (preclinical) studies&lt;br&gt;– experimental&lt;br&gt;(in vitro) studies&lt;br&gt;– animal studies&lt;br&gt;Source animal&lt;br&gt;Recipient animal&lt;br&gt;Study protocol&lt;br&gt;Immunosuppression used&lt;br&gt;Rejection of transplant&lt;br&gt;Functioning of transplant/survival of recipient animal&lt;br&gt;Other considerations</td>
<td>Do these studies show the mechanisms involved and how they can be modified to increase the chance of a successful outcome in humans?&lt;br&gt;Have all aspects of the mechanism been studied?&lt;br&gt;Was the same source animal used as proposed for the human trial (if not, provide justification)?&lt;br&gt;Was the recipient animal a suitable model for human transplantation (preferably baboon)?&lt;br&gt;Did the preclinical study protocol reflect the proposed clinical trial protocol (eg implantation site, duration, immunosuppressive protocol)?&lt;br&gt;Were there any clinical toxicological, pharmacological or immunological issues arising from the drug regimen used?&lt;br&gt;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)&lt;br&gt;How well did the xenotransplant perform? Did it sustain life or reverse disease symptoms of the recipient?&lt;br&gt;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)?</td>
</tr>
<tr>
<td>Animal-to-human (clinical) trials&lt;br&gt;– previous trials&lt;br&gt;using the proposed&lt;br&gt;protocol&lt;br&gt;– trials using the&lt;br&gt;related protocol</td>
<td>Source/study protocol/outcomes&lt;br&gt;Source animal/study&lt;br&gt;protocol/outcomes</td>
<td>As for animal-to-animal studies&lt;br&gt;(Note: this will only apply for phase II or III clinical trial applications where there is already some phase I trial evidence available)&lt;br&gt;Do the results of related clinical trials help to understand the possible outcomes of the proposed trial?</td>
</tr>
</tbody>
</table>
C. SAFETY (risk analysis for infection risks)

<table>
<thead>
<tr>
<th>RISK ANALYSIS</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard identification</td>
<td>Source animal (and pedigree): – nonhuman primate, pig, other</td>
<td>Infectious agents present (exogenous and endogenous)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard characterisation</td>
<td>Infectious agent of concern</td>
<td>Infectivity to patient (infectious dose and dose response) Mode of transmission and infectivity for contacts Incubation/window period (ie potential for early diagnosis before it spreads to other people) For PERV, data on gene mapping, secretion and infectivity Type of genetic modification Relationship between genetic modification and infectious agents (could modification increase the potential for infectivity?) Genetic modification of source animal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure assessment</td>
<td>Type of procedure</td>
<td>Vascularised organ or nonvascularised tissue or cells In vivo transplant or ex vivo perfusion Barrier or no barrier Agents used Immunologically protected site (eg brain) or not Long or short term (eg permanent or bridging transplant) Based on available information</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression of recipient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Site of transplant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Length of exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estimated exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact/consequences</td>
<td>Human infection</td>
<td>Nature of disease (pathogenicity) Potential for transmission (related to mode, incubation period, 'window' for diagnosis etc) Potential for treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk characterisation</td>
<td>Overall assessment of potential for human infection and spread of infection Disclosure of areas where not enough information is known to assess risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk management</td>
<td>Protocols to maintain risk below acceptable levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Screening for infectious agents (eg PERV)</td>
<td>What test will be used to screen for infectious agent? What is the sensitivity and specificity of the test? How often will participants and contacts be screened? What arrangements are in place for storage of samples?</td>
</tr>
<tr>
<td></td>
<td>Other surveillance measures</td>
<td>What other disease surveillance measures are in place at the local, national and international level?</td>
</tr>
<tr>
<td></td>
<td>Procedures if infection occurs</td>
<td>What procedures will be followed if a participant becomes infected?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk communication</td>
<td>Have there been discussions with experts, stakeholders and the community about the level and acceptability of risks, including uncertainties?</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Based on assessment of all relevant experimental and preclinical studies and clinical trials relating to infectious agents of concern

PERV = porcine endogenous retrovirus
## D. INFORMATION AND CONSENT

<table>
<thead>
<tr>
<th>PARTICIPANT</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research participant</td>
<td>Information</td>
<td>Is the information that will be given to research participants sufficient to help them decide whether to consent to the procedure or not (eg efficacy and safety issues, alternative treatments available, requirement for long-term monitoring, measures that may be required if an infection is detected)?</td>
</tr>
<tr>
<td>Voluntary consent</td>
<td></td>
<td>Is the person who will present the information to the research participant suitable for the task (eg independent of the research team)? Are safeguards in place to ensure that the research participant’s consent to the procedure is obtained voluntarily and without coercion?</td>
</tr>
<tr>
<td>Long-term follow-up (monitoring)</td>
<td></td>
<td>Is the information that will be given to research participants about lifelong monitoring sufficient to encourage them to commit to and comply with these measures (eg tests involved, frequency, measures that may be required if an infection is detected)? Are there any arrangements in place to facilitate compliance with monitoring requirements (eg travel arrangements, home visits)? If a patient withdraws from the trial (ie does not continue with long-term monitoring), how will this affect the overall risk assessment for the trial?</td>
</tr>
<tr>
<td>Confidentiality</td>
<td></td>
<td>Does the protocol include measures to ensure that the confidentiality of the research participant is safeguarded within the constraints of the necessary arrangements for identifying and monitoring close contacts?</td>
</tr>
<tr>
<td>Close contacts of research participant</td>
<td>Risk status</td>
<td>Is the risk status of close contacts of the research participant clearly defined?</td>
</tr>
<tr>
<td>Information</td>
<td></td>
<td>Is the information that will be given to close contacts of the research participant sufficient for their role in the decision process (eg potential outcome for the research participant, their own risk status, requirements for monitoring)? Is the person who will present the information to close contacts suitable for the task?</td>
</tr>
<tr>
<td>Voluntary involvement</td>
<td></td>
<td>Are there safeguards in place to ensure that close contacts (including carers) are completely comfortable with their involvement in the trial?</td>
</tr>
<tr>
<td>Monitoring</td>
<td></td>
<td>Is the information that will be given to close contacts about monitoring requirements sufficient to encourage them to commit to and comply with these measures (eg tests involved, frequency, measures that may be required if an infection is detected)? Are there any arrangements in place to facilitate compliance with monitoring requirements (eg home visits)? If a close contact does not comply with the monitoring requirements, how will this affect the overall risk assessment for the trial?</td>
</tr>
</tbody>
</table>
## E. ANIMAL WELFARE

<table>
<thead>
<tr>
<th>ANIMALS</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonhuman primates</td>
<td>Rationale/justification for use</td>
<td>Is the use of nonhuman primates justified in this trial?</td>
</tr>
<tr>
<td></td>
<td>Number to be used</td>
<td>Is the proposed number of animals acceptable for this procedure?</td>
</tr>
<tr>
<td></td>
<td>Source</td>
<td>What is the source of the animals?</td>
</tr>
<tr>
<td></td>
<td>Level of containment</td>
<td>Is the proposed level of containment appropriate for the trial?</td>
</tr>
<tr>
<td></td>
<td>Animal husbandry information:</td>
<td>Do the conditions comply with all aspects of the Code of Practice?</td>
</tr>
<tr>
<td></td>
<td>– housing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– environmental enrichment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– transport requirements</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– pre- and postsurgery care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– appropriate anaesthetic and analgesic regimes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– immunosuppression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– length of time animals would be held in laboratories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– number of experimental and surgical procedures to be conducted on an individual animal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– special dietary needs</td>
<td></td>
</tr>
<tr>
<td>Pigs</td>
<td>Rationale/justification for use</td>
<td>Is the use of pigs justified in this trial?</td>
</tr>
<tr>
<td></td>
<td>Number to be used</td>
<td>Is the proposed number of animals acceptable for this procedure?</td>
</tr>
<tr>
<td></td>
<td>Source</td>
<td>What is the source of the animals?</td>
</tr>
<tr>
<td></td>
<td>Genetic modification(s)</td>
<td>Will the proposed genetic modifications alter the essential nature of the pig (ie are they ethically acceptable)?</td>
</tr>
<tr>
<td></td>
<td>– What is the nature and extent of the modification(s)?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Does the modification significantly alter the animal?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level of containment</td>
<td>Is the proposed level of containment appropriate for the trial?</td>
</tr>
<tr>
<td></td>
<td>Animal husbandry information:</td>
<td>Do the conditions comply with all aspects of the Code of Practice?</td>
</tr>
<tr>
<td></td>
<td>– housing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– socialisation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– appropriate food</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– adequate number and appropriate qualifications of animal technicians involved in routine care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– appropriate use of analgesics and anaesthetics</td>
<td></td>
</tr>
<tr>
<td>Other species</td>
<td>Similar considerations to the above</td>
<td>Compliance with the Code of Practice</td>
</tr>
</tbody>
</table>
### OVERALL ASSESSMENT OF PROPOSAL

<table>
<thead>
<tr>
<th>Issue</th>
<th>Criterion</th>
<th>Yes/no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public good</td>
<td>Does the research serve the common good?</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>Is the research scientifically sound? Do the benefits justify the risks?</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>Does the research expose the participants or society to any unreasonable risks?</td>
<td></td>
</tr>
</tbody>
</table>
| Human ethics of protocol | Is the research therapeutic in design? Does the research protocol respect the human dignity of 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 the trial?  
Are the safety and rights of close contacts of the research participants adequately protected? |        |
| Animal ethics of protocol | Does the research protocol respect the animal dignity and welfare of animals used in the trial?                              |        |

### APPROVAL

<table>
<thead>
<tr>
<th>APPROPAL</th>
<th>YES/NO</th>
</tr>
</thead>
</table>
Public comment invited

Draft guidelines

Comment is invited on any aspect of the draft guidelines. If approved by the NHMRC after public consultation, the proposed guidelines will form the framework by which the preferred regulatory body and human research ethics committees will evaluate xenotransplantation research protocols. It is a requirement of the *NHMRC Act 1992* that before guidelines can be adopted, they must be subjected to public consultation. This involves providing well-developed draft guidelines for public comment so that the proposed regulatory framework is clear to the community and to stakeholders.

Advice on application of the guidelines

Comment is also invited on any aspect of the advice on application of the guidelines. In particular the working party wishes to learn if: (a) the advice is seen to be thorough and complete; and (b) whether it contains principles not truly covered in the broad guidelines and which therefore should be moved into the prescriptive guidelines. It is anticipated that an early task of the (proposed) national xenotransplantation committee will be to review and issue an updated version of this advice to researchers.
SUMMARY OF THE DISCUSSION PAPER
Summary of the discussion paper

Introduction

This public discussion paper has been prepared by the Xenotransplantation Working Party, which was set up by the National Health and Medical Research Council (NHMRC) to advise the NHMRC Council on xenotransplantation research in Australia and to prepare draft guidelines for the regulation of xenotransplantation clinical trials in Australia.

Xenotransplantation is the term used for the transplantation of cells, tissues or organs from one species to another (such as from pigs to humans). It was initially thought unlikely to succeed but recent advances in molecular biology and immunology have made it appear more feasible. Xenotransplantation has become a focus for transplantation research in recent years because there are not enough human organ donors to meet the demand and many patients who would benefit from a transplant wait in vain for donor organs to become available.

Nonhuman primates (apes and monkeys) are not considered a suitable source for human transplantation for safety reasons, in particular the potential for nonhuman primate retroviruses to cross the species barrier and infect humans. Researchers have therefore turned their attention to pigs as source animals. A major thrust of current research programs involves the genetic modification of donor pigs with some key human genes so as to reduce the powerful immune response that occurs when pig tissues are transplanted into human recipients. However, a pig retrovirus has recently been identified and there are concerns that it may also be able to cross the species barrier to humans, possibly causing a new zoonotic infection in humans.

While acknowledging that the ethical and safety issues associated with xenotransplantation require careful consideration, most other western countries have decided to proceed with research under agreed guidelines. The working party was of the opinion that the best option for Australia is to allow research to proceed under guidelines that take account of ethical issues, protect the interests of research participants, ensure that animal welfare concerns are met and safeguard public safety. Draft guidelines are presented here for public comment with a discussion paper outlining the issues considered by the working party in developing the draft guidelines.

What is xenotransplantation?

Xenotransplantation is the transplantation of living tissue from one species to another (eg from pigs to human beings). Organ xenotransplantation (eg heart, kidney) is the most well-known procedure but the term also covers transfer of tissues and cells (eg cells from the pancreas that produce insulin). It also covers procedures that occur outside the body in which cells or fluids from the patient are cultured with or perfused through animal cells and returned to the patient.

What does xenotransplantation research involve?

The draft guidelines have been prepared to assist animal and human research ethics committees to assess proposals for xenotransplantation research, particularly clinical
trials. The focus of the draft guidelines is research that is directly related to the provision of xenotransplantation as a human therapy. This includes:

- **animal-to-animal studies** (preclinical studies) — in which proposed xenotransplantation procedures are tested on animals (eg pig-to-baboon kidney transplants); and

- **animal-to-human trials** (clinical trials) — in which animal products are used for xenotransplantation procedures on human beings (eg pig-to-human brain cell transplants).

A distinction is traditionally made between **therapeutic clinical trials** (conducted with the intent of providing a direct benefit to the trial participants) and **nontherapeutic trials** (conducted in order to obtain knowledge rather than to be of any direct benefit to the participants). Only therapeutic clinical trials are considered in this discussion paper and in the draft guidelines, because nontherapeutic trials of xenotransplantation are neither ethical nor safe.

### Serving the common good

As for other areas of medical research, an overriding consideration for xenotransplantation research is that it should serve the common good. Thus, while there may be differences of opinion within the community about specific ethical, practical or safety aspects of the procedures involved, the approaches taken should have overall acceptability within a broad cross-section of the community. In particular, because of the potential risk to the general public if a new infection emerges, the Australian community should be involved in decision making about whether to proceed with clinical trials.

The aim of this discussion paper is to facilitate a vigorous public discussion on xenotransplantation research, including the ethical and safety issues associated with it. It is therefore desirable that this discussion paper should be widely circulated and discussed. The working party proposes to hold an extensive public consultation process including public meetings in some major centres, media publicity and opportunities for professional and community groups to present submissions to the working party in person.

Community and stakeholder comments on any aspect of the discussion paper and draft guidelines are encouraged and questions have been included at key points in the text of the discussion paper to help direct these comments. A list of these key areas for comment is also included at the end of this summary.

### Ethical issues inherent in xenotransplantation

The working party first considered whether there is anything inherently unethical or unacceptable about using animal organs, tissues and cells for transplantation to humans. Such an ethical discussion involves serious questions about what might be thought to violate respect for the dignity of human beings or the welfare of animals.

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2 While use of primates as donors for xenotransplantation into humans is regarded as unacceptable, primates may be used as recipients in animal-to-animal research.
In relation to potential failures in respect for human beings, concerns include crossing the species barrier, potential loss of identity of the human recipient and the possible lack of a proper relationship between the giver and the receiver of a xenotransplant. The working party concluded that these concerns could be met, so long as the xenotransplant does not impair the essential psychological or genetic identity of the person receiving the transplant.

In relation to potential failure in the protection of animal welfare, it has been suggested that it may be inherently wrong to use animals for purposes related to human health, domesticate and rear animals to obtain xenotransplantation products, or to genetically modify animals to provide suitable sources of xenotransplantation products. The working party concluded that these concerns could be met, so long as xenotransplantation protocols are humane to animals and respect the essential characteristics and welfare of their species.

The working party acknowledged that, as for many other issues relating to human identity and the use of animals, there is likely to be a range of views in the community relating to these issues. However, the working party concluded that there was no ‘in principle’ objection to xenotransplantation, so long as other efficacy, safety and practical ethical considerations can be met.

**Social significance**

The use of xenotransplantation products will inevitably lead to an increase in demand for transplant procedures. This has implications for health care funding and resource allocation. On the one hand, funds may be diverted away from other procedures, and on the other hand, cost-effective alternatives may ultimately be developed to replace procedures (such as kidney dialysis) that are currently both very expensive and debilitating. These issues are complex and are beyond the scope of this discussion paper.

Justice and equity issues may also arise because altruistic allotransplants are currently funded publicly, while xenotransplantation ‘products’ will be sold commercially as therapeutic goods. The NHMRC booklet on *Ethical Issues Raised by Allocation of Transplant Resources* (1997) discusses similar issues relating to allotransplantation. As these are not immediate issues, they have not been addressed in any detail in this discussion paper.

**Ethical conduct of xenotransplantation research**

On the assumption that inherent objections can be satisfactorily answered, the working party identified a number of key principles to form a framework for the ethical consideration of specific trial proposals.

As for other clinical trials, research applicants and sponsors for animal-to-human xenotransplantation trials will be required to provide a comprehensive submission for assessment by the relevant regulatory authority and the human research ethics committee at the institution(s) where the research will be carried out.

The involvement of human participants in xenotransplantation research will be required to comply with all relevant ethical, social and scientific considerations outlined in the NHMRC *National Statement on Ethical Conduct in Research Involving Humans*. The
principles for the use of animals in research are set out in the NHMRC *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes*.

A number of key principles were identified by the working party as being crucial to be met before animal-to-human xenotransplantation research is allowed to proceed:

- the research must serve the common good;
- the research must be scientifically sound;
- the research must be therapeutic in design;
- the research must be based on relevant efficacy data from preclinical studies;
- the benefits must justify any risks;
- the research should not expose the participants, their contacts or society to any unreasonable risks;
- the research must respect the dignity of participants;
- participants must give adequately informed and voluntary consent;
- arrangements for monitoring and follow-up must take account of the participants’ right to withdraw from the trial; and
- the safety and rights of close contacts of the participants must be protected.

The working party also identified the following principles of animal welfare that also need to be considered:

- the research must respect the welfare of animals used in the trial; and
- animals must only be used when it is essential to do so and in the smallest numbers possible.

To develop draft guidelines that are specific for xenotransplantation research, the working party grouped the above principles into four broad areas that research sponsors and investigators will be required to address in their submissions:

- efficacy (effectiveness);
- safety (for both the recipient and the broader community);
- human ethics of the research protocol (particularly the need to obtain consent from the research participant, the need to obtain the concurrence of immediate contacts and the need for the assent of the general public); and
- animal ethics of the research protocol (particularly with respect to animal welfare).

**Scientific and technical issues in xenotransplantation research**

Most researchers now consider pigs to be the most suitable source animals for transplantation products: the anatomy and physiology of pigs are similar to those of humans, pigs are domesticated and easy to breed, and they are suitable for genetic manipulation. Some other animals (eg rodents, fish) are being considered for some cellular and ex vivo procedures.
The major obstacles to successful xenotransplantation include anatomy and physiology (size, function, biochemistry etc) and immunology (rejection). Of these, the main obstacle to any organ or tissue transplantation, particularly any that depend on the establishment of a blood supply (ie a vascularised organ), is rejection. For allotransplants, this has been largely overcome by tissue matching of donors and recipients and immunosuppression of the recipient.

For xenotransplantation, the former strategy is not possible and the latter is not adequate to suppress the immune reactions that occur. These include a fast and powerful ‘hyperacute’ rejection (HAR), which occurs within minutes or hours of a vascular organ xenotransplant, and further reactions that occur within a few days, causing blood clotting and death of the transplanted organ.

The most promising approach to overcoming both the physiological and the immunological barriers to xenotransplantation is by inserting some key human genes into the donor pigs (that is, by genetic modification of the pigs), as well as treating the recipient with immunosuppressive or other drug therapy. However, there are potential problems associated with these approaches, including the risk of providing an environment in which animal viruses may be able to infect human transplant recipients, initiating a new infectious disease in humans.

Assessment of xenotransplantation research proposals

Will xenotransplantation work (efficacy)?

History

Between the 1960s and 1990s, a few nonhuman primate organs were transplanted into humans overseas. None of the trials were very successful and they were discontinued, mainly because at that time other alternatives (such as allotransplantation) were becoming available and appeared to provide much better outcomes.

There have been some trials of pig-to-human and mouse-to-human cellular transplants and ex vivo liver perfusion is currently being trialled overseas as a bridging procedure for people waiting for a liver transplant. To date, only one such trial has been carried out in Australia (ex vivo perfusion of a bioartificial liver device for three research participants).

Current research

Studies of pig-to-primate transplants of kidneys, hearts, lungs and livers have shown that organs from genetically modified pigs can survive longer than organs from unmodified pigs, but survival was generally measured in weeks or months. Further source animal genetic modification and use of immunosuppressant drugs is being investigated in animal-to-animal xenotransplantation studies.

Researchers are currently investigating whether isolated cells can be transplanted to treat certain metabolic, degenerative and genetic diseases, such as diabetes, Parkinson’s disease and Huntington’s disease. Cellular transplants do not have such severe rejection problems as vascularised organs. In rodents, diabetes has been successfully treated by transplanting pancreatic islet cells but this has not yet been successful in primates or large animal models. Nor has it been successful for approximately 12 participants who have
received fetal pig islet tissue to date. A few patients have been treated with pig brain cells to treat Parkinson’s disease, with mixed results.

Ex vivo liver perfusion has been developed to ‘buy time’ while potential transplant patients wait for a suitable donor. Initially, whole animals or whole organs were perfused (e.g., pigs and baboons) but bioreactors containing isolated liver cells are now being developed. Other ex vivo methods, such as skin culture for later grafting for burns, are also being developed.

Assessment of efficacy

In most circumstances, the initial evidence for efficacy will be based on relevant animal-to-animal studies, with pigs as the source animals and nonhuman primates as the recipients. Related experimental and animal-to-animal studies, as well as any previous animal-to-human trials, may also provide helpful information. The decision about what defines a successful animal-to-animal transplant will vary according to the type of, and indication for, transplantation (for example, whether it is intended as a permanent or ‘bridging’ procedure). However, in general terms, the transplant should have the capacity to provide physiologically relevant and/or life-sustaining support for some months.

Is xenotransplantation safe?

Xenotransplantation is unusual among medical procedures because it carries risks for the wider community as well as for the individual patient. The major concern for public health is that viruses from animal xenotransplantation products may infect human transplant recipients. Retroviruses or other unknown, probably latent, viruses are the chief concerns. Such viruses may initially show no obvious signs of disease and may spread beyond the recipient into the general population, giving rise to an epidemic that only becomes obvious when others have been infected. Therefore, in addition to risks for the xenorecipient, there are potential health risks for close contacts, carers and the general public. Such risks must be assessed and weighed against the potential benefits of xenotransplantation, and management options considered. This can be achieved within a framework of risk analysis (risk assessment, risk management and risk communication).

There have been many examples of cross-species transmission of infectious agents. In some cases, the disease profile and mode of transmission have altered in the new host (e.g., HIV/AIDS). Because of the close relationship between human and nonhuman primates, and the existence of known infectious agents, nonhuman primates are no longer considered as the source for animal-to-human transplants. Pigs are now considered to be the most suitable source animals for human xenotransplantation products.

A number of zoonotic infections have been transmitted from pigs to humans (e.g., Japanese encephalitis, influenza, and Menangle viruses) but it should be possible to control these infections by appropriate herd management and laboratory testing. Concern has centred on endogenous retroviruses, which usually remain latent in their host tissues but can sometimes be activated by an external stimulus. Pig endogenous retrovirus (PERV) has been shown to infect human cells in culture, creating concern that there is an unknown risk that this virus may be activated in xenotransplant recipients and cause clinical infection that could spread to others in the community.

Factors that may affect the risk of infection include source animal husbandry and how the xenotransplantation product is produced; the type of xenotransplant, its placement and
immunosuppression of the patient; and the infection control procedures used during and after the procedure. Further procedures for the management of infection risks include screening and monitoring of xenotransplant recipients and contacts for infectious agents, collection and storage of tissue samples and maintenance of a national register.

**Assessment of safety (risk analysis)**

A template for risk analysis is proposed that includes consideration of the type of procedure, the source animals and the possible infectious agents involved to ensure that any infectious disease risks associated with a proposal are minimised and can be identified and contained should they occur.

**Human ethics of xenotransplantation protocols (information sharing and consent)**

Before any research involving humans can begin, investigators must obtain the consent of research participants. Such consent must be voluntary and uncoerced, and informed.

Because any risks associated with infection will be borne by close contacts of the research participant (e.g., health care providers, family or sexual partners), these groups also need to be involved in information sharing and decision making about the proposed trial.

**Information sharing and consent of research participants**

Potential xenotransplant recipients may be seriously ill and vulnerable. Extreme care is therefore needed to ensure that investigators give research participants all the information about the trial that they need in order to make an informed decision. If there are no other viable medical options, strategies are needed so that the research participant is not coerced into taking part in the trial.

It has been suggested that xenotransplantation trial participants should be asked to consent to compulsory monitoring for the rest of their lives and to movement restrictions if an infection emerges. Such measures would mean waiving the currently accepted right of research participants to withdraw from a trial at any time, may not be practical to apply and should not be relied on as infection control measures (this also applies to close contacts; see below).

The working party concluded that investigators should provide sufficient evidence of safety that there is no undue risk to the community if some participants choose to leave the trial. Nevertheless, lifelong monitoring of recipients will be necessary in early trials in order to provide important infectious disease information for the future. Research protocols should therefore facilitate compliance of participants with lifelong monitoring and with proposed measures if an infection occurs. Having entered the trial, xenotransplant recipients also have an ethical and social responsibility to comply with such provisions.

**Information for contacts**

Close contacts of xenotransplant research participants might be exposed to infection if a novel infective agent emerges. All relevant information about the trial, including the risks for the transplant recipient and for contacts, should therefore be provided to all family contacts, sexual partners and carers, ideally in a collaborative process with the treating
doctor, investigator and independent counsellor. Investigators should collect signed information sheets from close contacts, indicating that they have seen the information.

Close contacts may also need to be screened before the trial and contacted and tested if an infection emerges at any stage in the future. (Similar considerations apply for long-term follow-up of contacts to those described for participants, above.)

**Assessment of information sharing and consent arrangements**

Based on the above considerations, the trial protocols will need to clearly indicate the procedures to be used for informing the potential research participants and their close contacts about the trial (including the long-term surveillance and monitoring requirements) and obtaining their informed and voluntary consent to all aspects of the trial that affect them.

**Animal ethics of xenotransplantation trial protocols (animal welfare)**

Research involving animals must comply with the NHMRC *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (1997) (the Code of Practice) and must be approved and overseen by an institutional animal ethics committee (AEC). Institutions involved in research with animals must have facilities that comply with the requirements of the Code of Practice, including appropriately trained staff with veterinary backup.

Preclinical studies on xenotransplantation will involve nonhuman primates — specifically baboons — as transplant recipients, and pigs as source animals. Pigs will be the source animals for most human trials, although other species may be involved for some cellular transplant procedures.

The genetic modification of source animals raises particular issues that must be considered on a case-by-case basis to ensure that the proposed modification does not alter the animal in a significant way (ie that the animals retain the essential characteristics and dignity of their species).

The Australian Quarantine and Inspection Service (AQIS) oversees the import or export of animal tissue to Australia. Animals used to supply xenotransplantation products must be healthy and reared under high standards of animal welfare, whether in Australia or overseas.

**Assessment of animal welfare**

Research applicants and sponsors will be required to submit information showing that all relevant animal welfare issues have been addressed in the trial protocol.

**Current regulatory controls**

**NHMRC oversight**

Under the *National Health and Medical Research Council Act 1992* (NHMRC Act), the NHMRC has responsibility for research involving humans through its Australian Health Ethics Committee (AHEC), which administers the *National Statement on Ethical Conduct in Research Involving Humans* (1999). Under this statement, all proposals involving
human research must be approved and monitored by an institutional human research ethics committee (HREC). The NHMRC is also responsible for animal research through its Animal Welfare Committee, which administers the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (1997). Under this code all proposals involving the use of animals in research and teaching must be approved and monitored by an institutional AEC.

**Therapeutic Goods Act**

All therapeutic goods (including medicines and devices) for marketing and routine use are registered or licensed under the Commonwealth *Therapeutic Goods Act 1989* and amendments (TG Act), which is administered by the Therapeutic Goods Administration (TGA). The legislation allows the supply of unregistered therapeutic goods for experimental studies and clinical trials under the supervision of the TGA and NHMRC (through an HREC). Two schemes are available, one involving an initial safety assessment by the TGA followed by further review of the trial and approval of the trial protocol by the HREC, and one in which all the assessment is carried out by the HREC without involvement of the TGA. The choice of scheme depends largely on whether the HREC has access to the necessary scientific and technical expertise to assess the proposal. As this is unlikely for xenotransplantation research, the NHMRC has established a scientific advisory committee to provide advice on scientific and technical issues involved in gene and related therapies.

Other schemes under the TG Act for the use of unapproved therapeutic goods include the Special Access Scheme, the Authorised Prescriber Scheme and the Personal Use Scheme. HRECs do not normally have a role in the approval of goods under these schemes, which are decided by the TGA on a case-by-case basis. The working party does not consider that these schemes would be appropriate for xenotransplantation clinical trials and recommends that they should not be used.

**Gene Technology Act**

Xenotransplantation research involving genetic modification of source animals falls within the scope of the Commonwealth *Gene Technology Act 2000* (GT Act) and GT Regulations 2001, administered by the Office of the Gene Technology Regulator (OGTR). Research involving genetically modified organisms (GMOs) requires approval and licensing under the legislation, based on scientific risk assessment and wide consultation. Under the GT Act, products derived or produced from a GMO are defined as GM products and are regulated by the agencies involved in their use (eg TGA for medical products) with advice from the OGTR.

A GM pig created by insertion of human genes into the pig genome is a GMO and will be regulated under the GT Act and Regulations. Xenotransplantation products used in animal recipients are monitored by the AEC at the institution where the research is carried out, taking account of relevant NHMRC guidelines for the use of animals with appropriate monitoring to ensure that any infections passed from donor to recipient animals are contained.

Xenotransplantation products produced from a GM source animal for use in human xenotransplantation may fall within the definition of GM products and would be monitored by AECs for animal-to-animal studies and regulated by the TGA under the TG
Act for animal-to-human trials. Under some circumstances, however, they may require further assessment by the OGTR. Pig-derived tissue for xenotransplantation that has not undergone genetic modification will not fall within the GT Act.

Other legislation

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

International developments

United Kingdom
The United Kingdom Xenotransplantation Interim Regulatory Authority regulates xenotransplantation, which may be acceptable if certain criteria are met. There is a national registry of electronic data on transplant recipients and related information. As at April 2002, there were no clinical trials of xenotransplantation in progress.

United States
The United States Food and Drug Administration and the Department of Health and Human Services regulate xenotransplantation through several committees. A national database is being developed but, at the time of writing, information was available only through local registries. Limited clinical trials in xenotransplantation are under way.

Canada
Health Canada regulates xenotransplantation through national standards. There is no registry of relevant data and there are no surveillance facilities. As at April 2002, no clinical trials had been approved.

New Zealand
The New Zealand Ministry of Health regulates xenotransplantation; requirements are the same as for any other clinical trial. A trial on xenotransplantation of encapsulated pig pancreatic islet cells for treatment of diabetes was not successful and applications for follow-up trials have been rejected because of concerns about pig endogenous retrovirus (PERV) transmission. There are no clinical trials currently in progress.

European Union (overall)
Some member states of the Council of Europe are preparing guidelines to regulate xenotransplantation; others are not. In 2000, the Working Party on Xenotransplantation prepared a draft report on xenotransplantation; the final report was expected at the end of 2001. The draft document calls for the development of European guidelines to harmonise existing laws and strengthen inadequate legislation. Spain, Belgium and Germany have clinical trials under way, proposed or suspended pending further investigation.

World Health Organization
In 1998, the Office of Zoonoses Prevention and Control released guidelines for the prevention and management of xenozoonoses. The guidelines deal with the assessment of
the risk of transmission of contagious diseases from animal tissues to human recipients, but do not address ethics, animal welfare and socioeconomics.

Options for regulation in Australia

The working party has proposed three models for regulating xenotransplantation research in Australia. Each model would need to be underpinned by some legislative changes.

Model 1 — extension of the existing regulatory framework

There would be no change to the current regulatory controls for animal-to-animal (preclinical) xenotransplantation studies. The Gene and Related Therapies Research Advisory Panel (GTRAP) would oversee animal-to-human (clinical) xenotransplantation trials, with local review and approval by the institutional HREC. GTRAP already has the necessary scientific expertise to assess xenotransplantation research proposals, but it would need some additional members with expertise in animal welfare and ethics and perhaps more community input.

At present, GTRAP provides advice to institutional HRECs, which themselves make the final decision on whether or not to approve research. Under the new model, institutional HRECs could not allow research to proceed if it was not approved by GTRAP. As AECs and HRECs would be jointly involved in approving research at their institutions, there would need to be cross-membership between these committees.

This model would draw on GTRAP’s experience and knowledge of the issues involved and its links with the NHMRC, TGA, OGTR, AHEC and HRECs. There would be no need for a separate advisory body, so the model would be cost-effective. GTRAP includes active xenotransplantation researchers, which could create potential conflicts of interest; however, this is likely to be the case with any xenotransplantation committee because there are few people in the field. The NHMRC has well-developed processes for dealing with such concerns.

Model 2 — formation of a national xenotransplantation committee

As for model 1, there would be no change to the current regulatory arrangements for animal-to-animal xenotransplantation studies. For animal-to-human (clinical) trials, a single national xenotransplantation committee established under the auspices of the NHMRC would approve and oversee all xenotransplantation research and development in Australia.

The committee would not have the necessary expertise in all aspects of xenotransplantation safety and efficacy, so it would need the assistance of an expert advisory panel. GTRAP would fill this role, but the final decision to approve or not approve a proposal would rest with the national xenotransplantation committee.

As for model 1, institutional HRECs would decide whether to allow the research to proceed at their institutions, but only if the research was approved by the national committee, and AECs and HRECs would be jointly involved in decisions about whether research could go ahead at the institutions they represent.
The new national committee would use GTRAP as an expert advisory body. Separating the final decision-making committee from the scientific advisory group should increase community confidence in the independence of the processes. However, there would be potential for delays and increased costs, because some work may be duplicated while proposals are being examined by GTRAP and the new national committee. The national committee would also require some scientific expertise, thus increasing the potential for duplication of resources and once again bringing up the issue of possible conflict of interest.

**Model 3 — TGA as the sole regulatory agency**

The working party gave brief consideration to the possibility that the entire process of assessment of xenotransplantation proposals should be handled by the Therapeutic Goods Administration. The working party does not see merit in this idea, but comments on this possibility are welcome.

**Legislation requirements**

Whichever model is ultimately chosen to regulate xenotransplantation research will need to be underpinned by legislation. This may involve changes to the *NHMRC Act 1992*, the *Therapeutic Goods Act Act 1989* and/or the *Gene Technology Act 2001*, or the development of specific legislation for xenotransplantation.
Public comment invited

The following questions have been raised in the text of the discussion paper to prompt public and stakeholder debate over the issues raised. Responses to these and any other issues are invited. In particular, the working party wishes to learn if: (a) the paper is seen to be thorough and complete; (b) whether any important ethical principles have been omitted; and (c) whether the representation of the regulatory and legal issues in Australia is accurate.

Public comment is particularly sought on the proposed regulatory models outlined in Chapter 11.

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<td></td>
<td>Expertise required to assess human trial protocols</td>
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DISCUSSION PAPER
1 Introduction

1.1 Background

Xenotransplantation is the term used for the transplantation of cells, tissues or organs between species (such as from pigs to humans), as distinct from allotransplantation, in which cells, tissues or organs are transplanted between members of the same species (for humans this is usually by an altruistic donation). Although allotransplantation can be a very successful way of treating a variety of human illnesses, very few human donor organs are available for transplantation compared to the demand. Many patients who would benefit from a transplant wait in vain for donor organs to become available. Transplant specialists have therefore turned their attention to animals as a possible source of organs and tissues for human transplantation.

Xenotransplantation was initially thought to be very unlikely to succeed, but recent advances in molecular biology and immunology have made it appear more feasible. Many transplant research groups are now trying to understand and overcome the formidable physiological and immunological problems involved. Meanwhile, further possibilities for tissue and cellular transplants are being added to the techniques under consideration.

The major advances in gene technology over the past decade have increased optimism amongst some researchers. They now believe that it may be possible to overcome the overwhelming innate immune response of human recipients enough to allow an animal transplant to establish. If this occurs, further molecular techniques, plus development of new immunosuppressive drugs, may allow longer-term acceptance and functioning of the transplant. Hence, a major thrust of current research programs involves the genetic modification of donor animals with some key human genes so as to prevent their tissues from being recognised as ‘foreign’ by the immune system of the human transplant recipients. This research has been accompanied by a range of ethical, social and scientific concerns that require careful consideration.

Although nonhuman primates (apes and monkeys) are the most closely related species to humans, use of their organs, tissues and cells for human transplantation is no longer considered to be an option, for safety reasons. Safety concerns arise because nonhuman primate retroviruses have the potential to cross the species barrier and infect humans as is thought to have occurred with human immunodeficiency virus (HIV). Researchers have therefore turned their attention to pigs as source animals. Several breakthroughs have already been achieved, using gene technology, that make success seem more likely. More recently, however, a pig retrovirus has been identified and there are concerns that it too may be able to cross the species barrier to humans, possibly causing a new zoonotic infection in humans.

3 The way in which donor animals are modified with human genes is described in Section 4.4.1.
4 In the context of a discussion of xenotransplantation, the working party decided it was sensible to use the straightforward distinction between ‘animals’ and ‘humans’ (even though it recognises that humans are animals); this distinction is therefore used throughout the rest of this document.
1.2 National Health and Medical Research Council response

By 1997, the ethical, social and scientific concerns surrounding research on animal-to-human transplantation led the National Health and Medical Research Council (NHMRC) Research Committee to establish an ad hoc scientific/technical working party to produce a detailed summary of the state of the science of xenotransplantation, particularly with respect to safety and efficacy. The Research Committee referred the report of this group to the NHMRC Australian Health Ethics Committee (AHEC) to provide advice on the ethical aspects of xenotransplantation.

By December 2000, the pressure for clinical trials of xenotransplantation had increased but there were general ethical concerns about the technologies per se, and more specific concerns had also emerged about pig retrovirus infection of human cells. On the advice of AHEC and the Research Committee, the NHMRC established the Xenotransplantation Working Party to provide advice and guidelines to Council. The working party, which first met in early 2001, draws members from the AHEC, the Research Committee and the Gene and Related Therapies Research Advisory Panel (GTRAP), the Animal Welfare Committee (AWC), the NHMRC Council and the Consumer Health Forum; it has been assisted by a technical writer. A full list of members is shown in Appendix 1.

The aim of this discussion paper is to facilitate public consultation on xenotransplantation research and related practices (see Section 1.3.2). It has been prepared primarily by the members of the working party and does not yet reflect any input from consultations or submissions.

1.3 Scope

1.3.1 Terms of reference

The NHMRC established the Working Party on Xenotransplantation with the following terms of reference.

The Xenotransplantation Working Party (XWP) will:
1. report to NHMRC through the Australian Health Ethics Committee and Research Committee;
2. provide advice to Council on the scientific, ethical and technical issues related to xenotransplantation research involving humans;
3. 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
4. undertake wide consultation in the preparation of guidelines.
1.3.2 Preparation of the public discussion paper

This public discussion paper has been prepared to facilitate community input into the issues that need to be addressed to provide advice to the NHMRC and to finalise the guidelines for human research ethics committees (HRECs) and animal ethics committees (AECs) on the assessment of xenotransplantation research proposals. The discussion paper has been prepared with the following specific aims:

- to inform the community about the present state of xenotransplantation research and clinical application in Australia and elsewhere;
- to stimulate debate and public contributions about xenotransplantation research, including the ethical concerns, potential benefits and risks associated with this innovative approach to a serious clinical problem;
- to describe the way that xenotransplantation research is currently regulated in Australia and present options for the future; and
- to provide a framework for guidelines on the assessment of xenotransplantation research proposals.

The working party was asked to consider issues arising both for humans and for animals that are involved in xenotransplantation research. The focus is on research rather than established clinical practice because the latter is still likely to be a long way in the future and because the same issues are likely to arise if any xenotransplantation procedures become established practice. Further, the discussion and guidelines focus on aspects of xenotransplantation research that are directly related to the provision of xenotransplantation as a therapy to replace or augment diseased cells, tissues or organs in humans. Basic research not directly related to clinical practice provides essential background information for the preclinical and clinical applications, but is outside the scope of this discussion paper.

1.3.3 Target audience

The discussion paper is intended to inform the Australian community about the issues relating to xenotransplantation, including the following groups:

- health professionals (particularly those involved in transplantation);
- transplantation researchers (experimental, preclinical and clinical);
- veterinary professionals (involved in animal husbandry and research);
- members of human and animal ethics committees;
- biotechnology companies/sponsors of transplantation research;
- the Commonwealth Department of Health and Ageing, including the Therapeutic Goods Administration, the Office of the Gene Technology Regulator and related agencies;
- the NHMRC;
- State and Territory health departments; and
- consumer organisations and the general public.
The discussion paper will be of considerable interest to the general community, particularly consumer health and animal welfare groups, as well as to Australia’s international partners.

With this large target audience in mind, the discussion paper has been written as simply as possible, while describing accurately the current state of scientific knowledge in this complex technical field.

1.3.4 Information gathering

The working party reviewed the international scientific literature relating to the scientific, ethical and technical aspects of xenotransplantation research involving humans, including risk assessment and risk management.

The information gathering process aimed to provide a thorough review of the acceptability of xenotransplantation per se, an overview of the current evidence for the efficacy and safety of the procedures involved, and an insight into the ethics of the research methods, including human information and consent arrangements and animal welfare issues.

Individual members compiled information on different aspects of the topic and submitted it to the full working party. The working party reviewed the information and assessed the issues raised. Current and possible future regulatory options were reviewed in a similar way.

1.4 Development of the draft guidelines

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

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

The working party wishes to consult widely with the general public and all stakeholders on the issue of xenotransplantation. It therefore invites submissions on this discussion paper as well as on the draft guidelines. Respondents are asked to structure their comments around the questions highlighted throughout the document and listed on page xlvii.

In addition to advertising for public submissions, the working party will:

- directly contact individuals and organisations expected to be interested in the subject and able to assist the working party in its deliberations;
- provide opportunities for selected respondents to speak to it about their submissions;
- hold public meetings in a range of locations (in both the eastern and western areas of the country);
- provide opportunities for media coverage of the discussion paper; and
- make other arrangements as appropriate for broader community consultation.

1.6 **Structure of the discussion paper**

To introduce the subject of xenotransplantation to the general community, Chapter 2 of the discussion paper explains what xenotransplantation is, why it is considered to be important and why it involves risks and ethical considerations over and above most other medical research undertaken.

In the subsequent chapters of the discussion paper, the ethical, efficacy and safety information reviewed by the committee is summarised, including:

- ethical issues relating to xenotransplantation (Chapter 3);
- the scientific basis of xenotransplantation (Chapter 4);
- the potential efficacy of the technologies (Chapter 5);
- safety concerns relating to infectious diseases, risk assessment and risk management issues (Chapter 6);
- consent (Chapter 7);
- animal welfare issues (Chapter 8);
- current regulatory mechanisms in Australia (Chapter 9);
- a review of international guidelines on xenotransplantation (Chapter 10); and
- proposed regulatory models (Chapter 11).

The draft guidelines, which have been developed based on issues raised in the discussion paper, are included on page xix.
PART 1
Ethical and scientific principles
2 Definitions and key issues

OVERVIEW

What is xenotransplantation?
Xenotransplantation is the transplantation of living tissue from one species to another (eg from pigs to human beings). Organ xenotransplantation (eg heart, kidney) is the most well-known proposed procedure but the term also covers transfer of tissues and cells (eg pancreatic islet cells that produce insulin). It also covers procedures that occur outside the body in which cells or fluids from the patient are cultured with or perfused through animal cells and returned to the patient.

Why consider xenotransplantation?
Despite efforts to increase the number of human organ donors, demand outstrips supply: many people on waiting lists die before an organ becomes available. There is also a shortfall of cell and tissue products and new knowledge is opening up new therapeutic avenues, further increasing demand. To overcome this shortage, changes have been proposed to the consent rules for donation and to procedures for organ collection. However, the proposed arrangements are either unacceptable and/or do not result in a substantial increase in donations. Living donor programs have boosted the supply of kidneys but extension of these programs to other organs (eg liver), carries risks for the donor, which may not be ethically acceptable. Other alternatives, such as artificial organs and other cell and genetic technologies are also progressing but will not provide clinical solutions in the near future.

Recent advances in molecular biology have made successful xenotransplantation more likely and xenotransplantation research is attracting increased attention and funding. Further diseases are also being considered for treatment. It is vital to consider the ethical, social and scientific implications of the technology so that guidelines can be adopted to inform decision making in this area.

What does xenotransplantation research involve?
One of the ultimate aims of this discussion paper is to develop guidelines to assist animal and human ethics committees to assess proposals for xenotransplantation research, particularly clinical trials. The focus of the proposed guidelines will be research that is directly related to the provision of xenotransplantation as a human therapy. This includes:

- animal-to-animal studies (preclinical studies) — in which proposed xenotransplantation procedures are tested on animals (eg pig-to-baboon kidney transplants); and
- animal-to-human trials (clinical trials) — in which animal products are used for xenotransplantation procedures on human beings (eg pig-to-human brain cell transplants).

A distinction is traditionally made between therapeutic clinical trials (conducted with the intent of providing a direct benefit to the trial participants) and nontherapeutic trials (conducted in order to obtain knowledge rather than to be of any direct benefit to the participants). Only therapeutic clinical trials are considered in this discussion paper, because nontherapeutic trials of xenotransplantation are neither ethical nor safe.

What are the key issues for consideration?
It is first necessary to consider whether there is anything inherently unethical or unacceptable about using animal organs, tissues and cells for transplantation to humans. These issues are discussed in Chapter 3 and the working party concluded that such inherent ethical objections can be satisfactorily answered. Secondly, it is important that any xenotransplantation research approved in Australia serves the common good and has broad public support. Once these considerations have been satisfactorily met, it is necessary to consider a framework of scientific and ethical principles within which specific procedures can be assessed. To this end, the working party identified four key areas: efficacy (effectiveness); safety (for both the transplant recipient and the broader community); practical human ethics (particularly the need to obtain consent from the research participant and to involve close contacts in decision making); and practical animal ethics (particularly with respect to animal welfare). These issues are discussed in detail in Chapters 5–8.
2.1 Definitions

2.1.1 What is xenotransplantation?

Organ and tissue transplants can be distinguished according to the source of the transplanted (relocated) material as follows:

- autotransplantation — transplantation (relocation) from and to the same individual (eg relocation of skin from the thigh to the arm to repair burn damage);

- allotransplantation — transplantation between individuals of the same species (normally between human beings matched by tissue typing); and

- xenotransplantation — transplantation between individuals of different species (eg from a pig to a human being).

2.1.2 What are the different forms of xenotransplantation?

Broadly understood, the term ‘human xenotransplantation’ refers to any procedure that involves the transplantation, implantation or infusion into a human recipient of cells, tissues or organs from a nonhuman animal source. In addition, the United States Food and Drug Administration (US FDA 2001) has distinguished two forms of xenotransplantation:

- any procedure that involves the transplantation, implantation or infusion into a human recipient of live cells, tissues or organs from a nonhuman animal source (called an ‘in vivo transplant’); and

- 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 (called an ‘ex vivo procedure’).

For the purposes of this discussion paper, the working party has further subdivided these two forms of transplant, as follows.

- In vivo transplantation:
  - organ transplants (eg heart, kidney, liver);
  - tissue transplants (eg skin);
  - cellular transplants
    - without a semipermeable capsule (eg fetal pig neural cells transplanted into the human brain for treatment of Parkinson’s disease); and
    - enclosed in a semipermeable capsule5 (eg encapsulated islets of Langerhans cells transplanted into the peritoneal cavity to treat diabetes).

- Ex vivo procedures:

5 A semipermeable capsule allows active molecules to pass through to the host while isolating the transplanted cells from the host blood circulation, thus reducing the risk of rejection and infection (see Section 5.3.1).
– perfusion of human body fluid through animal tissues or cells, which may or may not be separated by a semipermeable membrane (e.g., perfusion of human blood through a dialysis-like system containing animal liver cells, or perfusion of human blood through a whole pig liver); and

– growth of human cells on a feeder layer of animal cells for transplanting back to the same individual (e.g., growth of human skin or human stem cells on a mouse cell feeder layer).

This terminology will be used throughout the discussion paper because different considerations apply to the different types of procedures.

2.1.3 What are xenotransplantation products?

‘Xenotransplantation product’ is the term used to describe a live cell, tissue or organ that is used in xenotransplantation. The use of nonliving, inert (denatured and sterilised) tissues such as animal heart valves falls outside this definition; procedures involving these products have been used safely and effectively for over 20 years. The working party does not consider that the use of this type of tissue product represents transplantation, because the tissues are inert, and for all intents and purposes can be regarded as similar to mechanical products (such as artificial heart valves).

A major thrust in xenotransplantation research is concerned with genetic modification of the source animals (which is explained in Section 4.1). Thus, in many cases, xenotransplantation products will be obtained from genetically modified animals.

QUESTION

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

2.2 Why do we need to consider xenotransplantation?

2.2.1 Current research environment

Until a few years ago, most researchers considered xenotransplantation to be an attractive but unlikely solution to the shortage of donated organs for transplantation. However, recent scientific advances in genetic technology, immunology and other molecular and cellular techniques have made xenotransplantation much more feasible. In addition, an increasing range of conditions is now being considered for possible treatment using organs, tissues and cells, employing ex vivo as well as in vivo methods. Hence, xenotransplantation research is attracting increasing attention and funding throughout the developed world. It is therefore vital to consider the ethical, social and scientific implications of these new technologies before the demand for clinical trials becomes widespread. In this way, decision makers will have access to suitable guidelines and society will be prepared for further developments as they occur.
2.2.2 Burden of disease and demand for transplants

Demand for organs

Medical science has made important advances in successful allotransplantation of organs such as kidney, liver, heart and lung from human donors. Since its beginnings, solid organ transplantation has depended upon donation of organs from people who have died (known as cadaveric organs), most often as the result of an accident. However, as the use of transplantation has grown, the supply of organs has tended to diminish. Various means have been used around the world to increase donations, including changes to the legal definition of death, public awareness campaigns and, in some countries, a presumption of ‘opt in’ unless the person clearly indicated before they died that they did not wish to donate organs.

The lack of cadaveric organs has also led to the development of live donor programs (adult-to-child and adult-to-adult), often involving relatives but in some cases involving nonrelatives of the recipient. The first living donor programs were for kidney transplants, which posed little risk to the donor because the kidney is a duplicate organ. However, in recent times live donors have donated part of their liver, which is a much riskier procedure for the donor (see below).

Despite these developments, organ supply has not kept pace with demand. In Australia, as elsewhere, there are not enough donor organs available for transplantation. This is not just a minor shortfall that can be overcome by greater effort or funding; it is extreme and is increasing. Many people (children and adults) die whilst on waiting lists; others remain indefinitely unhealthy and debilitated for want of an organ or tissue. In the United States, as few as 5–10% of donor organs needed become available (Evans et al 1992, US FDA 1996). In Australia the supply of organs is lower than for most other western countries, with approximately 10 donors per million population per year, compared to 21 in the United States, 13 in the United Kingdom and 34 in Spain (which has an ‘opt in’ policy of presumed consent; see Section 2.2.3) (Australia and New Zealand Organ Donor Registry 2000). Table 2.1 shows recent supply and demand figures for Australia.

### Table 2.1 Organ transplants performed in Australia in 2000, and waiting list numbers in January 2001

<table>
<thead>
<tr>
<th>Transplants performed</th>
<th>Kidney</th>
<th>Heart</th>
<th>Liver</th>
<th>Pancreas</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadaver</td>
<td>350 (cadaver)</td>
<td>57 (plus 2 heart/lung)</td>
<td>149</td>
<td>26</td>
<td>90 (65 double/25 single)</td>
</tr>
<tr>
<td>Live donor</td>
<td>178 (live donor)</td>
<td>58</td>
<td>77</td>
<td>42</td>
<td>100</td>
</tr>
</tbody>
</table>

a Waiting list numbers are at a single time only; cumulative demand over the whole year is much higher. In addition, the numbers do not show people who are not selected to go on the waiting list (often because of an expectation that a suitable organ will not be available). On average, a patient can expect to wait 1–3 years for a donated kidney for transplant and 3–12 months for a donated heart; approximately 5% of kidney dialysis patients and 20–30% of potential liver and heart recipients die while waiting for a suitable transplant (NHMRC 1997ac).

b Total dialysis patients approximately 6000

Source: Australia and New Zealand Organ Donor Registry (www.anzdata.org.au/ANZOD/anzodwelcome.htm)

Approximately 500 kidney transplants are performed each year in Australia. However, the supply of cadaveric organs is diminishing and an increasing number of transplanted kidneys are from live donors (currently approximately 34% of all transplants). In contrast, the number of Australians requiring a kidney transplant has increased by approximately 10% per year over the past 10 years and this trend is projected to continue. In 1999, only
10.5% of patients on kidney dialysis between the ages of 15 and 59 received transplants. Thus, we are experiencing an increasing gap between kidney supply and demand, and this is reflected in the usual waiting time for a cadaveric transplant of 2–5 years. Given this situation, the importance of maximising the supply of organs and transplant survival times for those obtaining a transplant cannot be overstated.

Internationally, it has been estimated that the demand for organs in developed countries is growing at 15% per year. For example, in the United States records of the United Network for Organ Sharing show that in 1988 there were about 16,000 people registered on the national organ waiting list; in 1999 this had increased to about 77,000 (Herz 2001). Over the same period, the overall number of solid organ transplants declined by about 1% per year. Also, it is clear that, as waiting lists become too long, patients who might benefit from a transplant are not put on the list; consequently, official waiting list numbers are not a true reflection of the potential demand for transplants. The costs to society of these shortages of organs and tissues can be measured in mortality and morbidity of patients; in emotional, social and economic costs to their families; and in direct and indirect monetary costs to all, including the wider community. In many countries, social and cultural restrictions prevent organ donation from humans; in these countries, the need for an alternative organ source is even more acute. Research is proceeding to reduce or prevent diseases in the organs concerned, but this cannot be guaranteed to overcome the need for transplantation.

**Demand for tissue or cellular transplants**

Approximately 80,000 people in Australia (4 per 1000 population; 1 in 700 children) have type 1 (insulin-dependent) diabetes (ABS 1995). Recently, clinical pancreatic islet cell allotransplantation has become a successful and accepted treatment for type 1 diabetes. However, its use is currently restricted to a few dedicated research centres worldwide; islet allotransplantation is providing a solution to only a small fraction (< 1%) of diabetics who may benefit from the procedure. If the technical issues can be overcome, pig pancreatic islet cell xenotransplantation has the potential for widespread clinical application.

Similarly, Huntington’s chorea and Parkinson’s disease are both disabling degenerative diseases of the brain. In Australia, Parkinson’s disease occurs in approximately 1 in 1000 adults, rising to about 15 in 1000 in the elderly (Selby and Herkes 1996). Huntington’s disease occurs in approximately 4–10 per 100,000 population (Harper 1991). For both these diseases it has been hypothesised that transplantation of fetal pig neural cells into the brain could overcome the neurological deficits.

**Demand for ex vivo procedures**

Ex vivo procedures can be used as temporary measures until a suitable organ donor is found. For example, there has been considerable research on methods to provide external perfusion of a patient’s blood through liver cells (a similar concept to kidney dialysis machines), thereby maintaining life until either the patient recovers from an acute cause of liver failure or a suitable liver becomes available for transplant. The effectiveness of the current techniques is far from perfect but without them many patients awaiting liver transplantation will die before a suitable organ is found (Allen et al 2001).

People with very extensive burns could benefit from grafts of skin grown ex vivo over mouse fibroblasts.
2.2.3 Alternative sources of organs and tissues

Various alternatives have been suggested to overcome the shortage of human organs, tissues and cells available for transplantation. The options are outlined below.

Presumed consent

It has been argued that public policy should be changed to one in which consent to being an organ donor is presumed unless the deceased person has earlier made clear that he or she does not want to donate. This system is used in some countries overseas (eg Spain and Norway) and the number of organs available for transplantation has increased significantly in those countries (Australia and New Zealand Organ Donor Registry 2000; see Section 2.2.2). This option has been rejected in the United States, however, on the grounds that it is unethical.

In Australia, as in other countries, there are various obstacles that can prevent the recovery of organs and tissues from a person whose death has been determined by the brain function criterion, even if he or she has registered consent before death. For example, relatives may refuse to proceed with the donation or there may not be suitable surgical facilities available to remove the organs. A system of presumed consent, even if it were thought to be ethically acceptable by the Australian community, would not necessarily overcome these difficulties.

Hospital procedures

Policies and procedures in hospitals could be changed to overcome the obstacles preventing recovery of organs and tissues from a person whose death has been determined by the brain function criterion and who registered consent before death (see under Presumed consent, above). Improvements in this area may increase the number of available organs, but the shortfall of transplantable organs and tissues is currently so great that this option is unlikely to greatly reduce the length of waiting lists.

Payment for organs

Overseas, it has been suggested that the law should permit payment to those who agree to sell organs and tissues or to the families who consent to cadaveric donation (Caplan 1991, Wight 1991). But creating a market for human organs and tissue is considered to beethically unacceptable to most Australians and by national and international organisations that have reviewed this issue (NHMRC 1997b). However, the extreme shortage of organs for transplantation in the United States and elsewhere has prompted calls for the introduction of programs to support payment for kidneys from either living or cadaveric donors (Friedlaender 2002, Wyeth-Ayerst Pharmaceuticals 2002).

Donations by relatives

Another way of solving the organ shortage problem is for living donors, for example relatives, to donate an organ (where there is a dual system, ie lung or kidney) or part of an organ (ie half the liver to another adult or part of the liver to a child).

The donation of kidneys in this manner has become accepted practice, but the donation of half an adult liver is a recent procedure and is controversial because of the risks to donors from undergoing such major surgery. For adult-to-adult liver transplantation, the procedure puts the donor at serious risk of temporary or permanent liver failure, or even death. To date, there have been more than 1000 living donor transplants worldwide and at
least four deaths of adult donors have been reported (McCaughan and Lynch 2001). This situation clearly raises ethical issues, particularly in regard to obtaining truly informed and uncoerced consent in emotionally difficult situations (NHMRC 1997b).

### Artificial organs

Another proposal is to use mechanical or artificial organs. However, the production of safe and effective mechanical alternatives that can be used over a long term is probably some decades away. Currently, some mechanical devices are used as a short-term ‘bridging’ procedure for people waiting for an organ to become available.

### ‘Grow your own’ cells

Recent scientific work on the culture of human stem cells has raised hopes for future treatments to repair human organs and to treat a range of diseases. Stem cells are early, unspecialised cells that can, under certain conditions, be induced to mature into specialised cell types (e.g., heart, muscle, liver), which, it is hoped, will provide a source of human transplantation products (for both autotransplantation and allotransplantation). Although the field of ‘tissue engineering’ using stem cells is developing rapidly, there are still many hurdles that must be overcome before it will be possible to grow complex organs ‘in a test tube’. With our present state of knowledge, hopes for this technology should realistically be limited to techniques involving infusion of cells into the body (e.g., infusing stem cells into a diseased organ so that the new cells will grow and replace the damaged cells). In addition, the extraction of stem cells from human embryos is ethically controversial.

Moreover, stem cell technology cannot be regarded as an ‘alternative’ to xenotransplantation because current stem cell lines are grown on animal feeder layers and therefore come within the definition of xenotransplantation as ex vivo procedures (see Section 2.1.2).

**QUESTION**

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

### 2.2.4 Xenotransplantation

Because of the shortage of human organs and tissues for transplantation and the lack of another suitable alternative (at least in the short term), the use of animal organs and issues as transplantation products for humans has emerged as a potentially viable option.

As we continue to better understand and manage the body’s immune response to transplanted tissues, many scientists believe that successful xenotransplantation may be possible and that further research on this technology could lead to an increased supply of organs for transplantation.

Regardless of any of the issues discussed above, xenotransplantation poses a scientific challenge that, as for other areas of endeavour, scientists will want to pursue. It is therefore necessary for stakeholders and the community to discuss the issues involved and for government to develop a regulatory process.
2.3 What does xenotransplantation research involve?

As xenotransplantation is still an unproven technique, the impetus at this stage is for further research to find out if it can work and, if so, whether it is safe for use in humans. There are also broader ethical questions that need to be resolved, including whether one accepts, in principle, the use of animals in this way (see Section 2.4).

Researchers now believe that they know enough about the human immunological response to xenotransplants to design methods that might suppress this response sufficiently to allow animal organs or tissues to be accepted by humans and to function normally. This may involve some genetic manipulation of the source animals to suppress the immunological factors that would otherwise cause rejection. The research is still at a very early stage of development and a great deal still needs to be done before xenotransplantation can be considered as a routine therapeutic option (see Chapter 5).

Like all promising advances in medicine, xenotransplantation needs to undergo thorough preclinical studies and clinical trials to determine whether it works (ie its efficacy) and whether it is a safe procedure for use in humans. Throughout this discussion paper we refer to preclinical studies as ‘animal-to-animal studies’ and clinical trials as ‘animal-to-human trials’.

2.3.1 Animal-to-animal xenotransplantation studies

In this discussion paper the term ‘animal-to-animal study’ is used to describe preclinical animal research involving transplantation of cells, tissues or organs from one animal to another in order to determine the efficacy and safety of a proposed procedure in an animal model before proceeding to animal-to-human trials (clinical trials; see Section 2.3.2).

By analogy, for new drug research, extensive studies are done to test the pharmacology and toxicology of the substance, including acute, short-term and long-term effects. These studies use mainly small animals (mice, rats, rabbits, dogs) and some larger animals, including nonhuman primates. The studies use strict protocols that ensure the most useful results are obtained with due regard to animal welfare.

Similarly, for xenotransplantation, a range of research is needed using both small and large animal models. The goal is to obtain good information about what can be expected to happen in a human situation (eg by using nonhuman primates as organ recipients6).

All scientific research involving animals must follow protocols for study design that comply with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC 1997d) and be approved by animal ethics committees in the institutions involved (for further details see Chapter 9).

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6 While use of primates as donors for xenotransplantation into humans is regarded as unacceptable, primates may be used as recipients in animal-to-animal research.
2.3.2 Animal-to-human xenotransplantation trials

In this discussion paper the term ‘animal-to-human trial’ is used to describe clinical research involving transplantation of cells, tissues or organs from an animal to a human for the therapeutic benefit of the human to replace or augment diseased tissues (ie therapeutic clinical research).

Only one animal-to-human clinical trial of xenotransplantation has been carried out in Australia to date: a trial of an ex vivo liver perfusion method using a bioartificial liver (three participants). Some trials have been carried out overseas and some are currently in progress with regulatory approval in the United States and Europe. These trials involve cellular transplantation or ex vivo procedures; the working party is not aware of any trials being conducted on organ xenotransplantation anywhere in the world (see Section 5.5 for further details).

It is important to distinguish therapeutic and nontherapeutic clinical research, as follows:

- **therapeutic research** is research conducted with the intent of providing direct benefit to the participants; and
- **nontherapeutic research** is research conducted in order to obtain knowledge rather than to be of any direct benefit to the participants (although it may be).

Because of the potential risks involved, only therapeutic research is considered to be acceptable for animal-to-human xenotransplantation trials. When the animal-to-animal studies show that a xenotransplantation procedure is successful and safe when used in animal recipients, animal-to-human trials will be designed to test its use in humans.

The process of testing new therapeutic procedures through clinical trials may take many years and involve several phases. For new drugs, the first trials (phase I clinical trials) are to determine safety, pharmacological activity and dosage. For treatments with significant side effects, these trials are necessarily small and exploratory, usually involving only a few participants for whom there are no other therapeutic options and who, after being given all the necessary information, agree to take part in the trial. For other treatments, for which side effects are not an issue, phase I trials may be more extensive and include volunteer subjects.

If the phase I trials are successful, the next stage is to set up larger (phase II) trials, involving more subjects, to study efficacy and safety. These are followed by phase III trials, which are much larger still and are usually conducted as randomised placebo controlled trials in several clinical centres to determine clinical health benefit and the incidence of adverse reactions.

In the case of xenotransplantation, these conventional phases for clinical trials do not apply in the same way. Phase I trials in this case are likely to involve a very few participants for whom a definite therapeutic benefit should be expected. Such trials are not likely to provide a definitive answer with respect to infectious disease safety. If phase I trials are therapeutically successful, however, phase II trials will involve wider use of the protocol technology and phase III trials may include randomised comparisons with other procedures and a more detailed assessment of infectious disease safety. Clinical trials must follow strict protocols for study design, comply with the National Statement on Ethical Conduct in Research Involving Humans (NHMRC 1999) (referred to as the
‘National Statement’) and be approved by the human research ethics committees (HRECs) in the institutions involved (see Chapter 9).

**QUESTION**

*Is it agreed that animal-to-human xenotransplantation trials should be for therapeutic research only and not be undertaken for nontherapeutic purposes?*

### 2.3.3 Marketing approval and routine clinical practice

If all the clinical trials (phases I–III) confirm the efficacy and safety of a procedure, its sponsor may apply to the Therapeutic Goods Administration (TGA) for approval to market the product. The application must include all the experimental, animal and human data, which will be reviewed by the TGA before it approves the product for marketing and routine clinical practice. Similar considerations of efficacy, safety, consent and animal welfare will apply to such marketing approval as those presented in this discussion paper.

However, this document focuses on providing a framework for guidelines that will assist ethics committees to assess research proposals, rather than on routine clinical practice. This is because, considering the obstacles that remain to be overcome through animal-to-animal studies and animal-to-human trials, routine clinical practice is not likely to occur in the foreseeable future.

### 2.4 What are the key issues for consideration in xenotransplantation research?

#### 2.4.1 Serving the common good

**Ethical considerations**

Xenotransplantation raises a number of ethical issues that will be debated by the community as a whole. These issues are discussed in Chapter 3 and include consideration of inherent ethical and social issues relating to whether there is anything wrong in principle in obtaining organs and tissues from animals (that is, whether xenotransplantation is objectionable in itself, irrespective of any possible undesirable consequences, which might or might not be avoidable), concerns about respect for human life and concerns about the welfare and right to life of animals. It is unlikely that all members of the community will agree on these issues (as they do not for other issues concerning the use of animals by humans, such as for food or for medical research).

The aim of this discussion paper is to provide information about xenotransplantation so that an open and frank debate can be held among all relevant community and stakeholder groups, including the general public.

**Risk communication**

It has been suggested that if xenotransplantation research might put society at large at risk of an infection, there is an ethical obligation to inform society of that risk and to determine the conditions under which an informed society might be willing to assume that risk (Bach et al 1998, 2001).
However, it is equally held that we should not discard any potentially beneficial technology simply because there are perceived potential risks. As indicated in Chapter 6, there are processes to assess risk activities and develop risk management strategies. These are based on keeping risks below levels that are considered ‘acceptable’ by a broad consensus of scientific evidence and opinion. Acceptability is, in turn, related to the benefits of the activity, the distribution of those benefits, and the seriousness of the consequences of the adverse event, should it occur. Acceptable risk is determined by risk assessment, risk communication, stakeholder consultation and, ultimately, the political process.

Public opinion

In the past decade or so, there has been a shift in public attitudes towards some aspects of medical technology, particularly genetic modification, from general acceptance of new advances to some distrust. So far, there has been very little research to find out what the attitudes of the general public towards xenotransplantation really are.

In Australia, Mohacsi et al (1995, 1997) surveyed 1728 acute care nurses and 113 kidney dialysis patients and found that 61% of nurses ‘strongly disagreed’ with the question ‘Would you accept an organ from a species distant to humans (eg pig or sheep)?’ while only 42% of dialysis patients were willing to accept an animal organ. Arundell and McKenzie (1997) surveyed 277 patients awaiting cadaver transplantation (with a 65% response) and found that 74% were aware of xenotransplantation but only 4% considered xenotransplantation a first-choice therapy. Some 55% said they would accept a xenotransplant if human organs were not available, while 57% thought there could be specific risks associated with xenotransplantation.

More recently, Biotechnology Australia has surveyed the general public on their views about ‘the use of human genes in animals for growing organs’. This was carried out as part of a wider survey on biotechnology in general. The results are shown in Table 2.2.

Table 2.2 General population survey of attitudes towards ‘introducing human genes into animals to enable them to grow organs for transplant (such as pigs for human hearts)’

<table>
<thead>
<tr>
<th>Issue</th>
<th>Percentage of respondents who ‘definitely agree’ or ‘tend to agree’ (n = 1000)</th>
<th>1999</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>This is a useful application for society</td>
<td></td>
<td>70</td>
<td>67*</td>
</tr>
<tr>
<td>This is a risky application for society</td>
<td></td>
<td>66</td>
<td>75*</td>
</tr>
<tr>
<td>This application is morally acceptable</td>
<td></td>
<td>56</td>
<td>47*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage of respondents who are aware of the technology (n = 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you heard of this application?b</td>
</tr>
</tbody>
</table>

a Words in quotes are actual words used by the interviewer to introduce the topic.
b This question related to the use of gene technology (ie genetic modification of the animals) rather than to xenotransplantation per se.

* = statistically significant change since 1999


The results of the Biotechnology Australia survey showed a high awareness of the use of gene technology for xenotransplantation overall (86% in 2001), quite high (approximately 70%) acceptance of the usefulness of gene technology for this purpose, concerns about its risk in about the same proportion of people (approximately 70%) and no clear consensus
on moral acceptability (approximately 50%). From 1999 to 2001, there were a decline in acceptance of the usefulness of the technology, increased concerns about risk and a slight decline in moral acceptability.

Biotechnology Australia rated the issue of genetic modification of animals for xenotransplantation purposes as ‘emerging as a prominent issue amongst the Australian population’.

2.4.2 Other key issues

Some special issues in xenotransplantation research require consideration beyond the usual careful scrutiny given to other human research proposals. These are:

- the efficacy of the procedure and the stage at which it is appropriate to allow clinical research to go ahead (discussed in Chapter 5);
- the risks relating to the possibility of a new infectious disease emerging with potentially serious consequences for the wider community (discussed in Chapter 6);
- the human ethics of the research protocol relating to information provided to the transplant recipient and their immediate contacts (who may be in the front line for contracting an infection if it were to occur), and the consent or agreement to the procedures obtained from these groups, respectively (discussed in Chapter 7); and
- the animal ethics of the research protocol relating to the acquisition, care and use of animals (discussed in Chapter 8).

These important areas of concern form the basis for Part 2 of this discussion paper. To help determine where community support and concern lie in relation to this complex issue, respondents to the public consultation are invited to respond to each of these issues separately.
3 Is xenotransplantation acceptable? Ethical and social issues

OVERVIEW

The basis of ethical consideration of xenotransplantation
To provide a framework for discussing ethical and social aspects of xenotransplantation, the working party has considered the following issues:

- the ends — that is, the appropriateness of the goals of the research;
- the means — that is, the ethical issues that are inherent in xenotransplantation;
- the consequences — that is, the ethical issues raised by proposals to conduct clinical trials; and
- the social significance — that is, the wider social significance of xenotransplantation clinical trials.

Ethical issues inherent in xenotransplantation
An ethical discussion about animals as sources of transplantable organs and tissues — with the implication that, whatever the potential for human health, we perhaps ought not to do it — involves serious questions about what violates respect for the dignity of human beings and what violates the welfare of animals.

Respect for human beings
Three issues relating to proper respect for human beings are considered:

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

In reply, it is argued that these concerns can be met so long as the xenotransplant does not impair the essential psychological or genetic identity of the person receiving the transplant.

Animal welfare
Again, three issues are considered:

- Is it wrong to use animals for purposes related to human health?
- Is it wrong to domesticate and rear animals to obtain xenotransplantation products?
- Is it wrong to genetically modify animals to provide suitable xenotransplantation products?

In reply, it may be argued that these concerns can be met so long as xenotransplantation protocols are humane to animals and respect the essential characteristics and welfare of their species.

Ethical conduct of xenotransplantation research

Research involving humans
Clinical xenotransplantation research requires ethical, social and scientific consideration based on the NHMRC National Statement on Ethical Conduct in Research Involving Humans. This should include the value of the research to society, respect for human dignity, scientific integrity and benefits to the participants (therapeutic efficacy), safety for the participants and society as a whole, and consent by research participants. Other issues include the possible need for extended follow-up of research participants and contacts to track any novel infections that may emerge.

Research involving animals
The principles for the use of animals in research are set out in the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and include justification of the research, respect for animals, and consideration of their welfare. The genetic modification of animals raises ethical issues that will need to be considered on a case-by-case basis.

Social significance
The use of xenotransplantation products will inevitably lead to an increase in demand for transplants, which has implications for health care funding and resource allocation, possibly diverting funds away from other procedures. It also raises justice and equity issues, because altruistic allografts are currently funded publicly but xenotransplantation may initially only be commercially available. These issues are complex and beyond the scope of this discussion paper.
3.1 The basis for ethical consideration of xenotransplantation

Ethics is sometimes thought to be merely a matter of individual preference or cultural convention. Ethical decisions can certainly be very personal, and ethical judgments have complicated connections with cultural conventions, but this discussion proceeds on the assumption that ethics is a form of human inquiry in which it is possible to articulate reasoned and reasonable principles of conduct.

Ethics addresses the question of ‘How is it best for us to live, as individuals and as a society?’ For individuals, this can be described as a matter of personal ethics, for society as a matter of public policy. Although there is an overlap between these two topics, they raise different questions. Questions to do with public policy have wider ramifications than those to do with individual ethics and they may have implications for the kind of society Australia has become or wishes to become.

What is a satisfactory way of reasoning in ethics, whether about matters of personal values or matters of public policy? This is a matter of some debate among moral philosophers — some of whom emphasise attention to the likely consequences of any proposals and some of whom emphasise attention to some basic duties we have towards each other and towards animals. The approach adopted here is that adequate ethical and social consideration of xenotransplantation must include assessment of the following issues.

- **The ends** — that is, the goals of animal-to-human clinical trials of xenotransplantation (eg to discover new knowledge, to overcome a shortage of organs for transplantation, to develop new therapies — see Section 2.2);

- **The means** — that is, the ethical questions raised by the procedures to be undertaken (eg whether xenotransplantation violates respect for the dignity of human beings or the welfare of animals, whether consent can be truly informed and truly free and whether close contacts of the research participants should also be asked to consent);

- **The consequences** — that is, the ethical questions about the likely consequences of animal-to-human trials of xenotransplantation (eg the outcome for the participant, the risks, consent requirements and animal welfare issues); and

- **The social significance** — that is, the wider social significance of xenotransplantation, including questions about justice in the allocation of resources.

This chapter first outlines fundamental issues relating to the use of animal organs or tissues in humans in order to determine if there are any inherent objections to xenotransplantation research that might prevent any further consideration of the issue (see Section 3.2). It then considers the other issues outlined above (see Section 3.3).
QUESTION
Are there other important ethical issues that need to be considered in this debate about xenotransplantation?

3.2 What are the inherent ethical issues that relate to xenotransplantation?

The potential for xenotransplantation to save the lives or improve the health of people currently on waiting lists for organ donation or with presently incurable conditions such as Parkinson’s disease or diabetes is discussed in Chapters 2, 4 and 5. Further research may show that xenotransplantation can be done successfully, but the question of whether it should be done at all needs to be examined and resolved by the community. In other words, the community should ask whether xenotransplantation is objectionable in itself, irrespective of any possible desirable or undesirable consequences, the latter of which might or might not be avoidable (Caplan 1999).

An ethical discussion about using animals as sources of transplantable organs and tissues (with the implication that, whatever the potential for human health, we perhaps ought not to do it) involves questions about respect for the dignity of human beings and respect for the welfare of animals (Somerville 2000, Pontifical Academy for Life 2001). These arguments are set out briefly below and deserve careful consideration both by the researchers committed to the potential therapeutic benefits of xenotransplantation and by the community at large.

3.2.1 Respect for humans

Crossing the species barrier
Xenotransplantation ignores a deep-seated taboo in many human cultures against crossing the species barrier between animals and humans. This taboo was a common theme in ancient mythology, which is full of stories of strange hybrids of human beings and animals and warnings against bestiality (Fisher 1999). It is also said that in hybridising animals with human beings, xenotransplantation would violate the reverence and respect due to human beings (Kass 1997). Such a strongly felt and deep-seated taboo should not be dismissed as a worthless remnant of a primitive belief system.

In reply, it may be argued that, as long as xenotransplantation does not impair the essential psychological or genetic identity of the human being receiving the transplant (and as long as it can be shown to be safe as well as clinically efficacious), these concerns can be met (Pontifical Academy for Life 2001).

Identity of the recipient
It is said that xenotransplantation may confuse personal identity. Allotransplant recipients sometimes suffer psychological problems, including loss of identity, and fear that they might take on aspects of the donor’s personality, sexuality or other life experiences. Such feelings could be worse for xenotransplant recipients, who may feel they are somehow less human than before.

In reply, it may be argued that such ‘identity’ problems could be managed in the ways in which they are currently managed in allotransplantation programs (ie identified as
potential psychological consequences of the treatment and addressed as part of the process of obtaining genuinely informed and uncoerced consent).

**Lack of a proper relationship between giver and receiver**

It is said that organ transfer should not be thought of as the trading of consumable goods or even the exchange of community resources. Rather, it is argued, organ transfer should involve the kind of communality between giver and receiver that is implied in the notion of organ ‘donation’. That is, the donor deliberately decides to share his or her life with another (or the donor’s family deliberately decides that a deceased person would have wanted to share his or her life with others). On this view, to be morally acceptable, transplantation between one individual and another should be genuinely an altruistic gift or at least should involve some relationship of solidarity or community between the individual whose body is the source of the organ and the individual who is the recipient of the organ. This ‘shared life’ model of organ transfer implies that xenotransplantation is unacceptable because it cannot involve either genuine gift-giving or a relationship of compassion and solidarity between giver and receiver (Fisher 1999).

In reply, it may be argued that, although organ transfer between humans should be marked by the moral equivalence found in genuine gift-giving, this is not an ethical requisite of animal-to-human transplants. Rather, the relationship of human beings to animals ought to meet a different standard: the standard of humane stewardship for living creatures with their own essential animal characteristics, welfare and a capacity to suffer (Pontifical Academy for Life 2001).

### 3.2.2 Respect for animals

It is sometimes said that killing animals in order to use their organs and tissues for transplantation into human beings is morally unacceptable. There are several aspects to this argument, which are discussed below.

**Speciesism**

One argument relies on the idea that there is a moral equivalence between at least some animals (those who are self-conscious, such as primates) and human beings because they possess the same cognitive attributes. Treating animals as resources for humans involves the morally objectionable prejudice of speciesism (Singer 1999). A different version of this argument does not assert such moral equivalence, but still claims that higher animals are creatures of moral worth, that they have some moral standing, and that therefore they ought not to be treated merely as means to human ends (Clark 1997).

In reply, it may be said that though human beings and animals have much in common, including sensory awareness and the capacity to feel pain, there are morally significant differences between human beings and animals, in particular the human capacity for practical judgment and choice. Any argument that minimises these differences is untrue to both the human and animal ways of life (Tobin 2001).

**Animals treated as mere human property**

It is argued that it would be morally unacceptable to use animal organs and tissues even if it were possible to avoid actually killing animals in future transplantation programs. Proponents of this viewpoint say that for at least some animals, the conditions for
domestication and rearing needed to ensure that their organs or tissues are fit for human transplantation do not respect the essential characteristics or welfare of the animal species. Rather, the process treats animals as human property, ignoring their capacity to live their lives as they prefer (Clarke 1997).

In reply, it may be said that the conditions in which animals will need to be reared to be suitable for transplantation need not constitute an abuse of animals; rather, people should treat animals humanely (eg not cause them unnecessary pain and discomfort) and reasonably (eg not waste them or otherwise harm them). Just as it is possible to rear and kill animals for human consumption in humane and reasonable ways, so it should be possible to rear and kill animals for xenotransplantation in humane and reasonable ways. Animal ethics committees (AECs) regularly consider such issues for a variety of research proposals. Furthermore, for many years the community has utilised processed animal products such as pig heart valves and pig insulin.

**Genetic modification of animals**

To overcome the significant problems of rejection that occur with cross-species transplantation of organs or tissues, much current research is aimed at genetically modifying animals (eg pigs) with human genes so that their organs and tissues are not rejected by a human body (see Section 4.4 for an explanation of how human genes are used in this process). This may be thought to be contrary to respect for the essential characteristics and dignity of the animal species concerned as it treats animals as (re)designable systems for human use. Some people have also expressed concerns about the implications of genetic modification on animals, because it interferes with the natural processes of reproduction and evolution. A pig that is modified with human genes to minimise rejection by the human immune system may be just like any other pig, but this cannot be assumed.

In reply, it can be said that genetic modification of animals is not a new technique specific for xenotransplantation but has been used as an important tool in scientific research and animal husbandry for over 20 years (see Section 4.1.1). As a general rule, if the genetic manipulation does not inflict any unnecessary suffering upon the modified animal or interfere with its ability to lead a normal life, such modification has been considered to be acceptable.

In response to the issue of ‘naturalness’, the consensus reached by several overseas reviews (eg United States, United Kingdom, Canada, the Organisation for Economic Co-operation and Development) is that the insertion of human genes (consisting of minute amounts of DNA) into a pig chromosome does not significantly change the essential characteristics or welfare of the pig. However, it is agreed that this position may need ongoing monitoring and review, depending on the extent of the genetic manipulation that is required.

**QUESTION**

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

### 3.3 Ethical conduct of xenotransplantation research

If the inherent ethical objections to xenotransplantation outlined in Section 3.2 can be adequately answered, it is then necessary to consider the practical ethical issues
associated with the conduct of xenotransplantation research. These issues can broadly be classified as those that relate to human beings (the ethical conduct of animal-to-human trials) and those that relate to animals (the ethical conduct of animal-to-animal studies and the care and welfare of source animals for clinical trials).

3.3.1 Research involving humans

Established ethical principles for human research

There is now a well-established and widely accepted set of ethical principles for determining whether a proposal to conduct a clinical trial of a new procedure on human beings is ethically acceptable. In Australia, the most authoritative account of these principles is given in the National Statement on Ethical Conduct in Research Involving Humans (National Statement; NHMRC 1999).

The National Statement sets out four groups of basic principles to guide ethical decisions relating to human participation in clinical trials:

- integrity, respect for persons, beneficence and justice;
- research merit and safety;
- consent; and
- ethical review and conduct of research.

These principles are described in detail in the National Statement.

Under the current arrangements for clinical research (see Section 9.3), research projects involving humans must be reviewed by the human research ethics committee (HREC) in the institution where the research will take place and the review must follow the guidelines and processes described in the National Statement.

Much of the decision making of HRECs depends on weighing up the benefits to the research participants (or to the community as a whole) against the risks of a particular protocol. Many novel protocols are reviewed. Xenotransplantation presents some particular challenges: each proposal will require HREC scrutiny before the proposed research is approved.

Researchers are required to suspend or modify their research if the risks to participants are found to be disproportionate to the benefits. The results of the research (however funded) must also be made available to allow public scrutiny and contribute to public knowledge.

Principles for the ethical conduct of xenotransplantation research involving humans

When applied to xenotransplantation, the established ethical principles described above indicate that, given the current state of our knowledge and expertise, very serious ethical, social and scientific consideration is needed before an animal-to-human trial in xenotransplantation can be approved in Australia.

In addition, two groups of people can be distinguished whose rights and needs may be affected in xenotransplantation research involving humans:

- individual xenotransplantation recipients; and
• the wider community (particularly carers and close contacts of xenotransplantation recipients), who may be affected by an infection should one arise as a result of using animal organs or tissues.

The National Statement defines research participants broadly to include those who are the principle focus of the research and also those upon whom the research has an impact. However, the working party considered that, while close contacts should be given careful consideration in any research protocol for xenotransplantation, it is not helpful to consider them as research participants per se (see Section 7.1).

Based on these considerations and the factors already described in Chapter 2, the working party identified the following important principles that need to be met before xenotransplantation research involving humans is allowed to proceed.

• The research must serve the common good (see Chapter 2).
• The research must be scientifically sound, and based on previous preclinical studies (see Chapters 4 and 5).
• The research must be therapeutic in design (see Section 2.3.2 and Chapter 5).
• The benefits must justify any risks (see Chapters 5 and 6).
• The research should not expose the participant, their close contacts or society to any unreasonable risks (see Chapter 6).
• The research must respect the dignity of participants (see Chapter 7).
• Research participants must give adequately informed and voluntary consent (see Chapter 7).

The working party identified two additional factors that are unique to xenotransplantation research and that need careful consideration.

• Research participants may need to be closely monitored for many years in case of infection. That is, there may need to be more emphasis on keeping participants in a trial than would normally be the case (see Chapter 7).
• The safety and rights of close contacts of the research participant must be protected. The assent of close contacts may therefore be required so that they can be screened before the trial and further monitored if a research participant develops an infection (see Chapter 7).

### 3.3.2 Research involving animals

Established ethical principles for animal research

The principles for the humane use of animals for scientific purposes are set out in the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (Animal Research Code, NHMRC 1997d). The code covers all aspects of the care, use of and interaction with animals for scientific purposes, with emphasis on the following principles:
• The research must be justified in terms of establishing information relevant to the understanding of humans or animals, and after weighing the potential effects on the welfare of the animals.

• Researchers must treat animals with respect and consider their welfare as an essential factor when planning and conducting experiments.

• Animals must be used only when it is essential to do so and in the smallest numbers possible.

• Procedures must minimise the impact on the animals.

Protocols for all experiments with animals must be referred to institutional AECs for approval. Much of the decision making of AECs depends on weighing up the benefits (to animals or humans) and the risks (to experimental animals) of a particular protocol. AECs review many completely novel protocols. Xenotransplantation presents some particular challenges; each proposal will require AEC scrutiny before the proposed research is approved.

**Principles for the ethical conduct of xenotransplantation research involving animals**

Based on these considerations and the factors already described in Chapter 2, the working party identified the following important principles that need to be met before xenotransplantation research involving animals is allowed to proceed.

• The research must serve the common good (see Chapter 2).

• The research must respect the welfare of animals used (see Chapter 8).

• The research must be scientifically sound (see Chapters 4 and 5).

• The benefits for humans must justify the use of animals (see Chapter 5).

In addition, as discussed in Section 3.2.2, the genetic modification of animals for use as the source of xenotransplantation products raises ethical issues. However, AECs already have guidelines for genetic modification and appropriate animal welfare in respect of other research and treat each proposal on a case-by-case basis. As long as the degree or type of modification does not interfere significantly with the overall characteristics of the animal species, it is not considered ethically unaccetable.

### 3.4 Social significance

#### 3.4.1 Allocation of resources/funding

Increasing the supply of organs and tissues for transplantation by the use of xenotransplantation products will inevitably lead to an increase in demand for such products. This has funding implications for the health care system as well as resource allocation implications for the initial research and subsequent health care.

Xenotransplantation research may be very costly and there is a possibility that investment in it may divert research funds away from other approaches to organ failure and also from other important health problems. However, the costs involved in
transplant procedures themselves, once they are established in clinical practice, vary a great deal depending on the type of transplant. Some transplant procedures, such as heart and liver, are specialised and relatively costly but others, such as kidney transplants, are less costly than maintaining a patient on hospital-based dialysis (in addition to the non-financial benefits of improvements to health and lifestyle and returning the recipient to a productive lifestyle).

At this early stage in the development of xenotransplantation, we cannot predict all the costs that may be involved for ongoing supervision and treatment of xenotransplantation recipients. Ideally, the costs of ongoing treatment and care will eventually be matched by the savings made in restoring recipients to healthy and productive lives, but it is too early to know whether this hope will be realised.

### 3.4.2 Justice

Some of the social implications of integrating xenotransplantation into the Australian health care system have already been mentioned. Other social implications also need consideration, in particular difficult issues to do with justice in the allocation of health care resources. The technology holds out great promise, but initially it may only be used for a relatively few people at a great cost. These hard questions ought not to be ignored in this context.

If xenotransplantation proves to be feasible, the necessary clinical development of the technologies will probably be carried out with the support of biotechnology companies, and xenotransplantation may initially only be available to those who are able to pay a relatively high cost. The health care system may thus be faced with the choice of offering altruistic allotransplantation, which is funded in Australia through the public health care system, or privately developed xenotransplantation products. Whether the two forms of treatment will have relative advantages or disadvantages for any particular condition remains to be determined.

These issues are complex and are beyond the scope of this discussion paper.

The NHMRC booklets *Donating Organs after Death: Ethical Issues* (NHMRC 1997a) and *Ethical Issues Raised by Allocation of Transplant Resources* (NHMRC 1997c) discuss similar social and resource allocation issues in relation to allotransplantation.

**QUESTION**

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

Scientific and technical issues

OVERVIEW

Since the 1960s, there have been a few trials of clinical xenotransplantation overseas, including organs (e.g. heart, kidney), cells (e.g. pancreas, brain) and ex vivo procedures (e.g. liver perfusion). These trials showed that for vascularised organs the major obstacles to successful xenotransplantation are anatomy and physiology (size, function, biochemistry) and immunology (rejection).

Source animals

Two main groups of animals have been used as the source of xenotransplantation products: nonhuman primates (e.g. baboons, chimpanzees) and pigs. However, the use of nonhuman primates has been discontinued in most countries because of concerns about the potential for spread of infection. Most researchers now consider pigs to be the most suitable source animals for transplantation products: the anatomy and physiology of pigs are similar to those of humans, pigs are domesticated and easy to breed, and they are suitable for genetic manipulation. Some other animals (e.g. rodents, fish) are being considered for some cellular and ex vivo procedures.

Anatomical and physiological barriers to xenotransplantation

Obstacles to xenotransplantation include anatomical problems (e.g. structural issues such as the size and growth rate of the animal organs) and physiological problems (e.g. biochemical, pharmacological and endocrinological factors that may influence transplanted animal organs, tissues or cells). Such obstacles are likely to be more serious for organs with a complex metabolic function, such as the liver, than for a largely mechanical organ like the heart.

Immunological barriers to xenotransplantation

The main obstacle to any organ or tissue transplantation, particularly those that depend on the establishment of a blood supply (i.e. a vascularised organ), is rejection. For allotransplants, this has been largely overcome using two strategies: tissue matching of donors and recipients; and immunosuppression of the recipient.

For xenotransplantation, the former strategy is not possible and the latter is not adequate to suppress the immune reactions that form the natural early defence against infection and other foreign materials. The reaction includes a fast and powerful ‘hyperacute’ rejection (HAR), which occurs within minutes or hours of a vascular organ xenotransplant, causing blood clotting and death of the transplant. If the transplant survives HAR, another acute antibody-mediated reaction may occur within a few days, with coagulation of white blood cells, further clotting and death of the transplant (this is called delayed xenotransplant rejection, or DXR).

HAR and DXR, which are mediated largely by the innate immune system, do not usually occur for allotransplants, in which rejection is caused by an acquired T-lymphocyte response stimulated by minor immune differences between the donor and recipient histocompatibility antigens. However, this reaction can be successfully controlled by immunosuppressive drugs. Little is known about T-cell rejection of xenotransplants because few transplants have survived HAR and/or DXR. However, it appears that a range of immune incompatibilities will stimulate a powerful T-cell mediated response that may not be suppressed by current drug therapies.

Solutions

Researchers predict that the best chance of successful xenotransplantation will occur by genetically modifying the source animal as well as treating the recipient with immunosuppressive or other drug therapy. Genetic modification of source animals by inserting some key human genes to help to make xenotransplants behave more like allotransplants is currently the most promising approach to overcoming the biochemical, endocrinological and immunological barriers to xenotransplantation. However, there are potential problems associated with these approaches, including the risk of providing an environment in which animal viruses may adapt to human conditions.
4.1 Introduction

Researchers in the field of transplantation believe that animal organs, tissues and cells will eventually be successfully transplanted into humans. However, obstacles remain in at least two major areas: anatomy and physiology (compatibility in terms of size, function, growth, ageing, biochemistry and so on) and immunology (rejection reactions). This section summarises the technical issues relating to these challenges and describes progress in overcoming them for the various types of xenotransplantation procedures defined in Section 2.1.2. Chapter 5 further discusses the current state of research for the different procedures and the prospects for success (efficacy).

4.1.1 Procedures

As described in Section 2.1.2, xenotransplantation covers a range of procedures, from transplantation of vascularised organs (those that require a blood supply) such as a kidney or heart, to cellular transplants such as pancreatic islet cells or brain cells, and ex vivo (external) procedures such as blood perfusion through animal liver cells.

Since the 1960s, there have been several animal-to-human trials of xenotransplantation overseas, including vascularised organ transplants, cellular transplants and ex vivo procedures. Primate kidneys, hearts and livers, and a pig heart, pig neurones and pig pancreatic islet cells have all been transplanted into humans; ex vivo perfusion of pig livers in acute liver failure is currently under clinical trial in several centres in the United States and Europe. Chapter 5 gives further details of these trials and the current progress being made for each of these procedures.

4.1.2 Source animals

Some earlier trials used nonhuman primates (eg baboons, chimpanzees) as source animals for xenotransplantation products for humans. However, considerable concern has been expressed about the use of these species because of the high risk of transmission of infection (see Chapter 6 for further details on infectious disease risks).

Regulatory authorities around the world have taken different approaches to this issue. The United Kingdom has banned the use of nonhuman primates as source animals (UK DHAGEX 1997). The United States has not banned the use of nonhuman primates per se, but has required researchers and sponsors to show that the procedure is safe (ie does not have infectious disease risks). This essentially precludes the use of nonhuman primates as source animals because of the transmissibility of baboon endogenous retrovirus (Patterson 1998, US DHHS 2001).

Researchers, the biotechnology industry (sponsors) and the wider community generally agree that nonhuman primates are not a suitable source of xenotransplantation products for any of the proposed therapies (organs, tissues or cells; in vivo or ex vivo). Currently, both researchers and ethicists consider pigs to be the most likely and appropriate source of organs and tissues for xenotransplantation. The anatomy and physiology of pigs are very similar to those of humans; pigs are domesticated animals that are easy to breed; and, importantly, pigs are suitable for genetic manipulation (Figure 4.1). Nevertheless, researchers are considering the use of other species for cellular transplants (including pigs, cattle, fish and mice).
Genetic modification of source animals

Genetic modification of animals was initially developed and perfected in laboratory mice. Since the 1980s, hundreds of different genes have been introduced into various mouse strains for research on gene regulation, tumour development, immunity, disease processes, development, ageing etc.

The most common method of producing genetically modified (GM) animals is to microinject a purified sample of the donor DNA into the male genetic material (pronucleus) in a fertilised egg before it fuses with the female pronucleus. If successful, the injected DNA integrates into the genome of the embryo that is formed when the male and female pronuclei fuse. Offspring that show the required genetic trait can be further crossbred to produce a purebred GM strain.

The human genetic material used to produce GM pigs is identified from a ‘library’ of sequences produced by systematically fragmenting human DNA molecules and artificially copying (cloning) the fragments required (based on information obtained from genetic mapping techniques, including the Human Genome Project).

4.2 Anatomical and physiological barriers to xenotransplantation

Transplanting organs, tissues or cells between species presents some physiological and anatomical problems that affect the choice of animal species. An obvious example is the size of the source animal’s organs in comparison to those of the recipient. Other problems may include:

- the orientation of the organ in the human recipient compared to the donor (eg vertical orientation of the pig heart in humans versus a horizontal orientation in pigs);
- the growth rate of the transplanted organ in humans (eg if transplanted into a child);
- and
- the life expectancy of the donor animal compared with human life expectancy (ie will the organ survive for the rest of the life of the human or need to be replaced at a later stage).
Another problem may arise if the recipient’s red blood cells are larger than the small blood vessels (capillaries) of the source animal; this mismatch will prevent the transplanted organ from developing a successful blood supply.

There may be other biochemical, pharmacological or endocrinological problems if functional molecules in the xenotransplantation product are mismatched with receptors in the recipient or vice versa. For example, kidneys produce a substance called erythropoietin (EPO), which is a hormone that regulates the production of red blood cells. People with kidney failure therefore become anaemic and need to be treated with human EPO. Pig EPO (produced by pig kidneys) is not recognised by the human receptor (Zaidi et al 1998), however, and therefore kidney xenotransplant recipients will need to continue treatment with human EPO.

Despite these issues, which are the subject of current research, there appear to be no insurmountable physiological barriers to the use of pig hearts and kidneys, or a range of cellular products. Life-preserving pig heart and kidney transplants have been performed in baboons without obvious major physiological incompatibility (see Section 5.2.2). However, further clinical trials are needed to determine if other problems are likely to arise in humans.

The obstacles to xenotransplantation of the liver are potentially much greater. The heart and kidneys are relatively simple mechanical organs that make and respond to a fairly narrow range of simple chemicals common to all relevant species, but the liver is far more complex and produces and responds to many complex substances. This raises the number and complexity of potential ligand–receptor incompatibilities to possibly insurmountable levels. However, perfusion of blood through a pig liver or an ex vivo device containing liver cells (bioartificial liver) can provide adequate temporary support in liver failure.

Fewer physiological issues are expected in the case of tissue or cellular transplants, because the molecular interactions are less complex and it is hoped that problems can be overcome by genetic modification of the donor animal.

4.3 Immunological barriers (rejection)

4.3.1 Immune response to transplants

The main obstacle to any organ or tissue transplantation (whether it is an allotransplant or xenotransplant) is rejection of the transplanted organ or tissue by the immune system of the recipient. This is because the immune system of all animals, including humans, has evolved to distinguish ‘self’ from ‘nonself’ and to eliminate ‘foreign’ molecules or organisms that enter the body. This system, mediated by white blood cells (T cells, B cells, macrophages, monocytes etc)\(^7\) and blood plasma proteins (antibodies, complement), is extremely effective for preventing infection by microorganisms and eliminating other foreign material that enters the body but makes it difficult to transplant

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\(^7\) The components of the immune system discussed here (T cells, B cells, complement, natural killer cells, major histocompatibility complex and so on) are all defined in the Glossary.
organ, cells or tissues from one person or animal species to another without them being rejected. In simple terms, the immune response of mammals has two components.

- **Innate response** — this is the rapid, first line of defence against many common infectious microorganisms and other foreign material, such as xenotransplants. It involves naturally occurring or preformed antibodies (T-cell independent B-cell responses), complement, the thrombotic (clotting) system, natural killer (NK) cells and phagocytic cells such as macrophages that literally engulf the foreign material and neutralise it with secretions.

- **Adaptive or acquired response** — this response is initiated more slowly than the innate response but ultimately gives rise to long-term immunity. It involves the production of antibodies that are tailored to neutralise specific foreign molecules (antigens) on invading microorganisms or other materials. It has two components: antibody-mediated (or humoral) immunity (involving T cells and B cells) and cell-mediated immunity (involving T cells only).

The immunological barriers to xenotransplants differ from those to allotransplants because of the greater molecular difference between the donor and transplant recipient tissues. This causes a much greater response by the innate immune system than occurs for allotransplantation. This fundamental difference increases the speed and intensity of the rejection response and is a major reason why xenotransplantation is not a current clinical reality.

For allotransplants (human-to-human transplants), the innate immune response is not stimulated very much and the main barrier to success is the acquired response, which responds to minor differences in the major histocompatibility complex (MHC) antigens between the matched donor and recipient. In this case, direct recognition of these differences by recipient T cells causes a predominantly cell-mediated response. With care and experience, however, this response can be suppressed sufficiently to prevent rejection but not so completely that the transplant recipient is overwhelmed by infection. We have no discriminatory capacity to deal with innate immunity, which is an essential early defence against infection and the main barrier to xenotransplantation. The main features of the rejection response to allotransplants and xenotransplantation are shown in Table 4.1.

It is impossible to overcome the powerful innate response to xenotransplants with current immunosuppressive drugs. Attention has therefore turned to a new approach in which the source animal is genetically modified to create better compatibility between the donor and recipient tissues. GM pigs expressing human immune regulatory genes have already been generated and a number of further modifications to minimise the degree of molecular incompatibility are proposed (see Section 4.4). It is hoped that this approach, combined with the development of improved immunosuppressant drugs to overcome the acquired response, may allow xenotransplants to establish as successfully as allotransplants.
Table 4.1  Comparison of immune responses to a matched human allotransplant and pig xenotransplant (vascularised organ transplant)

<table>
<thead>
<tr>
<th></th>
<th>Matched human allotransplant</th>
<th>Pig xenotransplant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tissue matching between recipient and donor</strong></td>
<td>Same species</td>
<td>Different species</td>
</tr>
<tr>
<td></td>
<td>Tissue matching to ensure maximal immunological compatibility</td>
<td>No tissue matching</td>
</tr>
<tr>
<td><strong>Natural antibodies in recipient</strong></td>
<td>Not present because of tissue matching</td>
<td>High levels of natural, preformed antibodies to sugar-based molecules found on pig cells</td>
</tr>
<tr>
<td><strong>Innate immune response</strong></td>
<td>No acute graft rejection</td>
<td>Acute graft rejection due to antibody binding to blood vessel lining initiating complement and clotting reactions (hyperacute and delayed xenotransplant rejection reactions)</td>
</tr>
<tr>
<td></td>
<td>Minor reactions easily controlled by immunosuppressive drugs</td>
<td>Much too severe to be controlled by current immunosuppressive drugs</td>
</tr>
<tr>
<td><strong>Acquired immune response</strong></td>
<td>Some T-cell mediated reaction may occur due to minor tissue typing differences</td>
<td>High level of T-cell mediated response due to major tissue typing differences</td>
</tr>
<tr>
<td></td>
<td>Can be controlled by immunosuppressive drugs</td>
<td>Not tested with current immunosuppressive drugs because no transplants have yet survived the acute phase</td>
</tr>
</tbody>
</table>

Further details of the rejection reactions are given in Sections 4.3.2 to 4.3.4.

4.3.2 Innate immune response to xenotransplantation

Hyperacute rejection

Hyperacute rejection (HAR) occurs within minutes to hours of the transplantation of noncompatible organs or tissues. With xenotransplants, HAR occurs because all mammals except the higher primates (humans, apes and Old World monkeys) have cell surface molecules with a sugar determinant called galactose-α1,3-galactose (αGal). This ‘universal’ determinant (or antigen) occurs widely on the cell surfaces of pigs and other lower mammals (Galili et al 1988, Cooper et al 1993, Sandrin et al 1993). It is also present on most microorganisms, which means that humans and the other higher primates have naturally occurring (preformed) antibodies against it (anti-αGal antibody) as a result of previous infection with microorganisms. When a vascularised pig organ, for example, is transplanted into a human being, the anti-αGal antibodies circulating in the recipient’s bloodstream immediately react with pig cell surface αGal, causing HAR of the transplant (see Figure 4.2).

The mechanism of HAR involves preformed recipient anti-αGal antibodies binding to endothelial lining cells of blood vessels in the xenotransplant. This causes activation of
the ‘complement cascade’, which is the natural antibody-induced mechanism for killing pathogens or foreign cells, where complement is a complex of proteins present in blood plasma that assist (complement) antibodies in killing foreign cells. The result is that the edges of the endothelium retract, causing leakage from the blood capillaries and exposure of the underlying basement membrane (‘type 1 activation’). Platelets adhere to the exposed basement membrane, there is loss of a cell surface anticoagulant molecule called heparan sulfate, and human protein C is inefficiently activated by pig thrombomodulin. Together, these effects cause blood clotting (thrombosis) with associated cell lysis and death of the transplant (Platt et al 1991).

Complement is normally prevented from activating or damaging endothelium by inhibitory and regulatory molecules on the surface of the cells. The molecules include CD55 (decay accelerating factor), CD46 (membrane cofactor protein) and CD59 (membrane inhibitor of reactive lysis). These complement regulators are relatively species-specific in their action. Pig endothelium in a xenotransplanted organ is therefore not able to prevent human complement activation and the organ is rejected. Without the human complement regulators (CD46, CD55 and CD59), the human complement cascade is activated by transplanted tissues even in the absence of antibody.

Xenotransplants such as pancreatic islets or other cell or tissue transplants are not prone to HAR because they are not in direct contact with the blood supply and are therefore not in direct contact with either circulating antibodies or the complement and thrombotic systems. Livers are also relatively resistant to HAR, although they still undergo antibody-mediated injury when perfused with human blood (Satoh et al 1997).

**Delayed xenotransplant rejection (acute vascular rejection)**

Xenotransplanted organs that have avoided the innate HAR usually succumb to a complex of vigorous reactions, which has been called ‘delayed’ xenotransplant rejection (DXR) because it occurs somewhat later than HAR (see Figure 4.2). The most common form of DXR is acute vascular rejection (where the blood supply to the organ is progressively destroyed). This type of rejection probably starts as soon as the transplant is inserted and destroys a vascularised transplant within a few days.

The mechanism of DXR is not well understood. However, a very similar process can be seen in normal mouse hearts transplanted into mice that lack the *Gal* gene (*Gal* ‘knock-out’ mice) and have high levels of anti-αGal antibody (Pearse et al, in press). This suggests that DXR is mediated by anti-αGal antibody. Unlike HAR, there is little complement activation but there is ‘type 2 activation’ of blood vessel endothelium, involving stimulation of molecules such as E-selectin (which promotes adhesion of white blood cells) and production of procoagulant tissue factor. White blood cells, particularly NK cells and macrophages, accumulate and infiltrate the blood vessels, causing clotting, reduced blood flow and death of the transplant (Bach et al 1996, Kobayashi et al 1997, Ierino et al 1998, Kozlowski et al 1999). Even if the process is modified by immunosuppressive agents that suppress cellular infiltration, vascularised transplants fail due to damage to the blood vessels, mainly at the endothelial level.
4.3.3 Acquired immune response to xenotransplantation (cell-mediated rejection)

For allotransplants, the minor MHC differences between the donor and recipient are mainly recognised directly by recipient T cells, giving a predominantly cell-mediated response (in the form of a delayed-type hypersensitivity, or DTH, response). T-cell-mediated rejection of xenotransplants has not been well studied because it is difficult to overcome the innate responses, particularly in vascularised transplants.

Some direct recognition of MHC antigens occurs with xenotransplants, but to a lesser extent than for allotransplants (Yamada et al 1995, Dorling et al 1996c). This is because direct MHC recognition depends on many different interactions (e.g., between donor MHC antigen molecules and T-cell receptors of the recipient, adhesion receptors and ligands, or costimulatory molecules and their receptors). Such interactions are less likely to occur in
a xenotransplant due to the vast array of molecular differences between the donor and the recipient tissues.

Unfortunately, the relatively inefficient direct recognition of MHC antigens is more than compensated for by indirect recognition of the remaining very large number of xenoantigens (see Figure 4.3). These are processed and presented to CD4+ T cells by antigen-presenting cells in the transplant recipient (Dorling et al. 1996abc), generating a very powerful T-cell response (Dorling et al. 1996c) that cannot be suppressed by current immunosuppressant therapy. This form of rejection, which is not directed towards the blood supply, affects organ, tissue and cellular transplants.

Figure 4.3  T-cell mediated rejection of xenotransplants
4.3.4 Chronic rejection

The immune mechanisms of chronic rejection of allotransplants are not fully understood but they include proliferation of the endothelial (lining) cells of blood vessels leading to arteriosclerosis of the transplant. It is assumed that this type of failure could also occur with xenotransplants that have survived HAR, DXR and cell-mediated rejection, although the nature and extent of the problem is as yet unknown.

4.4 Possible solutions

4.4.1 Genetic modification of source animals

Recognition of the barriers to xenotransplantation outlined in Sections 4.2 and 4.3 has led to a new approach to overcoming them. This involves making major changes to the source animal to reduce the potential for physiological or immunological problems. To reduce the degree of molecular incompatibility, researchers have proposed the production of GM pigs that express some human genes.

Some of the physiological problems described in Section 4.2 may also be overcome by this approach. For example, pigs may be modified so that the relevant cells in pig kidneys express the gene for human EPO.

In terms of the immunological problems outlined in Section 4.3.2, researchers regard three general approaches to be the most promising for the prevention of HAR and DXR (see Figure 4.4):

- prevention of complement activation;
- prevention of xenoantibody binding; and
- prevention of thrombosis.

Prevention of complement activation

Genetic modification of pigs to express high levels of human complement regulators, in particular CD55 and CD59 (McCurry et al 1995, Byrne et al 1997, Cozzi et al 1997, Cowan et al 1999), is very effective in preventing HAR, even in the presence of complement activating anti-αGal xenoantibodies. The effect of expressing human CD46 in GM pigs has not been reported to date.

Several research groups, including one in Australia, have produced GM pigs expressing various combinations of H-transferase, CD55, CD46 and CD59 (Nextran Inc in Princeton, New Jersey, a subsidiary of Baxter Healthcare; Immerge BioTherapeutics in Boston USA, a subsidiary of Novartis; St Vincent’s Hospital (Melbourne) Ltd with Bresagen Ltd; and Alexion Pharmaceuticals, New Haven). Most researchers accept that the problem of HAR may be solved by this approach.

Prevention of xenoantibody binding

Organ transplants from the human complement regulator GM pigs are quickly destroyed by DXR, despite using strong, broad-based immunosuppression. To overcome this, attention has focused on further genetic modification of the pigs to eliminate or suppress the αGal antigen, thus preventing antibody binding. The galactosyltransferase enzyme
that generates the antigen has been inactivated in mice, completely eliminating the antigen (Thall et al 1995, Tearle et al 1996). However, inactivation of the galactosyltransferase enzyme gene in mice involves the use of embryonic stem cells, and this method has not been developed for pigs or other domesticated species.

Alternative strategies to eliminate the antigen are therefore being investigated. Most emphasis is being placed on inactivating the galactosyltransferase gene in fibroblast cells in culture and then transferring a nucleus from the genetically modified fibroblast cells to a cloned pig embryo, thereby producing a pig with an inactivated galactosyltransferase gene. In January 2002, two research groups (Immerge BioTherapeutics in Boston USA, and PPL Therapeutics in Edinburgh, UK) reported that they had produced cloned pigs with an inactivated galactosyltransferase gene (Lai et al 2002, Frankish 2002). It is expected that further crossbreeding over the next few years will produce a pig strain completely lacking the αGal antigen.

Prevention of thrombosis

Genetic modification of pigs to express high levels of human complement regulators, in particular CD55 and CD59, is very effective at preventing complement activation and HAR in pig-to-baboon transplants. However, xenotransplants are subsequently lost by a combination of cellular rejection and a coagulopathic state similar to disseminated intravascular coagulation (DIC). The mechanisms underlying the DIC-like condition are not fully understood at present but involve incompatibility between human blood coagulation factors and their equivalent receptors on pig endothelium. In particular, pig thrombomodulin is not compatible with human thrombin and protein C and pig tissue factor pathway inhibitor (TFPI) does not neutralise human factor Xa. It is proposed to overcome this xenotransplant-induced thrombosis by further genetically modifying the pigs to express human thrombomodulin and TFPI (Robson et al 2000).

![Diagram of genetic modification of the source animal (pig) to overcome obstacles to xenotransplantation](image)

**Figure 4.4** Genetic modification of the source animal (pig) to overcome obstacles to xenotransplantation
4.4.2 Other forms of immunosuppression

Researchers have proposed a range of solutions to suppress the immune response to xenotransplants. The approaches include the physical removal of preformed anti-\( \alpha \)Gal from the blood of transplant recipients, using antibody absorptive columns, inhibition of complement activation, bone marrow suppression, and other techniques. However, they have not proved very successful and are not considered to be appropriate long-term solutions to the problems outlined in Section 4.3.

If the powerful innate immune responses could be overcome using GM source animals, researchers would expect to be able to overcome cellular rejection by using immunosuppressive drugs similar to those used for allotransplantation patients. Researchers are developing and testing novel agents that are designed to suppress the different cellular responses involved in cellular rejection of xenotransplants.

4.5 Potential problems with genetic modification of pigs

Both naturally occurring anti-\( \alpha \)Gal antibody and complement are important in the lysis of enveloped viruses, at least in culture (Rother et al 1995; Takeuchi et al 1996, 1997). Some researchers have suggested that genetic modifications involving these genes, such as those described in Section 4.4.1, may promote a situation where GM pigs become susceptible to human viruses and humans become susceptible to pig viruses (Weiss 1998, Collignon and Purdy 2001).

4.5.1 Susceptibility of genetically modified pigs to human viruses

Pigs that have been genetically modified with human complement regulator genes may become susceptible to some human viruses. This is because certain human viruses enter cells by binding to complement regulator molecules. For example, echovirus binds to CD55 (Bergelson et al 1994, Ward et al 1994), as does Coxsackie B picornavirus (Bergelson et al 1995), while measles virus binds to CD46 (Dorig et al 1993). Expression of human complement regulator molecules by pigs may therefore make pigs susceptible to infection with these viruses. This is not necessarily a problem for the human recipient, who is naturally susceptible to these infections, but it could be a problem for the newly susceptible GM pig population. If infection became established in that pig population, viral mutations might occur that would permit the infection of normal pigs.

The donated organs or tissues from human complement modified GM pigs might also be susceptible to infection by human viruses in vivo (Griffiths 2000).

4.5.2 Susceptibility of humans to viruses from genetically modified pigs

Viruses produced by GM pig cells may not be recognised by the human immune system. This is because enveloped viruses acquire \( \alpha \)Gal from their host cell membranes as they are shed from cells. When such viruses infect a new host, they are recognised and quickly inactivated by an innate response (see Section 4.3.1). If GM pigs do not express the \( \alpha \)Gal antigen, however, pig enveloped viruses will be produced that do not carry the \( \alpha \)Gal antigen and are therefore resistant to the effects of anti-\( \alpha \)Gal antibody (Patience et al 1997). The concern is that if such viruses are present in an \( \alpha \)Gal-deficient xenotransplant,
they are more likely to be able to infect the human transplant recipient than are viruses from a non-GM xenotransplant.

Enveloped viruses can also acquire human complement regulatory molecules CD46, CD55 and CD59 and thus become resistant to human complement. This has occurred for HIV (Montefiori et al 1994, Saifuddin et al 1995, Stoiber et al 1996). Pig viruses that are shed from GM pig cells may become resistant to lysis by human serum (in addition to being resistant to anti-αGal antibody due to lack of αGal), allowing them to infect humans. We do not know how human naturally occurring antibody and complement ultimately contribute to human resistance to animal viruses, but these considerations indicate that a potential risk exists. Chapter 6 provides further analysis of infection risks.

![Diagram of virus infection](image)

**Figure 4.5** Susceptibility of humans to viruses from genetically modified pig cells: (A) virus shed by normal (non-GM) pig cell; and (B) virus shed by GM pig cell

**QUESTION**

Is the central role of genetic modification of source animals in the research clearly described and are the possible problems fairly stated?
PART 2

Ethical considerations for the assessment of xenotransplantation research proposals
5 Will xenotransplantation work?  
Prospects for success (efficacy)

OVERVIEW

History
Between the 1960s and 1990s, a few nonhuman primate organs were transplanted into humans overseas, including kidneys (12 recipients), hearts (2 recipients) and livers (5 recipients). Of these, the kidney transplants were the most successful, although the longest survival time was only nine months.

The trials were discontinued because other more successful procedures, including improved kidney dialysis and allotransplantation, became available at that time. The only pig-to-human transplant — a heart — was carried out in 1992 but it was rejected in less than 24 hours.

There have been some trials of pig-to-human and mouse-to-human cellular transplants. Ex vivo liver perfusion is currently being trialled overseas as a bridging procedure for people waiting for a liver transplant. To date, only one such trial has been carried out in Australia (ex vivo perfusion of a bioartificial liver device for three research participants).

Current research
Vascularised organ transplantation
Since the discontinuation of transplants from primates to humans in the early 1990s, there have been a few pig-to-primate transplants of kidneys, hearts, lungs and livers. These have shown that organs from genetically modified pigs can survive longer than organs from unmodified pigs, but survival was generally measured in only days or months.

Cellular transplantation
Researchers are currently investigating whether isolated cells can be transplanted to treat certain metabolic, degenerative and genetic diseases, such as diabetes, Parkinson’s disease and Huntington’s disease. Cellular transplants do not have all the rejection problems of vascularised organs; for example, HAR can be prevented by avoiding direct contact with the circulation. In rodents, diabetes has been successfully treated by transplanting pancreatic islet cells but this has not yet been successful in primates, large animal models or human clinical trials. A few patients have been treated with pig brain cells to treat Parkinson’s disease, with mixed results.

External (ex vivo) procedures
Ex vivo liver perfusion has been developed to ‘buy time’ while potential transplant patients wait for a suitable donor. Initially, whole animals or whole organs were perfused (eg pigs and baboons) but bioreactors containing isolated liver cells are now being developed. Other ex vivo methods, such as human skin culture supported on animal tissue for later grafting for burns, are also being developed.

Assessment of efficacy
As for other clinical trials, research applicants (investigators) and sponsors for animal-to-human xenotransplantation trials will be required to provide data on efficacy as part of a comprehensive submission for assessment by the relevant regulatory authority and the human research ethics committee at the institution(s) where the research will be carried out (see Chapter 11).

In most circumstances the initial evidence for efficacy will be based on relevant animal-to-animal studies, with pigs as the source animals and nonhuman primates as the recipients. Related experimental and animal-to-animal studies, as well as any previous animal-to-human trials, may also provide helpful information. The decision about what defines a successful animal-to-animal study will vary according to the type of, and indication for, transplantation (for example, whether it is intended as a permanent or ‘bridging’ procedure). However, in general terms, the transplant should have the capacity to provide physiologically relevant and/or life-sustaining support for some months.
5.1 Introduction

This chapter summarises the progress that has been made to date and prospects for future success for each of the different types of xenotransplantation procedures described in Section 2.1 and Chapter 4. This is followed by an overview of clinical xenotransplantation trials (animal-to-human) that are actually in progress worldwide (Section 5.5), a discussion of the issues relating to preclinical (animal-to-animal) evidence of benefit for novel xenotransplantation procedures (Section 5.6) and, finally, a proposed framework to assist the assessment of efficacy for proposals to conduct animal-to-human trials (Section 5.7).

IMPORTANT NOTE: The information provided in Sections 5.2 – 5.4 is quite technical and intended for readers with some knowledge of the transplantation research field. Other readers may prefer to refer only to the Overview information on the previous page and then proceed to Section 5.5.

5.2 Vascularised organ xenotransplantation

5.2.1 History

The first partially successful vascularised organ xenotransplants were performed in the early 1960s by Reemtsma et al (1964), who transplanted chimpanzee kidneys to six humans. The first patient survived 63 days. The most successful case had normal kidney function for 6.5 months. When the patient died from unknown causes at nine months, the kidneys appeared normal but there was microscopic evidence of chronic vascular rejection. Reemtsma suspended his clinical experimental program when haemodialysis and cadaveric renal transplantation became available in 1965 (Reemtsma 1989).

Starzl et al (1964) transplanted baboon kidneys to six humans. None of the transplants showed hyperacute rejection (HAR); one transplanted kidney functioned for two months. The transplants were well studied; the organs were lost as a result of severe vascular damage due primarily to antibody-mediated (humoral) immune mechanisms. Starzl also transplanted chimpanzee livers into three children between 1966 and 1973; the longest survival was 14 days (Starzl 1989).

After a long interval, clinical xenotransplant activity started again in the 1980s. A baboon heart was transplanted into a newborn baby in 1982 and survived 20 days (Bailey et al 1985). A pig heart was transplanted into a human in Poland in 1992, but it survived less than a day (Czaplicki et al 1992).

In 1992–93, Starzl and colleagues transplanted baboon livers into two humans. One patient survived for 70 days, but both cases were complicated by renal failure and the patients died from the complications of infection (Nalesnik et al 1993, Starzl et al 1993).

Table 5.1 shows a summary of these trials.
### Table 5.1 Human trials of vascularised organ xenotransplants

<table>
<thead>
<tr>
<th>Date</th>
<th>Type of xenotransplant</th>
<th>No. of participants</th>
<th>Results(^a)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963–65</td>
<td>Chimpanzee-to-human kidney transplant</td>
<td>6</td>
<td>Survival to 9 months</td>
<td>Reemtsma et al (1964)</td>
</tr>
<tr>
<td>1964</td>
<td>Baboon-to-human kidney transplant</td>
<td>6</td>
<td>Survival to 2 months</td>
<td>Starzl et al (1964)</td>
</tr>
<tr>
<td>1966–73</td>
<td>Chimpanzee-to-human liver transplant (children)</td>
<td>3</td>
<td>Survival to 14 days</td>
<td>Starzl (1989)</td>
</tr>
<tr>
<td>1985</td>
<td>Baboon-to-human heart transplant (newborn baby)</td>
<td>1</td>
<td>Survival to 20 days</td>
<td>Bailey et al (1985)</td>
</tr>
</tbody>
</table>

\(^a\) For multiple cases, the result shown is the most successful

### 5.2.2 Current research

The production of genetically modified (GM) pigs expressing human complement regulatory proteins (see Section 4.4.1) has led to several studies of vascularised organ xenotransplants in primates. These studies have been reviewed by Lambrigts et al (1998).

#### Kidney xenotransplantation

In one study, the Duke University/Nextran Inc group transplanted GM and non-GM pig kidneys to baboons (Diamond et al 1997). The GM kidneys expressed a single complement regulator — CD55, CD59 or CD46. The baboons were immunosuppressed with a variety of agents. Non-GM kidneys were rejected in 30–90 minutes; the GM kidneys had a mean survival time of 7.6 days (the longest 15 days).

In a second study, the same group reported 6–10-day (mean 7.5 days) survival of six pig-to-baboon kidney transplants in which the pigs were genetically modified to express the complement regulators CD55 and CD59, and the baboons were immunosuppressed with cyclosporine, cyclophosphamide and methylprednisolone (Lawson et al 1997). Non-GM control kidneys were rejected hyperacutely in a mean of 45 minutes. In both cases, the pathology of the rejected GM kidneys showed severe vascular damage and a mixed cellular infiltrate typical of delayed xenotransplant rejection (DXR).

Researchers from the Cambridge University/Imutran Laboratories (Novartis) group transplanted CD55 GM pig organs into primates (Zaidi et al 1997). However, this group used cynomolgus monkeys as the primate recipient. This is not a good model to test the prevention of HAR, because the HAR response is much reduced in cynomolgus monkeys compared to other primates and because non-GM kidneys are only occasionally rejected hyperacutely by this species. However, the median survival time increased from 6.5 days (8 hours to 30 days) for non-GM kidneys and 13 days (6 to 35 days) for CD55 GM kidneys. A more recent update on the results of this group has shown that life-supporting transplant function can be extended to 53 days by adding splenectomy to the immunosuppressive regimen (Schmoeckel et al 1998). The results are important because, like the GM pig-to-baboon kidney studies (Diamond et al 1997), profound immunosuppression (cyclosporine, cyclophosphamide and steroids, with or without splenectomy) was ultimately unable to prevent rejection.
Heart xenotransplantation

The Duke University/Nextran Inc group has used single complement regulator GM pigs as the source animal for heart xenotransplant experimentation (Diamond et al 1997; see above). Heterotopic cardiac transplants (where the native organ is left in place and the transplant is not life supporting) in immunosuppressed recipients receiving cyclosporine, cyclophosphamide and prednisolone survived a median of 5 days (maximum 15 days) compared to 30–90 minutes for non-GM hearts. As with the renal transplants, the pathology of rejection was HAR in control hearts and DXR (acute vascular rejection) in GM hearts.

In a further analysis of the contribution of humoral immunity, Lin et al (1998) used CD55/CD59 double GM pigs as source animals for cardiac tissue, as well as immunoglobulin depletion and immunosuppression. Transplant survival improved to a maximum of 29 days; there was no humoral-mediated acute vascular rejection in 5 or the 6 animals. Nevertheless, despite profound immunosuppression and immunoglobulin depletion, all the transplants failed or the baboon recipients died, largely as a result of complications of the treatment. This underlines the difficulty of using primates for studies where treatments must be prolonged and where frequent anaesthetics for biopsies and other tests are required.

The University of Minnesota/Alexion Pharmaceuticals group performed both heterotopic (not life-supporting) and orthotopic (where the donor organ replaces the native one and is life supporting) pig-to-baboon cardiac transplants using CD59 GM source animals (Kroskus et al 1997). Control transplants used non-GM hearts; recipients were treated with splenectomy, immunoglobulin depletion and immunosuppression with cyclosporine, methotrexate and steroids. Single control animals survived for 30 hours (orthotopic) or 5 days (heterotopic). The pathology in both was that of HAR. Three CD59 GM orthotopic heart recipients survived from 12 hours to 10 days; the time of survival seemed to be related to the efficiency of xenoantibody depletion at the time of transplantation.

The Cambridge University/Imutran Laboratories (Novartis) group transplanted 10 CD55 orthotopic cardiac grafts to baboon recipients immunosuppressed with cyclosporine, cyclophosphamide and steroids (Bhatti et al 1997). Five survived less than 24 hours and were judged to be technical failures; the remaining five survived 4–9 days, with two dying from complications of therapy and three developing acute vascular rejection. This group has recently presented a series of heterotopic (not life-supporting) pig-to-baboon heart transplants (Bhatti et al 1998). Control non-GM hearts survived a median of 5 days (0–10 days) while GM hearts survived a median of 26 days (10–99 days).

Lung xenotransplantation

The Duke University/Nextran Inc group performed nonlife-supporting unilateral orthotopic pig-to-baboon lung transplants (Daggett et al 1997). Non-GM lungs were rejected in 30 ± 20 minutes; CD55/CD59 double GM lungs transplanted to unmodified recipients survived 5.3 ± 1.6 hours; and GM lungs transplanted to recipients that had been immunodepleted of anti-source animal antibody by prior ex vivo absorption using a non-GM lung survived 17.3 ± 4.9 hours. These in vivo studies confirmed the observations in ex vivo models that lungs are particularly susceptible to immunological injury.

Liver xenotransplantation

There have not been any human liver xenotransplants since Starzl et al (1993) transplanted two baboon livers to humans in 1992–93 (see Section 5.2.1).
Ramirez et al (1999) performed five orthotopic pig-to-baboon liver transplants using GM (complement regulator) pig livers and three non-GM livers. The GM pig livers did not show HAR, and the baboons survived for 4–8 days before the livers failed metabolically without further sign of rejection. The livers from unmodified pigs were rejected by HAR.

5.3 Cellular xenotransplantation

5.3.1 Scope of procedures

The transplantation of isolated cells rather than whole vascularised organs has the potential to treat numerous metabolic and genetic diseases. These transplants may not have the same problems of physiological incompatibilities that vascularised organs have. Another major advantage is that in certain clinical settings a cellular transplant might be as effective as a whole organ transplant without the morbidity of major surgery (for example, the use of liver cells instead of a liver transplant to treat liver disease, or pancreatic islet cells instead of whole pancreas to treat diabetes). Furthermore, it may be possible to replenish the transplanted cells with a second donation to maintain the efficacy of the transplant with minimal comorbidity.

Another major advantage of cellular xenotransplants is that HAR may be avoided by placing the transplant away from direct contact with the blood circulation. This may involve placing the transplant in a subcapsular site (i.e., beneath the membrane sheath that surrounds certain organs such as the kidneys) and allowing the transplant to receive nutrients via infiltration of the recipient blood supply to the transplant site (neovascularisation). Alternatively, cellular transplants can be encapsulated (in a biopolymer coating such as agarose or collagen) before they are transplanted, so that there is a semipermeable barrier between the transplant and the recipient.

In most instances recipients of cellular xenotransplants require immunosuppression to prevent the strong T-cell mediated immune response, which is difficult to control. Several devices have the potential to overcome this problem, including diffusion chambers, microcapsules and smaller permeable membranes that surround individual cell clusters. Nevertheless, recipients of cellular xenotransplants will usually still require immunosuppression. In addition, they will be exposed to risks of zoonotic infection similar to those of recipients of organ transplants.

Cellular transplants have so far been used mainly for pancreatic islet transplantation, but the technology can theoretically be applied to a broad range of cells. These include hepatocytes (to treat enzyme defects), adrenal chromaffin cells (to treat intractable pain), genetically engineered cells (to produce clotting factor IX for haemophilia) (Yang et al 1994) and human parathyroid tissue to reverse hypoparathyroidism in rats (Hasse et al 1997).

With these methods, cellular transplants may be the first form of xenotransplant for which large-scale clinical trials are requested. This section gives an overview of the current status of clinical cellular xenotransplantation in humans. It concentrates primarily on the three major types of cellular transplant: pancreatic islet cells for the treatment of diabetes; neural cells for the treatment of nervous tissue disorders; and retrovirus-producing fibroblasts for the treatment of brain tumours.
5.3.2 Current research

Pancreatic islet cell xenotransplantation to treat diabetes

Recently, clinical pancreatic islet cell allotransplantation became a successful and accepted treatment (Shapiro et al 2000) for type 1 (insulin-dependent) diabetes. Studies of islet allotransplantation in humans have shown that transplanted islets can provide better diabetic control than intensive insulin therapy (Luzzi et al 1996). Thus, islet transplantation has the potential to reverse end-organ complications in diabetics (Fioretto et al 1998). Many potential recipients would benefit from the procedure but there are few human islet donors and the procedure is currently restricted to a few dedicated research centres worldwide. If the technical issues can be overcome, pig pancreatic islet cell xenotransplantation has the potential for widespread clinical application.

Animal-to-animal studies

Although pancreatic islet xenotransplantation has been successful in rodents, there are no convincing data that pig islets can control blood sugar levels in large animal models or primates. In fact, there have been only a few published studies that show that islets separated from the adult pig pancreas can provide useful control of blood sugar in syngeneic (in which donor and recipient are genetically identical), allogeneic or xenogeneic models (Mellert et al 1992). Pig islet autotransplants and allotransplants have been shown to reverse diabetes, but even in the case of allotransplantation, transplant survival was short term despite substantial immunosuppression (Mellert et al 1998). There are several possible reasons for this, both technical and immunological.

First, adult pig islets are notoriously difficult to isolate. Their connective tissue capsule is less well developed than for many other species, and the islets are more fragile and prone to fragmentation (Brandhorst et al 1995). Second, there are no sufficiently detailed studies on the most appropriate site for implanting an islet xenotransplant. For clinical islet allotransplants in humans, most success is achieved with intraportal infusions of islets into the liver (Jindal et al 1998) and not into a neovascularised space such as the kidney capsule. This finding has been confirmed with islet autotransplants in pigs and may be due to insufficient vascularisation in the kidney subcapsular space (Mellert et al 1998). This creates problems for islet xenotransplants, because liver implantation would mean exposure of pig islets to the circulation and they would therefore face the same antibody-mediated (humoral) rejection as vascularised organs (Bennett et al 2000). Finally, it has not been possible to prevent cellular xenotransplant rejection using current immunosuppressive strategies when the cells are transplanted at a nonvascularised site. Hence, it has so far been difficult or impossible to study the functional utility of adult pig islets in an appropriate animal-to-animal model.

Fetal pig tissue can also be isolated in sufficient quantities for human transplantation. It can differentiate and function appropriately in rodent models (Liu et al 1991, Korsgren et al 1993, Davalli et al 1994) and there has been one report of fetal islet cell clusters normalising blood sugar levels in a pig allotransplant model, but this has not been achieved in other species (Vo et al 2001).

Another way to overcome the problems of rejection and immunosuppression is to encapsulate the islets. Encapsulated islets can survive for long periods without immunosuppression of the transplant recipient. Microencapsulation has successfully reversed diabetes in rodent and large animal models, with little or no immunosuppression (Soon-Shiong et al 1993). Dogs have maintained normal blood sugar levels for 63 to 172 days with islets encapsulated in microspheres. The dogs were maintained on a very low
dose of cyclosporine. In dogs, bovine islet xenotransplants have been successfully used to reverse diabetes for some weeks, indicating that this technology can be used for xenogeneic tissue after some technical modifications (Lanza and Chick 1997ab)

**Animal-to-human trials**

*Fetal pig islet xenotransplantation*

Encouraged by successful studies with fetal pig islet cells in rodents, researchers at the Karolinska Institute in Sweden transplanted fetal pig islet cells to 10 diabetic kidney transplant recipients (Groth et al 1994). Research participants received a simultaneous fetal pig islet and human kidney transplant. Fetal pig islet cell clusters were placed under the renal capsule of the transplanted kidney or intraportally into the liver of some recipients. Sera from these patients showed a 10-fold increase in anti-αGal antibody titre (Galili et al 1995). No participant experienced a reduction in insulin requirements, but in four cases, porcine C-peptide (a byproduct of the synthesis of insulin) was detected in urine (Groth et al 1997). A biopsy of one of the islet transplants three weeks after transplantation showed viable islet tissue, suggesting that fetal pig islet transplants survived immediate cellular or antibody-mediated destruction with current immunosuppressive therapy (Groth et al 1994, Reinholt et al 1998).

*Encapsulated islet xenotransplants*

Based on the results with dogs, studies of encapsulated human islet allotransplants were started but have not been reported. There was also been a small study of pig islet xenotransplants (2 patients) with some evidence of graft function (Elliot et al 2000; see Section 5.5).

This strategy is still experimental, but further advances in islet isolation and preservation and in membrane technology could transform it into a clinically viable therapy that could be used to treat large numbers of patients. Recent advances in membrane technology have improved the viability of encapsulated islet tissue, but the isolation of sufficient viable insulin-secreting islet tissue to reverse diabetes in an adult human remains a major obstacle.

**Fetal pig neural cells to treat Parkinson’s disease and Huntington’s chorea**

Parkinson’s disease is a common and disabling chronic neurological condition caused by degeneration of the substantia nigra in the brain, with reduced levels of a neurotransmitter chemical, dopamine. In animals there is experimental evidence that transplantation of fetal pig neural cells into the substantia nigra can overcome the motor neurological deficits associated with Parkinson’s disease.

Huntington’s chorea is a degenerative disease of the brain that is associated with neural loss in the caudate–putamen, cerebral cortex, globus pallidus and substantia nigra. It has been hypothesised that strial cell replacement may overcome some of the neurological symptoms associated with Huntington’s chorea.

**Animal-to-animal studies**

Mammalian nerve axons can regenerate over long distances but are prevented from doing so within the brain because of the nonpermissive nature of the tissue environment. Fetal neuroblasts can ‘escape’ or neutralise this environment and can extend axons along existing myelinated fibre tracts (Wictoran et al 1990). They can also elongate along designated tracts towards the substantia nigra, pontine nucleus and cervical spinal cord, which are the normal targets for these neurones.
Xenogeneic neurones survive, function and form appropriate afferent and efferent connections within the brain (Hantraye et al 1992). They can survive in the long term with little or no immunosuppression because the brain is an ‘immunologically privileged’ site (a site where the transplanted neural tissue is protected from cell- and antibody-mediated rejection).

With respect to Parkinson’s disease, fetal pig neurones have been shown to correct dopamine deficits within the substantia nigra of rats (Huffaker et al 1989, Mahalik et al 1989, Galpern et al 1996, Isacson and Deacon 1996).

**Animal-to-human trials**

Following the success of xenogeneic neural transplantation in an experimental model, the United States Food and Drug Administration (FDA) approved a phase I clinical trial to assess the feasibility of this treatment in patients with Parkinson’s disease. The ventral mesencephalon was dissected from the brains of fetal pigs of 28 days gestation. Individual neural cells were isolated from tissue fragments and fetal pig neural cells were implanted stereotactically into the caudate and putamen of the substantia nigra of the patients. A postmortem examination was performed on one of the trial participants. The trial demonstrated long-term (7 months) survival of pig neural and glial cells and establishment of interconnections with the recipient’s own neurones. There was little evidence of a cellular rejection response (Deacon et al 1997).

This phase I study was not designed to demonstrate improvement in Parkinson’s disease itself, which is the objective of ongoing clinical trials. Nevertheless, preliminary reports suggest there are objective improvements in the motor capacity of patients with severe parkinsonism (Fink et al 2000). At this stage it appears that xenogeneic neuroblasts can differentiate and survive for long periods in the human brain when conventional immunosuppression is used. An FDA-approved phase II/III clinical trial sponsored by Genzyme Inc has been carried out to determine the efficacy of this treatment but a detailed report of the outcomes has not been published.

**Retrovirus-producing mouse fibroblasts to treat brain tumours**

Ezzeddine et al (1991), Culver et al (1992) and Takamiya et al (1993) showed that the implantation of mouse cells releasing retroviruses containing ‘suicide’ genes was effective against brain tumours in rodents. Subsequently, there have been clinical trials using this therapy in patients with inoperable cerebral tumours.

The procedure involves transplanting mouse fibroblasts that have been genetically modified in culture to express the functional components of a retrovirus into the malignant tumour. The cells are then transfected with the thymidine kinase (TK) gene of herpes simplex virus (HSV) type 1, which can convert the antiviral agent ganciclovir to a toxic metabolite. HSV-TK metabolises ganciclovir approximately 1000-fold more efficiently than does the native TK of the tumour patient. The transfected fibroblasts produce the retrovirus vector, which infects adjacent mitotically active tumour cells, making them susceptible to systemically administered ganciclovir.

This novel form of gene therapy/xenotransplantation has been used for hundreds of patients since the first clinical trials were published in 1993 (Oldfield et al 1993). Unfortunately, it has not been effective, for a variety of reasons, including rapid rejection of the fibroblasts because of the viral antigens expressed on their surface (Ram et al 1997).
5.4 Ex vivo procedures

5.4.1 History and scope of procedures

At present the most successful treatment for fulminant hepatic failure is liver transplantation. However, this therapy is limited by a shortage of donor organs and a need to find a suitable liver at short notice. In an attempt to ‘buy time’, researchers have developed xenogeneic liver cell-based perfusion systems that can act as a ‘bridge’ until a suitable liver for allotransplantation becomes available. Such systems are being used in clinical trials in the United States and Europe.

Pig, calf and baboon livers have been used intermittently since the early 1960s (Eisman et al 1965; reviewed by Abouna 1997). Baboon livers proved very successful in early studies, with 7 of 7 patients recovering consciousness and with maintenance of normal histology even after 24 hours of perfusion. However, for the reasons already outlined (see Section 4.1.2), the pig is now the preferred source animal. In trials with pig livers, reversal of coma has occurred in 30% of research participants, with improvement in consciousness in a further 40%. Pig livers maintained normal histology for up to 9 hours. There has been a resurgence of interest in pig liver perfusion using complement regulator GM livers (see Section 4.4) in the hope that the duration of perfusion can be extended. However, the use of isolated liver cells in perfusion columns (bioartificial livers) is likely to replace current ex vivo perfusion procedures as a bridging procedure (see Section 5.4.2).

5.4.2 Bioartificial livers

Bioartificial livers use isolated liver cells that are placed in an external perfusion device in which the pig cells are physically separated from the patient’s circulation by a semipermeable barrier but allow essential liver functions to occur though diffusion. Pig liver cells are isolated and purified, then propagated and cultured within a bioreactor (Riordan and Williams 1997). In most systems this consists of a hollow fibre module, similar to a synthetic kidney membrane, within which the liver cells attach to the matrix. Blood is pumped from the patient in a manner similar to haemodialysis and undergoes plasma separation. The plasma is passed through a charcoal column and then perfuses the bioreactor before being returned to the patient. A hollow fibre matrix separates the serum from the liver cells; molecules can diffuse across the membrane provided they are smaller than the pore size of the hollow fibre. Different researchers have used different pore sizes (0.03 µm to 0.2 µm) (Flendrig et al 1997, Watanabe et al 1997, Sheil et al 1998).

The semipermeable barrier is thought to reduce the risks of an infection passing from the animal cells to the patient and experience with this procedure to date has not shown any transfer of infection (Paradis 1999; see Section 6.3.3).

Most clinical experience with bioartificial livers comes from the Cedars–Sinai Medical Center in California. In 1997, the centre reported a phase I study of 31 people who received acute support by a bioartificial device (Chen et al 1997). For the group, the therapy had beneficial effects on intracranial pressure, level of consciousness and Glasgow coma score. Furthermore, there were quantifiable improvements in liver transaminases and bilirubin. Of the 21 research participants who were suitable for liver transplantation, 18 were successfully bridged to liver transplantation (Watanabe et al 1997). However, some of these people might have survived to transplantation without the
support of ex vivo liver perfusion. At present an FDA-approved phase II/III clinical trial is being carried out in the United States to determine the efficacy of the use of bioartificial livers as a bridge to liver transplantation in fulminant liver failure.

5.5 Overview of animal-to-human trials currently in progress worldwide

Some xenotransplantation trials are currently in progress with regulatory approval in the United States and Europe. These trials involve cellular transplantation (pig fetal neural cells for treatment of Parkinson’s disease) or ex vivo liver perfusion and skin culture procedures.

A small trial of fetal pig islet cells as a treatment for type I diabetes (2 patients) was carried out in New Zealand (Elliot et al 2000) but a follow-up study has been denied permission to proceed in New Zealand because of concerns about PERV infection and is now proceeding in Mexico (Valdes et al 2001).

An unidentified number of trials may also be proceeding in other countries (eg China) but the committee is not aware of any trials being conducted on organ xenotransplantation anywhere in the world.

The only animal-to-human clinical trials of xenotransplantation that has been carried out in Australia to date is a trial of an ex vivo liver perfusion method using a bioartificial liver (three participants). This trial was approved by a human research ethics committee (HREC) and was completed before the NHMRC oversight of xenotransplantation by the Gene and Related Therapies Research Advisory Panel (GTRAP) was started (see Chapter 9).

5.6 Assessing evidence of benefit

An important issue for the assessment of proposals for clinical trials of any new therapeutic procedure, whether it is a new drug, device or other technology, is the potential benefit of the therapy for the patient undergoing the trial (ie the efficacy of the procedure). For therapeutic trials of new drugs, there is generally a large body of preclinical (animal) and pharmacological evidence to back up the likely success of the treatment in humans. Trial participants are assured that, provided the trial protocol follows strict guidelines in terms of the entry criteria for participants, the treatment is likely to do more good than harm.

For xenotransplantation research, because of the difficulties of animal-to-animal (preclinical) xenotransplantation research (eg pig-to-baboon), animal-to-human (clinical) trial proposals are likely to be based on much less preclinical evidence than is usual for other therapeutic procedures. The relevant regulatory agency will need to assess the chance of success of the proposed procedure based on the data supplied, balanced against
considerations such as other treatment options, to determine entry criteria for the animal-
to-human xenotransplantation trial participants.8

5.6.1 Definition of xenotransplantation success

The historical background to and recent advances in the understanding of the biology of
xenotransplantation have fuelled debate on how to define the success of
xenotransplantation (Hastillo and Hess 1993, Michler 1996) and on the point at which
phase I clinical (animal-to-human) trials are justified based on efficacy alone (putting
aside considerations of safety discussed in Chapter 6).

There is no consensus. Some researchers suggest that a survival time of weeks to months
in animal models should be required before clinical application (Pierson et al 1993,
Dickson 1995). Others argue that we should wait until innate and humoral reactions
(HAR and DXR) are understood and overcome, or wait for ‘documented long-term
function in primates’ (Platt 1995, Bach et al 1997). Others want ‘at least the equivalent
hope of success’ as patients might have with an allotransplant (Steele and Auchincloss
1995). The formal guidelines of the Spanish Commission on Xenotransplantation include
the requirement for animal-to-animal studies that demonstrate six-month survival and
function of the particular types of xenotransplants before starting animal-to-human trials
(Bosh 1998).

Definitions of success in transplantation research are not fixed milestones that can be
simply set, achieved and passed. Rather, they vary depending on the starting point, the
history to that point, the alternatives both for the individual patient and for the particular
society, and the type of xenotransplant under consideration (eg cells, organs). Until more
animal-to-human trials are permitted, most of the information, particularly about
vascularised organ xenotransplants, must be derived from animal-to-animal studies, and
there are many difficulties with these.

Unlike animal studies for a new drug, where the information obtained from the animals is
usually gained from observation, sampling of body fluids and postmortem examination of
organs and tissues, appropriate animal-to-animal studies of xenotransplantation are very
difficult to perform. Baboons — which are the closest model to humans — are expensive,
very difficult to work with and usually require an anaesthetic for even simple
examinations or blood sampling. They are more prone to infection than humans and their
immunosuppression is less well understood. Consequently, estimates of efficacy in
baboons may not reflect what is achievable in humans. Therefore, there may be an ill-
defined point at which little or no further progress can be made without proceeding to a
human clinical trial.

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8 Because of the unique circumstances of xenotransplantation, it is highly unlikely that nontherapeutic trials in
humans would be permitted (see Section 2.3.2).
QUESTION
Is it possible to define a reasonable criterion for success in animal-to-animal studies, on which progression to phase I clinical trials (animal-to-human) can be based?

5.6.2 Evidence from animal-to-animal studies

In most circumstances the initial evidence for efficacy will be based on animal-to-animal studies, mainly pig-to-baboon. Such animal studies should be of direct relevance to the proposed animal-to-human clinical trial (e.g., the source animal for the transplantation product should be the same for both the animal studies and the proposed clinical trial and the immunosuppressive/induction protocols must be as similar as is possible). However, other related animal-to-animal studies may also provide helpful information.

Overall, the decision about what defines a successful animal-to-animal study will vary according to the type and indication for transplantation. However, in general terms, the transplant should provide physiologically relevant support for some months. In terms of organ transplants this should be life-sustaining. At the conclusion of the study, evidence should be provided that there is a reasonable prospect that in appropriate clinical circumstances the xenotransplant can provide longer support than that obtained in the animal-to-animal studies. In other words, if no animal survives beyond three months because of an untreatable form of rejection, this would raise doubts about proceeding to animal-to-human trials at that stage, if the objective was to provide long-term function.

5.6.3 Animal-to-human (clinical) trial evidence

Initially, there will not be any animal-to-human clinical trial evidence available for assessment, but as research progresses such evidence may be available for subsequent rounds of trials. For example, if there have already been some phase I or phase II animal-to-human clinical trials of the same protocol (as in the case of an application for a phase II or III trial), the evidence from these trials should be assessed by the sponsors. Animal-to-human trials of a related protocol may also provide useful information. Any animal-to-human trials that are relevant to the proposed trial should be assessed.

5.7 Proposed framework for assessment of efficacy

5.7.1 Data requirements and assessment

As with all therapeutic clinical trials, evidence of efficacy will be paramount in a decision to proceed. In the case of xenotransplantation, the main evidence will be derived from animal-to-animal studies. As discussed in Section 5.6, the number of such studies will be limited because of:

• practical considerations — the use of nonhuman primates in such studies means that only a few animals will be available for use; and

• scientific considerations — studies with nonhuman primates, while of considerable value, do not fully determine the equivalent response in humans.

Table 5.2 shows a broad outline of the data that the research applicant (investigator) and sponsor of a proposed trial will need to submit for assessment by the relevant regulatory
authority and the HREC at the institution(s) where the research is proposed to be carried out (see Chapter 11). It also shows key issues for assessment of the data by regulatory authorities.

**QUESTION**

*Are there clear criteria that should be used or developed to allow decisions to be taken that the animal-to-animal study evidence is sufficient to proceed to human trials?*

**5.7.2 Expertise required to consider efficacy**

In order to assess the issues raised in this chapter, the regulatory authority responsible for approving animal-to-human (clinical) trial proposals will need to include members with expertise in the transplantation field, in order to assess all the relevant information available and the potential for success of the procedure in humans.

Other areas of expertise that will be required by the regulatory authority are described in Sections 6.6.2, 7.4.2 and 8.6.2, and in Chapter 11 in relation to the organisational structure that would be involved.

**QUESTION**

*Are there any other areas of expertise that the regulatory authority responsible for xenotransplantation may need in order to consider the issues addressed in this chapter?*
Table 5.2  Data requirements for assessment of xenotransplantation efficacy

<table>
<thead>
<tr>
<th>RESEARCH</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed trial description/protocol</td>
<td></td>
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<tr>
<td>Rationale</td>
<td>Description of trial</td>
<td>What is the proposed procedure?</td>
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<td></td>
<td>Therapeutic benefit to participant</td>
<td>What is the expected therapeutic benefit to the research participants?</td>
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<td>(Note: nontherapeutic trials will not be permitted)</td>
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<td></td>
<td>Factors that may affect outcome</td>
<td>What are the gross physiological issues,</td>
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<td></td>
<td>biochemical/endocrinological factors and immunological barriers that</td>
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<td></td>
<td></td>
<td>may affect the outcome of this trial?</td>
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<td></td>
<td></td>
<td>Is it a permanent transplant, or a bridging procedure?</td>
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<td></td>
<td>Proposed strategies to ensure success</td>
<td>How does the investigator propose to overcome barriers to success (eg by</td>
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<td></td>
<td>genetic modification of the source animal)?</td>
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<td></td>
<td>Literature research</td>
<td>What is the evidence that this will succeed (including detailed assessment</td>
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<td></td>
<td></td>
<td>of preclinical studies)?</td>
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<tr>
<td>Source animal characterisation</td>
<td>Choice and justification of source animal species</td>
<td>What animal species will be used?</td>
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<tr>
<td></td>
<td>Anatomical, physiological and genetic considerations</td>
<td>What are the reasons for the choice of animal?</td>
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<td></td>
<td>Animal history/herd characterisation</td>
<td>What genetic modifications have been undertaken?</td>
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<td></td>
<td></td>
<td>What are the geographic origins, strain and genealogy of the source animal?</td>
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<td></td>
<td>Have all necessary measures been taken to ensure the quality of the</td>
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<td></td>
<td></td>
<td>xenotransplantation product?</td>
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<td></td>
<td>[See also advice in Table 6.1 (risk analysis for infection risks) and</td>
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<tr>
<td></td>
<td></td>
<td>Table 8.1 (animal welfare)]</td>
</tr>
<tr>
<td>Xenotransplantation product characterisation</td>
<td>Type of product</td>
<td>What type of product will be used (eg organ, tissue, cells)?</td>
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<tr>
<td></td>
<td>Treatment</td>
<td>Will the product be treated in any way after harvesting (eg encapsulated,</td>
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<tr>
<td></td>
<td>Quality control/good manufacturing practice (GMP)</td>
<td>cultured, stored)?</td>
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<td></td>
<td></td>
<td>Does the protocol take account of all relevant GMP and quality control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>considerations for the xenotransplantation product?</td>
</tr>
<tr>
<td>Participant selection</td>
<td>Criteria for selection of research participants</td>
<td>How will candidates with the best potential for clinically significant</td>
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<tr>
<td></td>
<td>Alternative therapies</td>
<td>improvement and increased quality of life be identified and selected?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Are there any adequate, safe and effective alternative therapies available?</td>
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<td></td>
<td></td>
<td>If so, does the protocol exclude patients who could benefit from these</td>
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<tr>
<td></td>
<td></td>
<td>alternatives from the trial?</td>
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</tbody>
</table>

*contd…*
### Table 5.2 (contd)

<table>
<thead>
<tr>
<th>RESEARCH</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence of efficacy/safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal-to-animal (preclinical) studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– experimental (in vitro) studies</td>
<td>In vitro studies of biochemical/endocrine/immunological responses relevant to therapeutic outcomes</td>
<td>Do these studies show the mechanisms involved and how they can be modified to increase the chance of a successful outcome in humans? Have all aspects of the mechanism been studied?</td>
</tr>
<tr>
<td>– animal studies</td>
<td>Source animal</td>
<td>Was the same source animal used as proposed for the human trial? (If not, provide justification)</td>
</tr>
<tr>
<td></td>
<td>Recipient animal</td>
<td>Was the recipient animal a suitable model for human transplantation (preferably baboon)?</td>
</tr>
<tr>
<td></td>
<td>Study protocol</td>
<td>Did the preclinical study protocol reflect the proposed clinical trial protocol (e.g., implantation site, duration, immunosuppressive protocol)?</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression used</td>
<td>Were there any clinical toxicological, pharmacological or immunological issues arising from the drug regimen used?</td>
</tr>
<tr>
<td></td>
<td>Rejection of transplant</td>
<td>How well did the xenotransplant survive (e.g., success of genetic modification in preventing rejection, or in vivo function and durability of encapsulation or other barriers to diminish rejection)?</td>
</tr>
<tr>
<td></td>
<td>Functioning of transplant/survival of recipient animal</td>
<td>How well did the xenotransplant perform? Did it sustain life or reverse disease symptoms of the recipient?</td>
</tr>
<tr>
<td></td>
<td>Other considerations</td>
<td>Are there any other considerations arising from the study that might affect efficacy (e.g., the tumourigenic potential of the transplant, migration of xenogenic cells etc)?</td>
</tr>
<tr>
<td><strong>Animal-to-human (clinical) trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– previous trials using the proposed protocol</td>
<td>Source/study protocol/outcomes</td>
<td>As for animal-to-animal studies (Note: this will only apply for phase II or III clinical trial applications where there is already some phase I trial evidence available)</td>
</tr>
<tr>
<td>– trials using the related protocol</td>
<td>Source animal/study protocol/outcomes</td>
<td>Do the results of related clinical trials help to understand the possible outcomes of the proposed trial?</td>
</tr>
</tbody>
</table>
6 Is xenotransplantation safe?
Analysis of infection risks (safety)

OVERVIEW

Risks, benefits and consequences
Xenotransplantation is unusual among medical procedures because it carries risks for the wider community as well as for the individual patient. The major concern for public health is that viruses from animal xenotransplantation products may infect human transplant recipients. Retroviruses or other unknown, probably latent, viruses are the chief concerns. Such viruses may initially show no obvious signs of disease and may spread beyond the recipient into the general population, giving rise to an epidemic that only becomes obvious when others have been infected. Therefore, in addition to risks for the xenotransplant recipient, there are potential health risks for close contacts, carers and the general public. Such risks must be assessed and weighed against the potential benefits of xenotransplantation, and options considered for their management.

Risk analysis
The usual framework for assessment of public health risks is risk analysis, including risk assessment, communication and management. Risk assessment is the scientific evaluation of known or potential adverse health effects that may result from exposure to a hazard. It includes hazard identification (what will it do to us?); hazard characterisation (how will it do it?); exposure assessment (how will we be exposed and to how much?); and risk characterisation (how likely is it and how bad will it be?).

Risk communication is the exchange of information and opinion that must occur among risk assessors, risk managers and all stakeholders (including the general public) in the decision process. Risk management is the process of weighing policy alternatives to accept, minimise or reduce assessed risks and to select and implement appropriate options.

Assessing and managing xenotransplantation infection risks
There have been many examples of cross-species transmission of infectious agents. In some cases the disease profile and mode of transmission have altered in the new host (eg HIV/AIDS). Because of the close relationship between human and nonhuman primates, and the existence of known infectious agents, nonhuman primates are no longer considered as the source for animal-to-human transplants. Pigs are considered to be the most suitable source animals for human xenotransplantation products.

A number of zoonotic infections have been transmitted from pigs to humans (eg Japanese encephalitis, influenza and Menangle viruses) but it should be possible to control these infections by appropriate herd management and laboratory testing. Concern has centred on endogenous retroviruses, which usually remain latent in their host tissues but can sometimes be activated by an external stimulus. Pig endogenous retrovirus (PERV) has been shown to infect human cells in culture. This has caused concern that there is an unknown risk that this virus may be activated in xenotransplant recipients, causing clinical infection that could spread to others in the community.

Factors that may affect the risk of infection include source animal husbandry and how the xenotransplantation product is produced; the type of xenotransplant, its placement and immunosuppression of the patient; and the infection control procedures used. Further procedures for the management of infection risks include screening and monitoring of recipients and contacts for infectious agents, collection and storage of tissue samples and maintenance of a national register.

Risk analysis template for xenotransplantation
Research applicants (investigators) and sponsors will be required to submit data on risk analysis as part of a comprehensive submission required for assessment by the relevant regulatory authority and the human research ethics committee at the institution(s) where the research will be carried out (see Chapter 11). A template for risk analysis is proposed that includes consideration of the type of procedure, the source animals and the possible infectious agents involved to ensure that any infectious disease risks are (a) minimised and (b) can be identified and contained should they occur.
6.1 Introduction

Most medical interventions (e.g., drug treatments and surgery) carry some risks for the patient. These may be in the form of side effects of a drug, risks of damage to other tissues during surgery or other harmful side effects of procedures. These risks must be balanced against the potential benefits of the procedure for an individual patient. The nature and extent of these risks are assessed from animal (preclinical) and human (clinical) evidence available for the procedure.

In the field of public health, there are many situations where it is not the risk to an individual that is paramount but the overall risk to the community (e.g., the health risks associated with various forms of air pollution or the risks associated with chemical residues in food). In many cases, the risks involved are small and difficult to quantify.

Although we would like it to be the case, science is, by definition, not able to deliver solutions to medical or other problems that carry no risks at all. Moreover, most of our day-to-day activities also carry some risks, which we generally accept because of the benefits that come from the activities (e.g., driving a car). The job of government regulators and ethics committees, in consultation with the community, is to determine the ‘acceptability’ of risks. Acceptability of a risk relates to a number of factors, including:

- the level of risk (how likely it is to happen);
- the severity of the adverse effect if it occurs (consequences); and
- the benefits that result from engaging in the activity associated with the risk.

For example, most people would not accept any additional health risk as a result of using a food colorant, but may be prepared to accept a small additional risk from a food additive that reduces the risk of another health problem such as food poisoning. However, a risk, however small, of an increase in an incurable, life-threatening disease such as cancer is less acceptable than an increased risk of a nonlife-threatening condition.

In the case of xenotransplantation, risks must be assessed at two levels. First, as for all other medical interventions, the procedures must be sufficiently efficacious and safe to do more good than harm to individual patients. This is related to the central ethical principal of beneficence (see Section 3.3.1). The potential benefits and current progress being made for various xenotransplantation procedures are summarised in Chapter 5; within the special constraints that xenotransplantation presents, they should be assessed in the same way as for other medical interventions based on animal-to-animal (preclinical) studies and animal-to-human (clinical) trials.

Second, xenotransplantation presents a much broader issue of public health/community safety because of the possibility of human xenozoonosis, in which a novel infectious agent transfers from the animal donor to the human recipient and then spreads to close contacts, health care workers and the general population. Experiences with other human xenozoonoses such as HIV/AIDS and bovine spongiform encephalopathy (BSE) make this prospect the cause of considerable concern.
6.2 Risk analysis

In recent times, there has been increasing community concern about a range of public health hazards. Consequently, people have developed a framework to assess and communicate risks and to find risk management strategies to minimise risks. The literature describes a number of variations on this method; they have slightly differing terminology but all include three interconnected components:

- assessment of the potential risk based on all the current scientific evidence available (*risk assessment*);
- communication with the community about the acceptability of the risk identified compared with the benefits derived from the procedure (*risk communication*); and
- management of the risk to maintain the acceptable level (*risk management*).

In this approach, a hazard and the risk associated with it are distinguished as follows:

- *hazard* — a biological, chemical or physical agent that may have an adverse health effect; and
- *risk* — the probability of an agent (a hazard) causing an adverse effect and the magnitude of that effect (expressions of risk can be quantitative or qualitative, and should include consideration of uncertainties).

6.2.1 Risk assessment

Within the framework outlined above, risk assessment is the scientific evaluation of known or potential adverse health effects resulting from human exposure to hazards. Although variously defined by different researchers and regulators, risk assessment generally includes the following steps (eg FAO/WHO 1995, ANZFA 1996):

- *hazard identification* — identification of the potential for an adverse effect, based on microbiological, toxicological or other data about the activity of the hazardous agent;
- *hazard characterisation* — determination of how the hazard causes the adverse effect (eg mechanism and dose–response);
- *exposure assessment* — evaluation of the frequency and level of exposure of a population to the hazard; and
- *risk characterisation* — integration of hazard characterisation and exposure data to provide a qualitative or quantitative estimate of risk, including the severity of the adverse effect (impact or ‘consequences’) in the population overall (eg with respect to other risks or factors affecting the wellbeing of the overall population).

6.2.2 Risk communication

Risk communication is the exchange of information and opinion on risks, benefits, consequences and acceptability that should occur among risk assessors, risk managers and all stakeholders (including the general public) in the decision process. It is not a process
of community education that occurs only after a decision has been made, but an integral component of the risk analysis process.

Risk communication can be achieved through expert advice, provision of unbiased information (where there is no conflict of interest), stakeholder consultation and public discussion.

6.2.3 Risk management

Risk management is the process of weighing policy alternatives to accept, minimise or reduce assessed risks and to select and implement appropriate procedures.

6.3 Xenotransplantation infection risks

6.3.1 General infection risks

Human xenotransplantation procedures are likely to be associated with the same wide range of viral, bacterial and other infections that are associated with allotransplantation and its accompanying immunosuppressive drug therapy (Fishman and Rubin 1998, Muir and Griffin 2001).

Public health concerns about the risks of xenotransplantation relate to the possibility that novel infectious agents (most likely latent viruses such as retroviruses) or known animal pathogens may be transmitted from the xenotransplant source to the transplant recipient, causing the emergence of a novel and potentially untreatable human infection (Collignon and Purdy 2001, Boneva et al 2001).

Such an infection may then be transmitted from an infected xenotransplant recipient to their close contacts and subsequently to the wider community. The continued emergence of new viral diseases in Australia and elsewhere, evidence of the rapid spread of new agents and increased understanding of the pathogenesis of current human pathogens means that these concerns are justified, although difficult to quantify.

There are many examples of cross-species transmission of infectious agents where the clinical illness and mode of transmission alter in the new host (Muir and Griffin 2001). Xenozoonotic viruses are potentially dangerous, because they may not be diagnosed with current tests and, by definition, their pathogenic behaviour is unknown.

6.3.2 Source animals

The types of potential infectious agents that can affect xenotransplantation depend on the source of the xenotransplantation product, which is, for the most part, pig or nonhuman primate.

Nonhuman primates

Nonhuman primates have been used as source animals for xenotransplantation in the past, but are not used today because of concern that they may be more likely than pigs or other domesticated animals to harbour novel pathogens (particularly retroviruses) with the potential to infect humans (see Section 4.1.2).
Several viruses have already been associated with cross-species transmission from nonhuman primates to humans; they include HIV-1, HIV-2, simian foamy virus, simian immunodeficiency virus (SIV), simian T-cell lymphotrophic virus (STLV), simian retrovirus and cercopithecine herpes (Boneva 2001). It is not clear how these transmissions occurred, but it is thought that slight changes in the viruses allowed them to infect a new host. The first described human xenozoonosis occurred through the nonhuman primate-to-human transmission of baboon cytomegalovirus following baboon liver transplantation (Michaels et al 2001).

The clinical features of some of the viruses associated with cross-species transmission from nonhuman primates to humans have been different from those observed in the normal host species. The mode of transmission has also sometimes changed in the human host; further transmission of these viruses to other people may be sexual (a feature of retroviruses and herpesviruses), respiratory (influenza), health care related (nosocomial) or vertical (ie from mother to child, as occurs for retroviruses, hepatitis viruses and herpesviruses). Endogenous retroviruses are also recognised in baboons and other nonhuman primates (see Section 6.3.3).

Although some nonhuman primates can be infected experimentally with prions — the putative causal agents of Creutzfeldt–Jakob disease (CJD), bovine spongiform encephalopathy (BSE) and related disorders — they are not known to normally harbour these agents. Pigs are not known to be naturally infected with prions.

**Pigs**

As described in Chapter 4, most current interest in xenotransplantation relates to the use of pig organs and tissues. In the past few years, several new zoonotic agents have been associated with pigs, including the Nipah virus (paramyxovirus), Japanese encephalitis virus (flavivirus) and Menangle virus (paramyxovirus). The last two were found in Australia (Mackenzie 1999). It is also recognised that some strains of human influenza, including those that resulted in previous pandemics, have been associated with swine influenza (Bikour et al 1995).

With appropriate herd management and laboratory testing, such zoonotic infections can be limited, although recent experience with Hendra, bat lyssa, Nipah and Menangle viruses demonstrates the potential for continued emergence of new zoonoses from unexpected sources (Mackenzie 1999).

It is now recognised that pigs carry an endogenous retrovirus — porcine endogenous retrovirus, or PERV (see Section 6.3.3). Reports that PERV can infect human primary cells and cell lines in vitro (Akiyoshi et al 1998, Le Tissier et al 1997, Patience et al 1997, Specke et al 2001) are of concern. They have raised the possibility that pig-to-human xenotransplants might result in infection of the recipient with PERV and that this infection may spread in the human population. Regulatory authorities, both national and international, are examining the implications of this issue in order to develop an appropriate regulatory and surveillance response that provides adequate safeguards while allowing appropriate clinical trials to proceed.

**6.3.3 Infectious agents of concern**

As mentioned earlier, some infectious agents (independent of those already recognised as a problem in immunosuppressed transplant recipients) may originate in the animal xenotransplant source and their behaviour in an immunosuppressed human is unknown.
Viruses are of most concern in this respect because they may be difficult to identify, there may not be effective therapies against them and they have various routes of transmission. Retroviruses can remain clinically latent in the host for a long time before emerging to cause varying types of disease. They can be transmitted to others by various routes (often different from the routes of transmission in the animal host). As demonstrated by HIV (which is also a retrovirus), such viruses may have a very significant community impact.

People examining the possibility of xenotransplantation have raised concerns about prions associated with CJD and BSE. However, with normal animal husbandry, these would not be expected to cause problems in xenotransplantation.

**Exogenous retroviruses**

Retroviruses are RNA viruses (ie their genetic material is made up of ribonucleic acid instead of deoxyribonucleic acid, or DNA) that infect a wide range of animals and have features that make them of particular concern in xenotransplantation. The exogenous retroviruses — for example HIV, SIV, human T-cell lymphotrophic virus (HTLV) and STLV — replicate using cellular machinery, are shed as fully functioning virus particles and spread horizontally from animal to animal. They also have the ability to integrate into the host cell genome, they display significant genetic variability, they can recombine with other retroviruses (thus generating new viruses) and they may occur at high levels in tissues of infected individuals.

Important features of retroviruses include clinical latency (where the first presentation may occur many years after the initial, often asymptomatic, infection); a range of disease manifestations, including direct immunosuppression (eg HIV); and an association with opportunistic infections, malignancy and central nervous system disease (reviewed in Coffin 1996).

Retroviruses are transmitted in various ways, including horizontal transmission from animal to animal in a population via sexual contact or blood, and vertical transmission from mother to offspring. A feature is their ability to move across species and emerge in the new species with a different pattern of disease and mode of transmission. For example, SIVs are transmitted horizontally between monkeys in the wild and are not associated with clinically apparent disease. However, following transmission to other nonhuman primates or to humans, clinical disease occurs and the modes of transmission may change. Most scientists now believe that this is what happened with HIV-1 and HIV-2.

**Endogenous retroviruses**

Endogenous retroviruses (ERVs) are partial or complete viruses that are integrated into the genome of their host, that only replicate with the genome and that are passed vertically from generation to generation as inactive proviruses. ERVs are present in many animal species, including humans, nonhuman primates and pigs. In some circumstances ERVs can become activated and produce infectious virus particles that can cause disease.

**Porcine endogenous retrovirus (PERV)**

In the context of pig-to-human transplantation, PERV has received particular attention. It is a type C retrovirus found in pig cells at approximately 50 copies per genome and is a member of a different subfamily of retroviruses to HIV. Several established pig cell lines produce PERV; some (PK15 and MPK) have been shown to infect pig, mink and human kidney cell lines. Irradiated PK15 cells can infect human diploid fibroblast lines, and B
and T lymphocyte cell lines. In some cases the infected cells are triggered to produce virus particles that can infect other cells. Human peripheral blood mononuclear cells can also be infected by PERV, but in this case the virus remains nonproductive (endogenous) (Patience et al 1997). A range of human cells and cell lines can be infected with PERV (Specke et al 2001).

In some studies, primary pig cell cultures (ie cells taken directly from pig tissues) and aortic endothelial cell cultures also produced PERV strains that were able to infect other pig and human cell lines (Wilson et al 1998, Martin et al 1998). Furthermore, once secreted by the human cell line, PERV no longer expressed α-1,3-Gal sugars and therefore could not be neutralised by human complement (Patience et al 1997). This may make xenotropic infection more likely, because research is under way to produce GM pigs for use in xenotransplantation that do not express αGal sugars (see Section 4.5.2).

Analysis of PERV genomes has shown two closely related forms — PERV-A and PERV-B (Le Tissier et al 1997) — that share 63–66% of sequences with the corresponding regions from gibbon ape leukaemia virus, feline leukaemia virus and Friend murine leukaemia virus (Akiyoshi et al 1998). All these retroviruses can cause cancer, immunosuppression and recombination. Other PERV variants also exist. PERV-A and DNA have been found in all domestic pig breeds tested and are expressed in many tissues, including heart and kidney. However, there is at least one breed of mini-pig that does not secrete PERV (Oldmixon et al 2002) and is therefore thought to be less of an infectious risk.

### 6.3.4 Potential for PERV infection of humans

To date, there has been no conclusive clinical or laboratory evidence of PERV infection in humans exposed to pig cells or tissues. Using serological assays and various molecular techniques to detect PERV DNA and/or RNA, Paradis et al (1999) retrospectively studied 160 people who had been treated by various ex vivo perfusion procedures using pig cells or tissues up to 12 years earlier. They found no evidence of PERV infection. However, in the same study, pig cells (microchimerism⁹) were detected in approximately one-quarter (23 of 100) of people exposed to pig spleen cells. PERV has been detected in porcine factor VIII used in haemophilia, although no serological evidence of PERV was detected in the recipients (Heneine et al 2001).

These studies are hampered by their retrospective nature, although they give some guidance in determining the diagnostic approaches to pathogens such as PERV. Another study found PERV DNA in mouse tissues after transplantation of pig pancreatic islet cells into immunodeficient mice (van der Laan et al 2000). No reverse transcriptase activity was detected and there was no evidence of active infection. Other animal studies have shown microchimerism but have not shown PERV in the absence of pig DNA (ie PERV has not transferred into human cells). Any nonhuman primate (preclinical) study or human (clinical) xenotransplantation trial using pig tissue would require strategies to monitor transplant recipients for the presence of PERV as part of ongoing surveillance.

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⁹ See Glossary
Like many other retroviruses, the PERV genome is more complex than first thought (Ericsson et al 2001). It is unlikely that many PERV sequences can form replication-competent viruses, but the ability of retroviral sequences to recombine means that interactions with human retroviral sequences could occur. Recombination between animal and human endogenous retroviruses (HERVs) has not yet been demonstrated in vitro or in vivo, but recombination is well documented for other retroviruses, such as HIV and avian and murine retroviruses (Vanin et al 1994, Robertson et al 1995).

HERVs make up about 1% of the human genome and are either multiple or single copy. The majority of HERVs are defective proviruses and are not able to complete a full replication cycle, although antigens may be expressed or induced (reviewed in Urnovitz and Murphy 1996). As HERVs are defective and some PERVs are capable of productive infection, recombination between replication-competent PERV and defective HERV to create a new retrovirus under the conditions of xenotransplant immunosuppression is a possible scenario, although there are no precedents for this. Such a hybrid virus may be better adapted to survival, replication and pathogenicity in humans. As some nonhuman primate cell lines and primary cells are permissive to PERV (Blusch et al 2000), nonhuman primate experiments to understand PERV transmission should be carried out where possible, although early evidence suggests that PERV is not easily transmitted to nonhuman primates via xenografts (Switzer et al 2001).

Although PERV possesses a reverse transcriptase gene, the reverse transcriptase inhibitors used to treat HIV infection are for the most part ineffective against PERV reverse transcriptase. Zidovudine has some efficacy against PERV in vitro. HIV-1 protease inhibitors also lack anti-PERV activity (Qari et al 2001).

Other human retroviral infections (in particular, HIV) have set precedents in terms of both individual and public health issues. We know that the pig genome can produce active endogenous retroviruses, although to date, definite PERV infection has not been documented in humans (or nonhuman primates) exposed to pig tissue, despite the long-term presence of pig cell microchimerism in some patients. However, understanding the genotypic and phenotypic features of PERV will be useful in detecting other endogenous retroviruses in pigs or other animals, and serves as a model for understanding potential xenozoonoses.

### 6.4 Assessing the public health risks associated with PERV

A chain of events would be required for PERV to pose a public health risk:

1. infectious PERVs must exist that are able to infect human cells (this condition has been met);
2. such viruses must be present in the germ line of pigs bred for xenotransplantation (this condition is met for most, but not all, such pig herds);
3. the viruses must be expressed in transplanted cells, tissues or organs (this has been demonstrated in vivo in immune deficient mouse models only);
4. expressed PERV must infect the xenotransplant recipient (risk unknown to date);
5. replication and spread through the recipient must take place (risk unknown and not demonstrated in any human or animal model); and
(vi) transmission to others must occur (risk unknown and not demonstrated in any human or animal model) (Stoye 1998).

These issues have been considered by several regulatory authorities and in particular by the United States Public Health Service. After considerable evaluation of the risks and public consultation that organisation felt it was appropriate for limited clinical trials to proceed, provided steps were put in place to further limit the infectious risk to the community. Essentially, this was to be achieved by a combination of informed consent, preclinical screening and patient surveillance. It was felt that the implementation of these measures would reduce the risk to the community to a level that was acceptable to health authorities and the community at large (US DHHS 2001). They proposed that clinical trials of pig xenotransplantation products could proceed provided there were:

- sensitive and specific assays for the preclinical detection of infectious PERV in pig xenotransplantation products;
- appropriate post-xenotransplantation screening for PERV and appropriate clinical follow-up of xenotransplant recipients; and
- the development of informed consent documents that indicated the potential clinical implications of the capacity of PERV to infect human cells in vitro.

It was felt by several of the experts involved with these recommendations that because these exposures occur under controlled circumstances, measures can be implemented to minimise the risk of xenotransplantation-associated infections. It is expected that xenotransplantation patients and their contacts will be monitored more closely than the average allotransplantation patient or the general population. Close monitoring of recipients should enable early identification of adverse outcomes, allowing for intensive efforts both to control infections that may occur and to prevent additional procedures that may result in new infections (Boneva et al 2001).

6.5 Managing the potential risks of infection

Factors that affect the risk of infection include the conditions under which source animals are reared, how the xenotransplantation product is produced, what health care infection control procedures are used during and after the procedure, the type of procedure involved, and the level of immunosuppression of the patient. These issues all need to be taken into account in assessing potential for exposure to infection, and documented procedures that address these issues need to be submitted by any investigator undertaking xenotransplant trials.

New strategies have been proposed that may further limit the infectious risk. These include using xenotransplant products from a herd of pigs that does not express or secrete PERV, elimination of infectious PERV through cloning and gene deletion technology, and vaccination of patients.

6.5.1 Source animal husbandry and production of xenotransplantation products

Just as strict safety standards are applied to the preparation of blood and blood products, good manufacturing practice principles will need to be applied to xenotransplant products
to minimise infection risks. They should specifically include documented procedures to
detect potential infectious agents, the maintenance of pedigreed source animals in specific
pathogen free environments, assessment of personnel who manage the animals and
prepare the xenotransplant products, assessment of safeguards for the transport of animals
and/or xenotransplant products, and continued monitoring for infectious agents.

Although lists of porcine pathogens are available and can be used to assess potential
source animal herds, data about the sensitivity and specificity of diagnostic assays are not
always available. Although the major current concern is with PERV, other infectious
pathogens also need consideration. For example, certain bacteria and other organisms
known to cause zoonotic infections in humans can be eliminated. Assays such as
serology, virus isolation, antigen detection and polymerase chain reaction (PCR),
amongst others, should be used to monitor the herd for all known organisms.

6.5.2 Placement of the xenotransplant and immunosuppression of the patient

The placement of the xenotransplant (eg into brain, blood, kidney), or the presence of
physical barriers between human and animal cells, may affect the possible emergence of a
xenozoonosis and its presentation. Relevant variables that require consideration are
whether the xenotransplant is:

- permanently implanted and directly exposed to the recipient (eg vascularised organs
  or cellular transplants);
- implanted but intended only as a temporary replacement or support until a human
  organ becomes available (these are often referred to as ‘bridges’);
- permanently implanted but contact with the recipient is limited by a semipermeable
  physical barrier, such as encapsulated xenogeneic islet cells (obviously the effective
  pore size and the possibility of rupture of the barrier are critical determinants of both
  function and the possibility of the passage of infectious agents); or
- temporarily exposed to the recipient, with or without a barrier (eg ex vivo perfusion
  systems).

For example, vascularised organ transplants where the cells of the graft are directly
exposed to the recipient’s circulation may pose a greater theoretical risk of transmitting
PERV and other viral infections than a cellular transplant that has a physiological or
mechanical barrier that separates it from the recipient’s circulation. The length of time
that the transplant is present may also have an impact on risk. A transplant that is present
to keep the patient alive whilst a suitable human organ is located (a bridging transplant)
may be of less risk than a life-saving organ xenotransplant that remains in the recipient
for years whilst the patient is on full immunosuppression.

Immunosuppression of the recipient increases their susceptibility to infection from all
sources, presumably including the risk of infection from the source animal tissue, and
also to other conditions, including cancer. As currently envisaged, immunosuppression
would be necessary for recipients of vascularised organ xenotransplants but may not be
necessary for all recipients of encapsulated pancreatic islet xenotransplants or ex vivo
procedures.
6.5.3 Screening and monitoring of infectious agents

Post-xenotransplantation clinical and laboratory surveillance is essential. Transplant recipients should be evaluated for life for transplant-related adverse events. Effective diagnostic facilities must be available for all transplanted patients. Laboratories undertaking recipient xenozoonoses testing should perform at the same level as pathology laboratories approved by the National Association of Testing Authorities. This includes documentation of the sensitivity and specificity of the assay in the testing laboratory, testing procedures, the use of appropriate controls, and the recording and storage of samples and test results.

Transplant recipients must be monitored for unexplained illnesses and clustering of illnesses, and the results must be reported to the human research ethics committee at the institution where the research is carried out and to the national body responsible for overseeing xenotransplantation research. Researchers will need to prepare a protocol for screening and monitoring the transplant recipient (including timing of sample collection) so that any transmission of infection is immediately detected.

In order to maximise the chance of early detection, the most sensitive test available for the infectious agent of concern must be performed. In addition to testing for specific pathogens such as PERV, assays that can detect a broad range of infectious agents (bacteria, fungi, mycoplasma and viruses) will need to be considered.

Relevant animal handlers, health care workers and intimate contacts of the transplant recipient should also be screened, or have blood collected for storage. There must be documented protocols to deal with accidental parenteral exposure by health care workers and intimate contacts of the transplant recipients.

6.5.4 Infection control procedures

Due to the infection risks associated with xenotransplantation, guidelines for the assessment and approval of proposed animal-to-human trials must include a requirement for appropriate infection control and public health measures. A xenotransplantation program must include a large number of specialists, from areas such as clinical infectious diseases, clinical virology, medical epidemiology and high-level laboratory support.

Adherence to current hospital infection control measures, such as standard and additional precautions, will reduce transmission of possible xenozoonoses.

There should be a procedure for handling a possible transmission of PERV, or other infection, to the transplant recipient, both in and outside the hospital. This should include management of the patient (including isolation), their family and intimate contacts, and health care or laboratory workers. Such precautions will depend on the nature of the transplant and the type of clinical illness, and would be guided by the infection control specialists that advise the investigators and local HREC. Any suspected xenozoonoses should be reported to the local HREC, the national register and the infectious diseases branch of the local State or Territory department of health. Animal and human health records will need to be stored for the same length of time as tissue samples (see Section 6.5.5).
Appropriate designs for infection control support and source animal and recipient testing (including storage) for xenotransplantation programs have been outlined in various published guidelines (eg in Europe and the United States; see Chapter 10).

### 6.5.5 Storage of tissue samples

Blood sera, leukocytes, tissue biopsies and transplant samples need to be collected before (baseline) and after xenotransplantation procedures, recorded and appropriately and stored for a prolonged period (a minimum of 50 years has been suggested by the United States Department of Health and Human Services (US DHHS 2001) to allow retrospective examination for xenozoonoses. Protocols will also need to include procedures for storage of tissue and other samples in the event of an infection or unexplained illness. Such samples need to be linked to the animal and human health records.

### 6.5.6 National register

All xenotransplant recipients must be recorded on a national xenotransplant register and their information updated regularly, as determined by the national body that will oversee xenotransplant trials.

### 6.6 Proposed risk analysis framework

#### 6.6.1 Data requirements and assessment

Based on these considerations, the research applicant (investigator) and sponsor of a proposed trial will be required to submit data on risk analysis as part of a comprehensive submission for assessment by the relevant regulatory authority and the HREC at the institution(s) where the research will be carried out (see Chapter 11). This information will be used to determine if the proposed xenotransplantation procedure presents an acceptable risk to the community. Table 6.1 shows a broad outline of the data required and the main issues for assessment by the regulatory authority and HRECs, following the risk analysis framework described in Section 6.2.

The major concern is with PERVs that have the potential to infect the recipient and the community at large. However, other infectious disease issues also need consideration. Bacteria and other infectious organisms known to cause zoonotic infections in humans need to be eliminated. Source animals need to be monitored. Serology, virus isolation, antigen detection and PCR should be used to monitor the herd for all known organisms, including for known exogenous and endogenous retroviruses. Broad-range PCR with degenerate primers may be useful for monitoring the presence and burden of retroviruses. At a minimum, animals need to be monitored for their burden of viral and bacterial pathogens.
QUESTION

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

6.6.2 Expert advice required to assess infectious disease safety

In order to assess the issues raised in this chapter, the regulatory authority responsible for approving animal-to-human (clinical) trial proposals will need to include members with expertise in infectious diseases (animal and human), in order to assess the safety of the proposed procedures, particularly in relation to the risk of transfer of infectious diseases.

A person with experience of public health issues (preferably with experience of risk assessment) would also be required. Other areas of expertise that will be required for the national body that will oversee xenotransplantation clinical trials are described in Sections 5.7.2, 7.4.2 and 8.6.2, and in Chapter 11 in relation to the organisational structure that would be involved.

QUESTION

Are there any other areas of expertise that may be needed by the regulatory authority responsible for xenotransplantation in order to consider the issues addressed in this chapter?
### Table 6.1 Risk analysis for infection risks from xenotransplantation

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<th>RISK ANALYSIS</th>
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<td><strong>Risk assessment</strong></td>
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<td>Hazard identification</td>
<td>Source animal (and pedigree):</td>
<td>Infectious agents present (exogenous and endogenous)</td>
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<td>Hazard characterisation</td>
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<td>Incubation/window period (ie potential for early diagnosis before it spreads to other people)</td>
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<tr>
<td>Exposure assessment</td>
<td>Type of procedure</td>
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<td>– Estimated dose of agent</td>
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<td>Immunologically protected site (eg brain) or not</td>
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<td>Impact/consequences</td>
<td>Human infection</td>
<td>Nature of disease (pathogenicity)</td>
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<td>Potential for transmission (related to mode, incubation period, ‘window’ for diagnosis, etc)</td>
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<td>Risk characterisation</td>
<td>Overall assessment of potential for human infection and spread of infection</td>
<td>Potential for treatment</td>
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<td>Risk management</td>
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<td>Disclosure of areas where not enough information is known to assess risk</td>
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<td>Protocols to maintain risk</td>
<td>Screening for infectious agents (eg PERV)</td>
<td>What test will be used to screen for infectious agent?</td>
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<td>below acceptable levels&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>What is the sensitivity and specificity of the test?</td>
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<td>How often will participants and contacts be screened?</td>
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<td>What arrangements are in place for storage of samples?</td>
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<td>What other disease surveillance measures are in place at the local, national and international level?</td>
</tr>
<tr>
<td>Procedures if infection occurs</td>
<td></td>
<td>What procedures will be followed if a participant becomes infected?</td>
</tr>
<tr>
<td>Risk communication</td>
<td></td>
<td>Have there been discussions with experts, stakeholders and the community about the level and acceptability of risks, including uncertainties?</td>
</tr>
</tbody>
</table>

PERV = porcineendogenous retrovirus

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

<sup>b</sup> See Section 6.5
7 Human ethics of xenotransplantation

trial protocols

Information sharing and consent

OVERVIEW

Before any research involving humans can begin, investigators must obtain the consent of research participants. Such consent must be voluntary and uncoerced, and informed. In the case of research that is therapeutic in design, these participants will be people suffering from the relevant condition (ie patients, who undergo the experimental procedures for their own potential benefit).

In clinical trials, it is usually only the research participants who bear any burdens and risks of the procedure. For xenotransplantation, however, the risks associated with infection will also be borne by close contacts of the research participant (eg health care providers, family or sexual partners) and possibly the whole community (if a new infectious disease emerges). Therefore, the question arises as to the extent to which these other groups should be involved in information sharing and decision making about the proposed trial. The working party concluded that, while close contacts should be provided with all relevant information about the trial and included in the decision process, only the xenotransplantation recipients themselves should be required to give formal consent to the procedure.

Information sharing and obtaining the consent of research participants

Potential xenotransplant recipients may be seriously ill and vulnerable. Extreme care is therefore needed to ensure that investigators give research participants all the information about the trial that they need in order to make an informed decision. If there are no other viable medical options, strategies are needed so that the research participant is not coerced into taking part in the trial.

It has been suggested that xenotransplantation trial participants should be asked to consent to compulsory monitoring for the rest of their lives and to movement restrictions if an infection emerges. Such measures would mean waiving the currently accepted right of research participants to withdraw from a trial at any time, may not be practical to apply and should not be relied on as an infection control measure (this also applies to close contacts; see below).

The working party concluded that investigators should provide sufficient evidence of safety to show that there is no undue risk to the community if some participants choose to leave the trial. Nevertheless, lifelong monitoring of recipients will be necessary in early trials in order to provide important infectious disease information for the future. Research protocols should therefore facilitate compliance of participants with lifelong monitoring and with proposed measures if an infection occurs. Having entered the trial, xenotransplant recipients also have an ethical and social responsibility to comply with such provisions.

Information for contacts

Close contacts of xenotransplant research participants may be exposed to infection if a novel infective agent emerges. All relevant information about the trial, including the risks for the transplant recipient and for contacts, should be provided to all family contacts, sexual partners and carers, ideally in a collaborative process with the treating doctor, investigator and independent counsellor. Investigators should collect signed information sheets from close contacts indicating that they have seen the information. Close contacts may also need to be screened before the trial and to be contacted and tested if an infection emerges at any stage in the future. (Similar considerations apply for long-term follow-up of contacts as for those described for participants, above.)

Assessment of information sharing and consent protocols

Based on these considerations, research applicants (investigators) and sponsors will be required to submit protocols for (a) obtaining informed and voluntary consent of research participants; and (b) informing and consulting with close contacts about infection risks. The information will form part of a comprehensive submission for assessment by the relevant regulatory authority and the human research ethics committee at the institution(s) where the research will be carried out (see Chapter 11).
7.1 Introduction

Before any research involving humans is undertaken, the consent of the research participants must be obtained under the conditions set out in the National Statement on Ethical Conduct in Research Involving Humans (National Statement; NHMRC 1999). As described in Section 2.3.2, the National Statement distinguishes between therapeutic and nontherapeutic research, but only therapeutic trials — that is, trials that aim to improve the health of the transplant recipient — are considered in this discussion paper because nontherapeutic trials of xenotransplantation are neither ethical nor safe.

Ordinarily, for clinical trials, it is the individuals who receive the procedure or treatment who are asked to consent to the procedure because it is they who will bear the burdens and risks of participation. In the case of xenotransplantation, others will also bear some of the risk, because a virus transmitted to a trial participant may be subsequently transmitted to their immediate contacts (eg their health care providers, their family and other intimates).

Therefore, the question arises as to whether these contacts, who may otherwise have no knowledge of the risks to which they are being subjected, should be considered to be ‘research participants’ and asked to formally consent to involvement in the study. The National Statement defines research ‘participants’ as follows:

The definition of participants in the Statement includes not only those humans who are the principal focus of the research endeavour but also those upon whom the research impacts, whether concurrently or retrospectively. (NHMRC 1999, p7)

Under this definition, both xenotransplant recipients and their close contacts could be defined as research participants. However, to include close contacts as research participants with formal consent arrangements would require the development of a new set of ethical principles, particularly in relation to the issues of the right to withdraw and long-term follow-up (see Sections 7.2 and 7.3). The working party decided that this was not necessary because it is not practical to rely on the involvement of contacts. We have therefore used the term ‘research participant’ in this discussion paper to denote the individuals who will be offered a xenotransplantation product or be invited to undergo a xenotransplantation procedure.

However, it is important that all close contacts of xenotransplant recipients should be given precise, clear and detailed information about the procedure, any risks to themselves and the proposed risk management procedures. The involvement of xenotransplant recipients and close contacts in information sharing and decision making about a proposed trial are discussed further in Sections 7.2 and 7.3.

On a wider level, the risk of infection could potentially affect the whole community (if a new infectious disease emerges), so some form of overall public assent is required before such research is allowed to go ahead at all. The role of the general public in decision making about xenotransplantation research was discussed in Section 2.4.1.

QUESTION
Do you agree that only xenotransplant recipients themselves, and not their close contacts, should be regarded as ‘research participants’?
7.2 Consent by research participants

7.2.1 Principles

Before a trial proceeds, the research participant (ie the xenotransplant recipient) must be asked to give his or her consent to taking part in the trial. As with other important decisions that individuals make about their lives, decisions of medical consent should be both free and uncoerced (voluntary), and based on a sound understanding of what is at stake (informed).

- A voluntary decision is one made without undue pressure, coercion, force or persuasion against one’s will. A person’s decision may not be voluntary if people who are powerful or influential have put too much pressure on them, or if they have not had the opportunity to consider all the relevant aspects of the situation.

- An informed decision is one based on relevant information about the decision, presented to research participants at their level of comprehension. Any information is relevant if it is important to the particular person making the decision (including purpose, methods, demands, risks, inconveniences, discomforts and possible outcomes of the research).

These principles are set out in the NHMRC General Guidelines for Medical Practitioners on Providing Information to Patients (NHMRC 1993) and the National Statement (NHMRC 1999). For xenotransplantation research, it is very important for the person providing information to be frank about the experimental nature of the procedure so that the potential participant does not develop any false preconceptions about the chances of success.

Ensuring that these criteria are met is part of what is involved in respecting the dignity of every human being and requires that great care be taken. A person may refuse to participate in a research project and need give no reasons or justification for that decision. Good research ethics traditionally also require that participants should be free at any time to withdraw their consent to further involvement in the research, and that participants understand this before they agree to participate. These conditions, which form part of the 1996 World Medical Association Declaration of Helsinki, are set out in the National Statement (NHMRC 1999).

7.2.2 Provision of information

At the time of the proposed trial, potential xenotransplant recipients may be seriously, or even terminally, ill and therefore vulnerable to unrealistic expectations of benefits. In these circumstances, some people may be willing to agree to treatment options that are not in their best interests. A question arises about the capacity of such seriously ill people, whose only chance of survival may be to receive experimental therapy, to give genuinely voluntary and informed consent to participation in a clinical trial (Hughes 1998). Xenotransplantation is not unique with respect to these issues; similar circumstances can occur for other research on people who are dying (eg cancer research). The National Statement states that terminal care investigators must take particular care not to exaggerate the prospect of benefit from research participation in order to justify a higher risk than that involved in the patient’s current treatment. In the case of xenotransplantation, the proposed procedure may carry significant risks for the research
participant, which need to be matched by a real prospect of benefit compared with their current treatment.

Investigators therefore need to ensure that proposed transplant recipients are given meaningful information, including the results of animal-to-animal studies, and previous animal-to-human trials if any exist, so that they have all the available information at hand to make an informed decision based on realistic prospects of a good outcome together with knowledge of the risks. Because it may be difficult for the investigator or treating doctor to remain impartial when discussing information about the trial, it may be preferable for an independent counsellor to provide frank and unbiased information to the research participant.

Even when a thorough attempt is made to inform research participants of the point of the clinical trial, sick or vulnerable patients may not understand the complex nature of the trial and the risks involved. Investigators need to develop protocols to overcome these difficulties, thus ensuring that potential trial candidates have the necessary information, support and time to make an appropriate decision.

7.2.3 Voluntary consent

Potential xenotransplant recipients may not have any other options for treatment of their condition. This means that there will be a lack of choice, which could be construed as coercion. Investigators need to develop protocols that include steps to ensure that this situation is avoided and that consent when obtained is genuinely voluntary.

7.2.4 Right to withdraw from trial or follow-up

Clinical trials in xenotransplantation may increase the risk of emergence of new infections associated with viruses transmitted from animals to humans (see Chapter 6). Therefore, it has been argued that clinical trial participants should be asked to waive their traditional right of withdrawal from the trial and to agree in advance to being followed up for the rest of their lives. It has also been argued that individual research participants and their contacts should be asked to agree in advance to being quarantined if they develop a zoonotic infection. Two questions arise from these proposals.

- Would it be prudent to assume that sick and vulnerable people will abide by such promises?
- Would it be ethical to require them to make such promises?

In response to the first question, it is common experience among health professionals that research participants do not always abide by agreements made at the outset of a research trial (eg women who are asked to agree not to become pregnant during a trial do become pregnant). This indicates that it would not be prudent to rely on such promises as an infection control measure.

In response to the second question, it is clear that to place such restrictions on research participants or contacts would be counter to currently accepted ethical practice, as enshrined in the Declaration of Helsinki and the National Statement (NHMRC 1999; see Section 7.1). A new set of ethical principles would therefore need to be developed to justify such measures. The working party did not consider this necessary because, as
discussed above, it would not be prudent to rely on such restrictions as an infection control measure.

Taking these considerations into account, the working party tentatively concluded that investigators should be required to provide evidence of the safety of the proposed procedure so that such restrictive monitoring or quarantine is not necessary. Nevertheless, the working party also recognised that information gathered from the first human trials that are conducted will be important in assessing future risk. Therefore, investigators must try to achieve lifelong monitoring of recipients and must have procedures in place that are not onerous for the recipient and that help to ensure compliance with this request (eg they should make arrangements for follow-up in the recipient’s own home). Likewise, having entered the trial, xenotransplant recipients have an ethical and social responsibility to continue to provide information on a long-term basis if at all possible, even if the procedure is not successful in their case.

While it is expected that, under these circumstances, most patients will adhere to the request for lifelong monitoring, individual recipients may withdraw their consent. The risk assessment should take this into account to ensure that it will not produce undue risk for the community.

QUESTIONS

*Are trials that require lifelong monitoring and follow-up for emerging infectious diseases acceptable?*

*Do you agree that there should be an ethical and social responsibility on the research participant to remain in the trial for long-term follow-up?*

### 7.2.5 Confidentiality

Because contacts and carers of the trial participant may need to be informed about the trial, the confidentiality normally held between the patient, who is also the research participant, and his or her treating physician may need to be broadened to include the contacts. If not handled carefully, this could lead to discrimination against the trial participant within their local and wider communities. Trial protocols should minimise this potential problem by providing very clear information about the benefits of the trial, the risks involved and the risk management procedures that are in place to protect the participant, close contacts and the wider community. Participants in early trials may also be subjected to unusual and intense public and media scrutiny and inquiries.

These issues should be explained to research participants before the trial. Measures should be in place to protect participants’ privacy and to protect them from unwanted media coverage.
7.3 **Informing and consulting close contacts of the research participant**

The close contacts of xenotransplantation research participants may be exposed to the risk of contracting a novel infectious disease, should one emerge. They should therefore be identified and counselled about the risks involved. Ideally, close contacts (particularly family members) should be involved from the outset in discussions with the treating doctor, the investigator and an independent counsellor. The investigator should provide clear information sheets for close contacts and, ensure that they have been sighted (for example by collecting signed copies of the sheets).

It has also been suggested that close contacts should be asked to agree to be monitored during the trial. The issue of monitoring and possible quarantine of research participants and contacts is discussed in Section 7.2.4. The working party has tentatively concluded that such measures would be difficult to apply and certainly should not be relied on as infection control measures. However, for some trials it may be advisable for the investigators to seek a list of close contacts and obtain preprocedure blood samples so that people can be contacted and screened if a novel infection develops in a trial participant.

Many factors may affect the ability of close contacts of the research participant to support a decision to proceed. These may include their relationship with the research participant (eg carer, family member, sexual partner), their perceptions of the risk involved, or other life options. Investigators must provide meaningful information to contacts of xenotransplant recipients, including the results of animal-to-animal (preclinical) studies, so that the contacts have at hand all the available information about any risks to themselves and the prospects of a good outcome for the research participant.

Family members and sexual partners of the xenotransplant research participant may feel considerable pressure to support the trial. Investigators must develop strategies to ensure that contacts of the research participant have realistic expectations and knowledge about all the issues involved.

**QUESTIONS**

*Does the discussion adequately cover the key issues for informing and consulting with close contacts of xenotransplantation research participants?*

*Is it acceptable for close contacts of a research participant to be identified and screened before the trial and contacted and tested if a novel infection emerges at a later date?*

7.4 **Framework for assessing information sharing and consent protocols**

7.4.1 **Data requirements and assessment**

Based on the above discussion, the research applicant (investigator) and sponsor of a proposed trial will be required to submit information on issues of consent relating to the proposed trial for assessment by the relevant regulatory authority and the human research ethics committee (HREC) at the institution where the research is proposed to be carried out (see Chapter 11). A proposed framework for the information required is shown in Table 7.1.
### Table 7.1 Framework for assessment of information sharing and consent protocols

<table>
<thead>
<tr>
<th>PARTICIPANT</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research participant</strong></td>
<td>Information</td>
<td>Is the information that will be given to research participants sufficient to help them decide whether to consent to the procedure or not (eg efficacy and safety issues, alternative treatments available, requirement for long-term monitoring, measures that may be required if an infection is detected)?</td>
</tr>
<tr>
<td></td>
<td>Voluntary consent</td>
<td>Is the person who will present the information to the research participant independent of the research team? Are there procedures to ensure that the information will be presented to the research participant in a way that is sensitive to cultural issues, disabilities etc? Are safeguards in place to ensure that the research participant’s consent to the procedure is obtained voluntarily and without coercion?</td>
</tr>
<tr>
<td></td>
<td>Long-term follow-up (monitoring)</td>
<td>Is the information that will be given to research participants about lifelong monitoring sufficient to encourage them to commit to and comply with these measures (eg tests involved, frequency, measures that may be required if an infection is detected)? Are there 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? If a patient withdraws from the trial, how will their health care be managed?</td>
</tr>
<tr>
<td></td>
<td>Confidentiality</td>
<td>Does the protocol include measures to ensure that the confidentiality of the research participant is safeguarded within the constraints of the necessary arrangements for identifying and monitoring close contacts?</td>
</tr>
<tr>
<td><strong>Close contacts of research participant</strong></td>
<td>Risk status</td>
<td>Is the risk status of close contacts of the research participant clearly defined? Is the information that will be given to close contacts of the research participant sufficient for their role in the decision process (eg potential outcome for the research participant, their own risk status, requirements for monitoring)? Is the person who will present the information to close contacts suitable for the task?</td>
</tr>
<tr>
<td></td>
<td>Information</td>
<td>Are there safeguards in place to ensure that close contacts (including carers) are completely comfortable with their involvement in the trial?</td>
</tr>
<tr>
<td></td>
<td>Voluntary involvement</td>
<td>Is the information that will be given to close contacts about monitoring requirements sufficient to encourage them to commit to and comply with these measures (eg tests involved, frequency, measures that may be required if an infection is detected)? Are there 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? If a close contact does not comply with the monitoring requirements, will this affect their ongoing health status?</td>
</tr>
</tbody>
</table>
7.4.2 Expertise required to consider ethical issues relating to human research protocols

In order to assess the issues raised in this chapter, the regulatory authority responsible for approving animal-to-human (clinical) trial proposals will need to include members with expertise in the following areas:

- ethical, regulatory and legal issues relating to research participant consent;
- the care of terminally ill patients;
- issues relating to provision of complex treatment information to research participants;
- ethical and legal issues relating to research participant confidentiality versus the rights of contacts and carers; and
- consumer concerns and public opinion.

Other areas of expertise that will be required by the regulatory authority are described in Sections 5.7.2, 6.6.2 and 8.6.2, and in Chapter 11 in relation to the organisational structure that would be involved.

QUESTION

Are there any other areas of expertise that may be needed by the regulatory authority responsible for xenotransplantation in order to consider the issues addressed in this chapter?
8 Animal ethics of xenotransplantation trial protocols
Protection of animal welfare

OVERVIEW

Research involving animals must comply with the NHMRC Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (1997) (the Code of Practice).

Preclinical studies of xenotransplantation involve nonhuman primates — specifically baboons — as transplant recipients, and (usually) genetically modified (GM) pigs as source animals. GM pigs will be the source animals for most human trials, although other species may be used for some cellular transplant procedures.

Animal ethics committees

Before any research using animals can proceed, research proposals must be approved by the institutional animal ethics committee (AEC), which includes at least one veterinarian, researcher, layperson and animal welfare representative.

AECs weigh up the benefits to animals or humans of a proposed protocol, and the ‘costs’ in terms of the welfare, essential animal characteristics and dignity of the experimental animals involved. Each proposal requires careful scrutiny by the AEC before commencement to ensure that animal welfare meets acceptable standards.

Animal husbandry

Institutions involved in research with animals must have facilities that comply with the requirements of the Code of Practice, including appropriately trained staff with veterinary backup. The NHMRC supports three nonhuman primate breeding and holding colonies, including one for baboons. These colonies comply with the Code of Practice and the NHMRC policy for the use of nonhuman primates in medical research. Animals used in preclinical studies have to be held in special colonies at an appropriate level of containment, housed in appropriate family groups that meet all of their special social and behavioural needs.

Pigs to be used as the source animal for animal-to-animal or animal-to-human xenotransplantation research must also be handled, housed and used in accordance with the Code of Practice, with appropriate containment facilities, housing and care.

Genetic modification of animals

The genetic modification of source animals raises particular issues that must be considered on a case-by-case basis to ensure that the proposed modification does not alter the animal in a significant way (ie that the animals retain the essential characteristics and dignity of their species).

Other issues

AECs must also consider the possible importation or exportation of xenotransplantation products. In Australia, the Australian Quarantine and Inspection Service (AQIS) has responsibility for overseeing the import or export of animal tissue. The NHMRC Animal Welfare Committee (AWC) would seek assurance that the animals used to supply xenotransplantation products are healthy and that they are housed under high standards of animal welfare, whether in Australia or overseas. GM animals that are imported into or exported from Australia should be raised in compliance with the relevant codes of practice.

Assessment of animal welfare

Based on these considerations, research applicants (investigators) and sponsors will be required to submit information addressing animal welfare issues as part of a comprehensive submission for assessment by the relevant regulatory authority, the AEC and the human research ethics committee at the institution(s) where the research will be carried out (see Chapter 11).
8.1 Introduction

Treating animals as a resource for organs and tissue for human beings may be morally unacceptable to some people; the basis for such inherent ethical concerns is discussed in Section 3.2.2. However, for the most part, the use of animals by humans is an accepted ethical practice in our society as long as it is done with due regard for the welfare of the animals concerned.

Any research involving the use of animals must comply with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC 1997d) (the Code of Practice). The aim of the Code of Practice is to ensure that animals used for research and teaching are treated humanely.

As outlined in Section 2.3, proposed protocols will need to be tested in preclinical (animal-to-animal) studies before clinical (animal-to-human) trials of xenotransplantation can be considered. Most animal-to-animal studies will use nonhuman primates — specifically baboons — as the xenotransplant recipients, and genetically modified (GM) pigs as source animals. GM pigs will also be the source animals for most animal-to-human trials, although other species may be involved for some cellular transplant procedures (see Section 4.1.2). As discussed in Section 4.1.2, nonhuman primates will not be used as source animals for donor tissues and organs in preclinical or clinical research.

8.2 The role of animal ethics committees

Animal ethics committees (AECs) in individual institutions are responsible for considering proposals for research using animals, and giving approval before any research can proceed. Membership of AECs is covered by the Code of Practice and must include at least one individual from the following categories: veterinarian, researcher, layperson and a person with a demonstrated commitment to animal welfare. The person in the last category is required to put aside their personal philosophies, which may oppose the use of animals for research purposes, in order to participate in a system that will assist in improving the welfare of experimental animals.

The Animal Welfare Committee (AWC) of the National Health and Medical Research Council (NHMRC) is aware of this potential personal conflict but acknowledges the importance of representation from animal welfare organisations in the system that approves research on animals.

The animal welfare lobby in Australia continues to have major input into all aspects of animal experimentation. Animal welfare groups are also members of the broad-based Code Liaison Group that is responsible for regular review of the Code of Practice. The views of these groups are always sought on proposed amendments to policy statements or new guidelines developed by the NHMRC. They are also represented on the National Consultative Committee for Animal Welfare (administered by the Department of Agriculture, Fisheries and Forestry — Australia).

Much of the decision making by AECs involves weighing up the benefits to animals or humans of a proposed protocol, and the ‘costs’ in terms of the welfare, essential characteristics and dignity of the experimental animals involved. Many of the protocols routinely submitted for consideration by AECs involve procedures not used before. Although it may present some particular challenges, the consideration of xenotransplantation protocols is similar to consideration of any other new protocol.
Before the proposed research can be approved, each case requires careful scrutiny through the AEC process to ensure that the animals involved as either donors or recipients of xenotransplants are not subjected to unacceptable conditions. Further details about the role of AECs, terms of reference and membership are given in Section 9.2 and Appendix 4.

8.3 Genetic modification of animals

For many years now, AECs have been considering applications based on genetic modification of animals. This experimental approach is particularly widespread for mice and is increasing for production animals in agriculture. The potential impact of individual changes is considered on a case-by-case basis.

The insertion of one or two human genes into a pig genome to minimise rejection by the human immune system is unlikely to alter the animal in a significant way. However, the nature and extent of genetic modification will need to be assessed on a case-by-case basis to ensure that the animals retain the essential characteristics and dignity of their species. Overall, AECs will need to be cautious in approving genetic modification of animals for xenotransplantation, to instigate a rigorous monitoring program and to learn from their early experiences of xenotransplantation technology — as they have done with emerging biotechnology in the past.

8.4 Animal husbandry

It is very important to maintain the highest standard of welfare for those animals used in xenotransplantation research — initially baboons and pigs. Institutions involved in research with animals must have facilities that comply with the requirements of the Code of Practice, including appropriately trained staff and veterinary backup.

8.4.1 Care of nonhuman primates as recipients in animal-to-animal xenotransplantation studies

The NHMRC supports three nonhuman primate breeding and holding colonies, one of which is the newly upgraded facility for baboons at Wallacia in New South Wales. The colony complies with the Code of Practice and the NHMRC Policy on the Use of Non-Human Primates in Medical Research (NHMRC 1997c) (the NHP Policy). The Code of Practice and the NHP Policy demand high standards of care and housing, with an emphasis on the general health and physical and social needs of the animals.

The animals used in animal-to-animal xenotransplantation studies would have to be held under conditions of defined health status and minimal disease. They would have to be housed according to the NHP Policy in appropriate family groups that meet all of their special social and behavioural needs. In considering a research proposal involving xenotransplantation, the institutional AEC would require detailed information on:

- housing
- environmental enrichment
- transport requirements
- pre- and postsurgery care
- appropriate anaesthetic and analgesic regimes
• immunosuppression
• the length of time animals would be held in laboratories
• the number of experimental and surgical procedures to be conducted on an individual animal
• special dietary needs.

Availability of nonhuman primates

At present the number of nonhuman primates available for research in Australia is not adequate for the volume of proposed animal-to-animal research. The existing facilities, including the baboon colony, are struggling to provide enough animals for funded projects already under way. Baboons have a long gestation period and give birth to only one infant at a time, so it will take a long time to breed enough animals of appropriate age and size. An expanded breeding program has been put into place, but it will be some time before enough animals are available for proposed research.

Some nonhuman primate research is being carried out overseas and some researchers in Australia import animals. AECs must address these situations to ensure compliance with the relevant codes and policies.

8.4.2 Care of pigs as source animals for animal-to-animal or animal-to-human xenotransplantation research

The pigs or other animals to be used as the source animals for animal-to-animal xenotransplantation studies must also be handled, housed and used in accordance with the Code of Practice. The animals would be specially bred and separately housed under conditions of defined health status and minimal disease. In considering a research proposal involving xenotransplantation, the institutional AEC would require that a number of animal welfare aspects related to breeding and keeping a significant number of animals for organ transplantation are considered. These include:

• housing
• socialisation
• appropriate food
• an adequate number of appropriately qualified animal technicians involved in routine care.

In addition, administration of analgesics and anaesthetics must be appropriate to the animals and the procedures to which they are subjected.

There must be precautions to prevent infection being transmitted to xenotransplant recipients (nonhuman primates or humans). Chapter 6 provides further information on the management of infection risks from source animals.

Availability and care of genetically modified pigs

Genetically modified (GM) pigs will be reared under licence from the Office of the Gene Technology Regulator (OGTR) (see Section 9.4). Colonies will be set up and owned by the biotechnology companies that develop the GM pigs and the animals will be raised under conditions of defined health status and minimal disease. Family-tree information and health status will be available for each pig and a history of all strains maintained in the colony. GM pigs will be housed in covered biocontainment areas, separated from non-
GM animals. Carcases will be disposed of according to the conditions set out in the OGTR licence.

Other considerations of housing, socialisation, food etc will be the same as for non-GM pigs.

8.5 Additional issues for consideration by AECs

8.5.1 Personnel

As well as approving the scientific and ethical issues associated with a proposal, the AEC must ensure that the personnel involved in the research have the necessary skills and expertise to handle the different species of experimental animals in accordance with the Code of Practice and other relevant policies.

The AEC must also ensure that all aspects of the project involving animals will be monitored by the researcher and that progress reports will be provided as appropriate. The AEC monitors the progress of any approved research by carrying out site visits.

8.5.2 Production, import and export of xenotransplantation products

Xenotransplantation products would need to be produced under closely monitored ‘quality control’ protocols to ensure that the source animals are free of infectious diseases and that the xenotransplantation products pose minimum risk to recipients of the tissue, whether animal or human.

At present, the Code of Practice (which, by definition, deals with ‘live vertebrate animals’) is not directly applicable to the import or export of animal tissues. The Australian Quarantine Inspection Service (AQIS) is responsible for overseeing the import and export of live animals and animal tissues, including all animal material proposed for use in xenotransplantation research (see Section 9.5.2). However, the NHMRC AWC would seek assurance that the animals used to supply xenotransplantation products are healthy and that they are housed under high standards of animal welfare, whether in Australia or overseas.

The Therapeutic Goods Administration (TGA) is responsible for the regulation of therapeutic goods (see Section 9.3.2). For animal-to-human trials, the TGA would consider quality assurance issues with respect to the transplantation product as part of the initial safety assessment of its Clinical Trial Exemption Scheme (CTX) clinical trial application (see Section 9.3.2).

8.5.3 Import or export of genetically modified animals

GM animals used for research purposes are covered by the Code of Practice. Under the Quarantine Act 1908, AQIS has responsibility to oversee the import and export of live animals, including GM animals. If GM animals are imported, the importer must also have approval from the OGTR under the Gene Technology Act 2000 (see Section 9.4).

The AWC would seek assurances that animals imported into Australia as part of a xenotransplantation research program were treated humanely and to high standards of animal welfare in their countries of origin.
Conversely, the AWC would seek to ensure that any animals exported from Australia were raised in compliance with the relevant codes of practice developed in the States and Territories for production animals.

Where GM animals are imported or exported, details about the source of the animals must be available. Currently, pig semen from GM animals that is exported from Australia must comply with the health requirements of the importing countries. AQIS codes of practice apply to artificial breeding centres in Australia and help ensure that health requirements are met.

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

8.6 Assessment of animal welfare issues

8.6.1 Data requirements and assessment
Based on these considerations, the research applicant (investigator) and sponsor of a proposed trial will be required to submit information addressing animal welfare issues as part of a comprehensive submission for assessment by the relevant regulatory authority, the AEC and the human research ethics committee at any institution where the research will be carried out (see Chapter 11). An outline of the information required is shown in Table 8.1.

8.6.2 Expertise required to consider ethical issues relating to animal research protocols
In order to assess the issues raised in this chapter, the regulatory authority responsible for approving animal-to-human (clinical) trial proposals will need to include members with expertise in the following areas:

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

Other areas of expertise that will be required by the regulatory authority are described in Sections 5.7.2, 6.6.2 and 7.4.2, and in Chapter 11 in relation to the organisational structure that would be involved.

QUESTION
Are there any other areas of expertise that may be needed by the regulatory authority responsible for xenotransplantation in order to consider the issues addressed in this chapter?
Table 8.1 Information required for assessment of animal welfare issues

<table>
<thead>
<tr>
<th>ANIMALS</th>
<th>DATA REQUIREMENT</th>
<th>ASSESSMENT</th>
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<tbody>
<tr>
<td>Nonhuman primates</td>
<td>Rationale/justification for use</td>
<td>Is the use of nonhuman primates justified in this trial?</td>
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<td></td>
<td>Number to be used</td>
<td>Is the proposed number of animals acceptable for this procedure?</td>
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<td></td>
<td>Source</td>
<td>What is the source of the animals?</td>
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<td></td>
<td>Level of containment</td>
<td>Is the proposed level of containment appropriate for the trial?</td>
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<td></td>
<td>Animal husbandry information:</td>
<td>Do the conditions comply with all aspects of the Code of Practice?</td>
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<td>– housing</td>
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<td>– environmental enrichment</td>
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<td>– transport requirements</td>
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<td>– pre- and postsurgery care</td>
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<td>– appropriate anaesthetic and analgesic regimes</td>
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<td>– immunosuppression</td>
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<td>– length of time animals would be held in laboratories</td>
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<td>– number of experimental and surgical procedures to be conducted on an individual animal</td>
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<td>– special dietary needs</td>
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<tr>
<td>Pigs</td>
<td>Rationale/justification for use</td>
<td>Is the use of pigs justified in this trial?</td>
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<td>Number to be used</td>
<td>Is the proposed number of animals acceptable for this procedure?</td>
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<td></td>
<td>Source</td>
<td>What is the source of the animals?</td>
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<tr>
<td></td>
<td>Genetic modification(s)</td>
<td>Will the proposed genetic modifications alter the essential nature of the pig (ie are they ethically acceptable)?</td>
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<td>– What is the nature and extent of the modification(s)?</td>
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<td>– Does the modification significantly alter the animal?</td>
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<td></td>
<td>Level of containment</td>
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<td></td>
<td>Animal husbandry information:</td>
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<td>– appropriate food</td>
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<td>– adequate number and appropriate qualifications of animal technicians involved in routine care</td>
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<td>– appropriate use of analgesics and anaesthetics</td>
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<tr>
<td>Other species</td>
<td>Similar considerations to the above</td>
<td>Compliance with the Code of Practice</td>
</tr>
</tbody>
</table>
PART 3

Regulation of xenotransplantation
9 Current regulatory controls

OVERVIEW

NHMRC oversight
The NHMRC is responsible for animal research through its Animal Welfare Committee, which administers the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (1997). Under this code all proposals involving the use of animals in research and teaching must be approved and monitored by an institutional animal ethics committee (AEC).

The NHMRC is also responsible for research involving humans through its Australian Health Ethics Committee (AHEC), which administers the National Statement on Ethical Conduct in Research Involving Humans (1999). Under this statement, all proposals involving human research must be approved and monitored by an institutional human research ethics committee (HREC).

Therapeutic Goods Act
All therapeutic goods (including medicines and devices) for marketing and routine use are registered or licensed under the Commonwealth Therapeutic Goods Act 1989 and amendments (TG Act), which is administered by the Therapeutic Goods Administration (TGA). The legislation allows the supply of unregistered therapeutic goods for experimental studies and clinical trials under the supervision of the TGA and NHMRC (through an HREC).

Clinical trials of therapeutic goods may be conducted under the Clinical Trials Exemption (CTX) or Notification (CTN) Schemes. A CTN application is submitted to the host institution HREC who assesses the ethics and scientific validity of the trial, the safety and efficacy of the product and the trial protocol. A CTX application is evaluated by the TGA before it is forwarded to the HREC who gives the final approval for conducting the trial at their site. The choice of scheme depends on whether the HREC has the necessary scientific and technical expertise to assess the proposal. As this is unlikely for xenotransplantation research, the NHMRC has established a scientific advisory committee to provide advice on scientific and technical issues involved in gene and related therapies. All clinical xenotransplantation research proposals should therefore be submitted under the CTX Scheme.

Other schemes under the TG Act for the use of unapproved therapeutic goods include the Special Access Scheme, the Authorised Prescriber Scheme and the Personal Use Scheme. HRECs do not normally have a role in the approval of goods under those schemes, which are decided by the TGA on a case-by-case basis. The working party recommends that these schemes should not be used for the supply of unregistered xenotransplantation products.

Gene Technology Act
The genetic modification of source animals falls within the scope of the Commonwealth Gene Technology Act 2000 (GT Act) and GT Regulations 2001, administered by the Office of the Gene Technology Regulator (OGTR). Research involving genetically modified organisms (GMOs) requires approval and licensing under the legislation, based on risk assessment and wide consultation. Under the GT Act, products derived or produced from a GMO are defined as GM products and are regulated by the agencies involved in their use (e.g. TGA for medical products), with advice from the OGTR.

A GM pig created by insertion of human genes into the pig genome is a GMO and will be regulated under the GT Act and Regulations. The xenotransplantation products produced from a GM pig may fall within the definition of GM products and would be monitored by AECs for animal-to-animal research and regulated by the TGA under the TG Act for animal-to-human research. Under some circumstances, however, they may require further assessment by the OGTR. Pig-derived tissue for xenotransplantation that has not undergone genetic modification will not fall within the GT Act.

Other legislation
Other legislation that affects xenotransplantation research includes State and Territory animal welfare and public health legislation and the Commonwealth Quarantine Act 1908, which controls the import and export of animal or human tissues and products.
9.1 Introduction

Regulatory control over xenotransplantation research in Australia is currently provided under the same arrangements as for other human and animal medical research. This involves a combination of ethical oversight under arrangements administered by the National Health and Medical Research Council (NHMRC) through its Australian Health Ethics Committee (AHEC), Animal Welfare Committee (AWC) and Research Committee. Statutory regulation is provided through Commonwealth therapeutic goods legislation and animal welfare and public health legislation at State/Territory levels. If the source animals have been genetically modified, regulation also involves gene technology legislation at the Commonwealth, State and Territory levels (gene technology legislation is not yet in place in all jurisdictions).

9.2 Research involving animals

9.2.1 NHMRC oversight of animal research

The NHMRC Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC 1997d) (Code of Practice) covers all aspects of the care and use of, or interaction with, animals for scientific purposes in medicine, biology, agriculture veterinary and other animal sciences. The Code of Practice was prepared by a joint working party of the NHMRC, Commonwealth Scientific and Industrial Research Organisation (CSIRO), Agricultural and Resource Management Committee of Australia and New Zealand (ARMCANZ), Australian Research Council (ARC), Australian Vice-Chancellors’ Committee (AVCC) and State and Territory governments, and has been endorsed by all parties. This extensive national endorsement extends the scope of the Code of Practice to cover all publicly funded animal research in Australia and a significant proportion of privately funded research where this is undertaken in institutions that are also covered by the framework. However, it does not cover an individual pursuing privately funded research in a private institution.

Compliance with the Code of Practice, which is monitored by the AWC, requires that all proposals involving the use of animals in research and teaching must be approved and monitored by an institutional animal ethics committee (AEC). In considering each proposal, the AEC must verify that the animal use is justified, and that the institution complies with the key principles of replacement, reduction and refinement. The role of AECs is described in Section 8.2. Terms of reference and membership details are given in Appendix 4.

When breaches of the Code of Practice are brought to the attention of the AWC, the AWC may recommend withdrawal of NHMRC funding from the institution where the breach occurred. In addition, action may be taken under the relevant State or Territory animal welfare legislation as outlined below.

9.2.2 Legislation

The NHMRC Act 1992 provides the legal basis of the NHMRC framework for the oversight of animal research. However, animal welfare legislation is a State/Territory responsibility. Most States and Territories have animal welfare legislation that mandates the NHMRC Code of Practice. Queensland and Western Australia are currently drafting
such legislation. Within this legislative framework, inspectors appointed by the State or Territory have the authority to investigate breaches of the Code of Practice and lay charges.

The provisions of the Gene Technology Act 2000 and the Gene Technology Regulations 2001 may apply if the research involves genetic modification of animals (See Section 9.4 for further details).

### 9.3 Research involving humans

#### 9.3.1 NHMRC oversight of human research

The NHMRC National Statement on Ethical Conduct in Research Involving Humans (National Statement) provides the framework for ethical consideration of research involving humans. The National Statement replaced the 1992 NHMRC Statement on Human Experimentation, itself first published in 1966. The National Statement was prepared by AHEC on behalf of the NHMRC and was the result of extensive public consultations over a three-year period. It has been endorsed by the AVCC, the ARC, the Australian Academy of the Humanities, the Australian Academy of Science, and the Academy of Social Sciences in Australia. It is also supported by the Academy of Technological Sciences and Engineering. This extensive national endorsement extends the scope of the National Statement to cover all publicly funded research in Australia and a significant proportion of privately funded research where this is undertaken in institutions that are also covered by the framework. However, it does not cover an individual pursuing privately funded research in a private institution or the use of offshore facilities to undertake this work. Although this is unlikely to occur for human xenotransplantation research in Australia, there are currently no powers through the NHMRC to prospectively assess, monitor or stop such research. Should this occur, however, the medico-legal implications of any work involving humans would still remain in force.

Under the National Statement, proposals for human research require prior assessment by an appropriately constituted human research ethics committee (HREC) at the institution where the research will be carried out. Institutional HRECs are responsible for approving and monitoring research involving humans. If human research is undertaken without appropriate approval by an HREC, or if an HREC is not in compliance with the National Statement, then all publicly (ie NHMRC) funded research in that institution may be forfeited.

The composition of HRECs is described in the National Statement. Each committee includes a chairperson, members with expertise in research, clinical practice and law, lay members with no affiliation with the institution and a minister of religion or community elder. Further details of HREC membership, terms of reference and roles are given in Appendix 3.

In the early 1990s, the NHMRC recognised that HRECs may not have the technical knowledge and resources to appropriately evaluate clinical trial proposals involving gene therapy. The NHMRC Research Committee therefore established the Gene Therapy Committee in 1994, which was later renamed the Gene and Related Therapies Research Advisory Panel (GTRAP). GTRAP provides advice directly to HRECs on individual research applications involving gene therapy. More recently the terms of reference were
expanded to include xenotransplantation until formal Australian guidelines to cover xenotransplantation are implemented. HREC have been advised by the NHMRC that proposals for human research in either gene therapy or xenotransplantation must be referred to GTRAP for advice. Information on GTRAP’s terms of reference and membership is given in Appendix 5).

9.3.2 Therapeutic Goods Administration oversight

The Commonwealth *Therapeutic Goods Act 1989* and amendments (TG Act) control the supply of therapeutic goods in Australia. 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 and is administered by the Therapeutic Goods Administration (TGA).

The TG Act requires the inclusion in the Australian Register of Therapeutic Goods (ARTG) of all therapeutic drugs and medical devices for use in humans that are imported, manufactured in Australia, supplied by a corporation, supplied interstate or to the Commonwealth Government or exported. Inclusion in the ARTG involves evaluation and approval by the TGA, licensing of manufacturers and postmarket surveillance. The legislation does not specifically address xenotransplantation products and a question thus arises as to whether the TG Act is applicable. The working party, on the advice of the TGA, believes that it is applicable, as outlined below.

**Definition of ‘therapeutic goods’ and ‘therapeutic use’**

The TG Act defines therapeutic goods as goods that are for therapeutic use, whether as the active component, as an ingredient or component in the manufacture of the goods or as a container or part of a container for the goods. Appendix 6 provides the full definition from the TG Act.

‘*Therapeutic use*’ means use in or in connection with:

(a) preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons or animals; or

(b) influencing, inhibiting or modifying a physiological process in persons or animals; or

(c) testing the susceptibility of persons or animals to a disease or ailment; or

(d) influencing, controlling or preventing conception in persons; or

(e) testing for pregnancy in persons; or

(f) the replacement or modification of parts of the anatomy in persons or animals.

The TG Act was written without specific consideration of xenotransplantation products. However, the definitions of a therapeutic good (see Appendix 6) and of therapeutic use (see above) appear to be broad enough to include xenogeneic cells, organs or tissues (xenotransplantation products) when used therapeutically to replace or augment diseased organs, cells or tissues, as would be the case for animal-to-human xenotransplantation trials.
QUESTION

Does the TGA Act need to be revised to specifically cover xenotransplantation products?

Supply of unregistered therapeutic goods

The TGA Act allows the supply of unregistered therapeutic goods under certain circumstances, including for initial experimental studies and clinical trials in humans, using the following programs:

- Clinical Trial Notification (CTN) and Clinical Trial Exemption (CTX) Schemes;
- Special Access Scheme (SAS);
- through authorised prescribers; and
- by importation for personal use.

The TGA Act gives HRECs a central role in controlling the supply of unapproved therapeutic goods, and any proposal for the use of therapeutic goods in a clinical trial must be approved by, and conducted under the supervision of, an HREC that has notified its existence to the TGA. These processes are described in more detail below.

Clinical trials application schemes

Application under either the CTX or the CTN schemes is required for all clinical trials of a product, where that use involves (TGA 2001):

- any product not entered on the ARTG, including any new formulation of an existing product, any new route of administration or, in the case of an existing medical device, any new technology, new material or new treatment modality; or
- use of a registered or listed product beyond the conditions of its marketing approval, including new indications extending the use of the medicine to a new population group and the extension of doses or duration of treatments outside the approved range.

CTN scheme

Under the CTN scheme, the research applicant (investigator), on behalf of the sponsor, submits an application to the HREC at the institution or organisation where the trial will be carried out (the ‘approving authority’) with all relevant material relating to the proposed trial, including the trial protocol. The ethics committee is responsible for assessing:

- the scientific validity of the trial design;
- the safety and efficacy of the medicine or device; and

---

10 All CTN and CTX trials must have an Australian sponsor. The sponsor is that person, body, organisation or institution that takes overall responsibility for the conduct of the trial and signs either the CTN form or the CTX form. The sponsor usually initiates, organises and supports a clinical study and carries the medico-legal responsibility associated with the conduct of the trial.
• the ethical acceptability of the trial process.

The TGA does not review any data relating to the trial. The HREC is responsible for approval of the trial protocol.

In some institutions a scientific review subcommittee may review the proposal before consideration by the HREC. The approving authority gives the final approval for the conduct of the trial at that site, having due regard to advice from the HREC. When the sponsor, the principal investigator, the HREC chair and the approving authority have signed the CTN form, the trial sponsor lodges it with the TGA before commencing the trial.

**CTX scheme**

Under the CTX scheme, the sponsor submits summary information directly to the TGA for evaluation and comment. The primary responsibility of the TGA is to review the safety of the product in broad terms. For clinical trials of medicines, this involves review of the information provided by the sponsor, including the overseas status of the medicine, proposed usage guidelines, a pharmaceutical data sheet, a summary of the preclinical (animal) data and clinical data. For medical device trials it involves examination of the design specifications and preclinical (animal) data. The application submitted to the TGA does not include the clinical trial protocol.

The TGA delegate decides whether to object to the proposed usage guidelines for the product. If an objection is raised, trials may not proceed until the objection has been addressed to the TGA delegate’s satisfaction. Even if no objection is raised, the delegate usually provides comments on the accuracy or interpretation of the summary information supplied by the sponsor. The sponsor must forward these comments to the HREC at any sites at which they intend to conduct trials under the CTX.

After reviewing the summary information received from the sponsor and any additional comments from the TGA delegate, the HREC in each host institution is responsible for considering the scientific and ethical issues of the proposed clinical trial protocols and approving the proposed trial protocol, as for the CTN scheme. The institution or organisation concerned (the approving authority) gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.

A sponsor cannot commence a CTX trial until:

- written advice has been received from the TGA regarding the application; and

- approval for the conduct of the trial has been obtained from the HREC and the institution at which the trial will be conducted.

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 the HRECs.

The sponsor may conduct any number of clinical trials under the CTX application without further assessment by the TGA, provided use of the product in the trials falls within the original approved usage guidelines. However, for each trial, the HREC concerned must approve the trial protocol and the institution or organisation must approve the conduct of the trial.
**CTN or CTX?**
The choice of which scheme to follow (CTN or CTX) lies with the sponsor and also with the institutional HREC, which can review the protocol and provide advice to the approving authority. 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.

HRECs are unlikely to have access to appropriate scientific and technical expertise for xenotransplantation research, which involves new and rapidly evolving technologies and emerging infectious disease safety issues. GTRAP has therefore been established by the NHMRC Research Committee to provide advice to HRECs on scientific and technical issues involved in gene and related therapies and, more recently, xenotransplantation research protocols. GTRAP has recommended that all human gene therapy research proposals should be submitted under the CTX scheme unless researchers can convince GTRAP that CTN is sufficient (NHMRC 2001). It would therefore seem appropriate that a similar recommendation be made for animal-to-human xenotransplantation trial proposals.

**Special Access Scheme**
The Special Access Scheme (SAS) provides arrangements for the import and/or supply of an unapproved therapeutic good on a single-patient, case-by-case basis. Patients who are eligible to receive an unapproved product under this scheme are either category A (persons notified to the TGA by a medical practitioner as being seriously ill with a life-threatening illness in whom premature death is likely without treatment) or category B (any person for whom the TGA or an external delegate gives approval to receive an unapproved product). HRECs do not have a role in SAS approvals except where approval is granted for a category B patient by an external delegate of the TGA, which is unusual because external delegations are rare.

Under the current legislation, approval of xenotransplantation products is possible under the SAS and applications would be reviewed on a case-by-case basis. However, the ethical and safety issues involved in animal-to-human xenotransplantation strongly indicate that SAS approval would not be appropriate for xenotransplantation products. This area needs to be addressed in any new legislation and is discussed further in Chapter 11.

**QUESTION**
*Does the Therapeutic Goods Act need to be amended to specifically ban the use of the Special Access Scheme for xenotransplantation?*

**Other schemes**
Under the TG Act and regulations, the TGA can grant a medical practitioner authority to prescribe a specified unapproved therapeutic good to specified recipients or classes of recipients (authorised prescriber). Requests by medical practitioners for authorisation to prescribe must be approved by the HREC at the practitioner’s institution, and the HREC must assess the safety of the product to be used and the suitability of the practitioner. This provision has been used primarily for access to new medications in special circumstances; the working party believes that the ‘authorised prescriber’ system is not intended for, and should not be used for, xenotransplantation research.

Importation of therapeutic goods for personal use is also exempt under the legislation and therefore no application or approval is required as long as the conditions applied to the
exemption are met. These conditions are set out in item 1 of Schedule 5 of the TG Act. Some xenotransplantation products would be covered under clause (b) of item 1, which prohibits the personal importation of products that are injections and contain material of human or animal origin. Other animal items are not excluded. While the working party considers that it is highly unlikely that personal importation provisions will be used for xenotransplantation products, this also needs clarification.

Under the current legislation, approval of xenotransplantation products is possible under any of these arrangements and each application would be reviewed on a case-by-case basis. However, the ethical and safety issues involved in animal-to-human xenotransplantation strongly indicate that such approvals may not be appropriate for xenotransplantation products. This area needs to be addressed in any new legislation and is discussed further in Chapter 11.

9.3.3 Long-term surveillance of new therapies

Follow-up of new drug clinical trials and use occurs in two phases. Before a new drug comes onto the market, the TGA assesses data on any side effects (supplied by the sponsors or obtained from overseas etc). After the drug is marketed, the Adverse Drug Reactions Advisory Committee, supported by the TGA, collects adverse events data locally and advises health professionals regularly. At times, either voluntarily or under instruction from the TGA, pharmaceutical companies issue warnings or remove drugs from the market.

Similarly for medical devices, adverse events are reported in the data supplied by a sponsor with an application for entry onto the ARTG (clinical trial reports, overseas data, etc) and are evaluated by the Clinical Section of the Conformity Assessment Branch of the TGA. Issues of concern have to be adequately addressed by the sponsor before the device can be recommended for entry onto the ARTG.

After the device is entered on the ARTG and comes onto the market, sponsors are required to submit yearly reports detailing efficacy and safety (including adverse events) for three years. Adverse events are also notified to the TGA via the medical devices Incident Report Investigation Scheme (IRIS) or via postmarketing reports submitted by sponsors. Device incident reports come from a variety of sources (sponsors, medical practitioners, patients, hospital staff etc) and are discussed weekly and actioned as appropriate. If any of these mechanisms raise concerns that require further action, then the Clinical Section initiates proceedings with the Secretariat and Recalls Section to address the concerns in the most appropriate manner (eg hazard alert, safety alert). Further advice can also be sought from the Therapeutic Device Evaluation Committee. In addition, the College of Surgeons is setting up a government-funded process for central data collection on new surgical procedures, called the Australian Safety and Efficacy Register of New Interventionsal Procedures. Health professionals and researchers also share information through publications and presentations to scientific meetings. Some or all of these processes will apply to xenotransplantation, as well as any central monitoring that may be advised as a result of the deliberations of this working group.

9.4 Regulation of research involving gene technology

The term ‘gene technology’ refers to techniques for modifying genes or other genetic material. As discussed in Section 4.4.1, xenotransplantation research may involve the
genetic modification of a source animal with human genes to help control the powerful immune reactions that cause rejection of xenotransplants. Thus it is necessary to examine if and how the new legislation governing gene technology applies to both animal-to-animal and animal-to-human xenotransplantation research.

Research involving genetically modified organisms (GMOs) is regulated under the Commonwealth Gene Technology Act 2000 (the GT Act) and Gene Technology Regulations 2001 (GT Regulations). The object of the GT Act is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.

The GT Act is administered by the Gene Technology Regulator (GT Regulator). The GT Regulator is provided with assistance and recommendations on regulatory matters by the staff of the Office of the Gene Technology Regulator (OGTR) and three advisory committees:

- Gene Technology Technical Advisory Committee (to provide scientific and technical advice);
- Gene Technology Community Consultative Committee (to provide community views); and
- Gene Technology Ethics Committee (to provide advice on ethical issues).

The GT Act covers both genetically modified organisms (GMOs) and genetically modified products (GM products) and it is necessary to clearly distinguish these two entities.
9.4.1 What are genetically modified organisms?

A GMO is defined in the GT Act as:

(a) an organism that has been modified by gene technology; or

(b) an organism that has inherited particular traits from an organism (the initial organism), being traits that occurred in the initial organism because of gene technology; or

(c) anything declared by the regulations to be a GMO, or that belongs to a class of things declared by the regulations to be GMOs.

The legislation regulates ‘dealings’ with GMOs, including the use of GMOs in humans. However, the definition of a GMO does not include human beings who have undergone somatic cell therapy (ie such persons do not need to be licensed under the GT Act).

What are ‘dealings’ with genetically modified organisms?

The GT Act operates through the definition of ‘deal with’, which, in relation to a GMO, means to:

(a) conduct experiments with the GMO;
(b) make, develop, produce or manufacture the GMO;
(c) breed the GMO;
(d) propagate the GMO;
(e) use the GMO in the course of manufacture of a thing that is not the GMO;
(f) grow, raise or culture the GMO; and
(g) import the GMO.

It also includes the possession, supply, use, transport or disposal of the GMO for the purposes of, or in the course of, a dealing mentioned in any of the paragraphs (a) to (g).

A person who ‘deals with’ a GMO requires appropriate notification or approval under the GT Act for:

- notifiable low-risk dealings (NLRDs, contained research work that has been demonstrated to pose minimal risk to workers, the general public or the environment, provided that specified conditions are met); or
- licensed dealings (research work with GMOs that requires safety assessment and oversight by a licence holder, with or without intentional release of the GMO to the open environment);
- registered dealings (procedures that have been licensed for some time and are considered safe for more general application).

The following activities do not require specific notification or approval under the GT Act:

- dealings with organisms that are not GMOs, as defined in the GT Regulations;
- dealings that pose minimal risk, such as research involving very well understood processes for creating or studying a GMO and that do not involve intentional release of the GMO into the environment (exempt dealings); and
• dealings already listed on the GMO Register (anyone may undertake the dealing once it is listed on the register, subject to any specified conditions attached to the dealing).

The gene technology regulatory system is based on rigorous scientific risk assessment and extensive consultation with expert advisory committees, government agencies and the public. Licensed dealings and NLRD are entered in the ‘Record of GMO and GM Product Dealings’, which is the comprehensive database of GMOs and GM products approved for use in Australia.

**Release of genetically modified organisms into the environment**

An important consideration for the GT Regulator when assessing an application for a GMO dealing is whether or not it is proposed that the GMO be intentionally released into the open environment (ie whether the GMO is going to be used outside of biocontainment facilities, such as growth of a GMO crop or release of GMO animals into the wild).

If the GMO is to be intentionally released into the environment, the GT Regulator must develop a draft risk assessment and risk management plan and provide the draft plan for public comment. In accordance with the object and the provisions of the GT Act, the GT Regulator must, before issuing a licence for release of a GMO into the environment, be satisfied that the release can be managed in such a way as to protect the health and safety of people and the environment.

9.4.2 What is a genetically modified product?

A GM product is defined in the GT Act as ‘a thing (other than a GMO) derived or produced from a GMO’.

In essence, 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. In contrast, GM products are derived from GMOs but are not viable, capable of reproduction or capable of transferring genetic material.

**How are genetically modified products regulated?**

GM products are generally regulated by other regulatory agencies, such as the National Registration Authority for Agricultural and Veterinary Chemicals (GM agricultural and veterinary chemicals); the Australia New Zealand Food Authority (GM foods); and the TGA (GM therapeutics).

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 GT Regulator of the decision regarding the GM product, so that the GT Regulator can include the information on the ‘Record of GMO and GM Product Dealings’.
9.4.3 Production of genetically modified animal tissue or organs for xenotransplantation (xenotransplantation products)

There are two stages in the production of GM animal tissue or organs for xenotransplantation, which are described below.

Stage 1: insertion of human genes into the donor animal genome
Source animals for xenotransplantation modified by gene technology to include human or other genes are classed as GMOs. Research to produce GM source animals, such as pigs, is therefore classified as a ‘dealing’ with a GMO under the GT Act. Investigators proposing to undertake such research must first have their proposal assessed by their institutional biosafety committee (IBC). The IBC assists the investigator to assess whether the work falls under the scope of the GT Act and Regulations, and whether it requires notification as an NLRD or licensing. The IBC also assists its organisation to comply with the requirements of the GT Act and Regulations, and any conditions imposed by the GT Regulator.

Xenotransplantation research does not involve an intentional release of a GMO into the open environment. Transgenic pigs or other GM source animals are kept in biocontainment facilities; animal products and byproducts not used in xenotransplantation are disposed of by appropriate methods.

Stage 2: removal of tissues from the donor animal and their transplantation into either an animal or a human recipient
Xenotransplantation products used in animal recipients are monitored by the AEC at the institution where the research is carried out, taking account of the Code of Practice and the NHMRC Policy on the Use of Non-Human Primates in Medical Research (NHMRC 1997e), with appropriate monitoring to ensure that any infections passed from donor to recipient animals are contained.

Xenotransplantation products used for human recipients are regulated primarily by the TGA under the TG Act, as described in Section 9.3. To obtain exemption from registration for use in an animal-to-human clinical trial, investigators and sponsors are currently required to apply under the CTX scheme for approval by the TGA and the HREC at the institution where the research is proposed, with scientific review and advice provided by GTRAP.

As well as coming under the definition of a therapeutic good, a GM xenotransplantation product (ie from a GM source animal) would also need to comply with the relevant regulations under the GT Act. GM xenotransplantation products would be most likely to be covered by the GT Act definition of a GM product rather than of a GMO. As such, under the Gene Technology (Consequential Amendments) Act 2000, the TGA will need to consult with and take account of advice from the GT Regulator about the use of GM xenotransplantation products, as discussed in Section 9.4.

However, as xenotransplantation products are unusual products under the current definitions of the GT Act, it is possible that some further assessment by the OGTR 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.
QUESTION

Is this an accurate summary of the Gene Technology Act and the role that the Gene Technology Regulator will play in the regulation of xenotransplantation research in Australia?

9.5 Other legislation

9.5.1 State and Territory public health acts

State and Territory public health acts may apply if it is considered that there is a risk to public health and safety from xenotransplantation research (e.g., the theoretical risk of adaptation of PERV to humans).

9.5.2 Australian Quarantine Act

The Commonwealth Department of Agriculture, Fisheries and Forestry — Australia (AFFA) and Australian Quarantine Inspection Service (AQIS) have powers under the Quarantine Act 1908 and related regulations to regulate the import into Australia of live biological material that may present a risk to human health and safety or the environment. This would cover animal material proposed for use in xenotransplantation research, whether or not it is genetically modified. Under these provisions, AQIS may also be able to prevent people who have received xenotransplants from entering Australia.

If the material being imported is a GMO that falls under the scope of the GT Act, the importer may also require approval from the GT Regulator. The GT Regulator assesses risks to human health and safety and risks to the environment posed by the GMO. The type of notification or approval necessary will depend on the type of GMO that it is intended to import (i.e., whether the GMO is an NLRD, is on the GMO Register or is licensed under the GT Act).

In general, it is anticipated that an organisation wishing to conduct dealings with a GMO in Australia (i.e., use it for research, breed or propagate it etc) will need to seek approval from the GT Regulator to undertake dealings with the GMO. As part of this approval the organisation will also need to seek approval from the GT Regulator to import the GMO, if this is necessary. The importer would then be one of the persons covered by the licence (or by notification of an NLRD) for the purposes of importing the GMO. These requirements are in addition to the requirements under the Quarantine Act for inspection and regulation by AFFA and AQIS.
## 10 International developments

### OVERVIEW

This chapter summarises international developments in the regulation of xenotransplantation research.

### United Kingdom

The United Kingdom Xenotransplantation Interim Regulatory Authority regulates xenotransplantation, which may be acceptable if certain criteria are met. There is a national registry of electronic data on transplant recipients and related information. As at July 2001, there were no clinical trials of xenotransplantation in progress.

### United States

The Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS) regulate xenotransplantation through several committees. A national database is being developed but at the time of writing, information was available only through local registries. Limited clinical trials in xenotransplantation are under way.

### Canada

Health Canada regulates xenotransplantation through national standards. There is no registry of relevant data and there are no surveillance facilities. As at July 2001, no clinical trials had been approved.

### New Zealand

The New Zealand Ministry of Health regulates xenotransplantation; requirements are the same as for any other clinical trial. A trial on xenotransplantation of encapsulated pig pancreatic islet cells for treatment of diabetes was not successful and applications for follow-up trials have been rejected because of concerns about pig endogenous retrovirus transmission. No clinical trials are in progress.

### European Union (overall)

Some member states of the Council of Europe are preparing guidelines to regulate xenotransplantation; others are not. In 2001, the Working Party on Xenotransplantation prepared a report on xenotransplantation. The document calls for the development of European guidelines to harmonise existing laws and strengthen inadequate legislation. Spain, Belgium and Germany have clinical trials under way, proposed or suspended pending further investigation.

### World Health Organization

In 1998, the Office of Zoonoses Prevention and Control released guidelines for the prevention and management of xenozoonoses. The guidelines deal with the assessment of the risk of transmission of contagious diseases from animal tissues to human recipients, but do not address ethics, animal welfare and socioeconomics.
10.1 Introduction

Since advances in molecular biology have provided fresh hope that xenotransplantation may become a clinical reality in the near future and with increasing transplant waiting lists in most countries, regulatory agencies in most developed countries have been addressing the problem of how to assess and regulate animal-to-human xenotransplantation proposals. The following is representative but not exhaustive of international developments in the regulation of xenotransplantation research overseas. Further information on the regulatory arrangements for xenotransplantation in other countries is available on the internet.11

10.2 Regulation of xenotransplantation overseas

10.2.1 United Kingdom

National committee

In late 1995, the Advisory Group on the Ethics of Xenotransplantation was formed under the chairmanship of Professor Ian Kennedy; in January 1997, it published a report to the government entitled Animal Tissue into Humans (UK DHAGEX 1997). The report’s main conclusion was that xenotransplantation could be acceptable provided that certain criteria were met. There were more than 60 detailed recommendations, including one for establishing a regulatory body to oversee the development of xenotransplantation in the United Kingdom. In response to this report, the government established the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) to regulate the development and implementation of xenotransplantation.

UKXIRA’s terms of reference are:

- To advise the Secretaries of State of the United Kingdom health departments on the action necessary to regulate xenotransplantation, taking into account the principles outlined in Animal Tissues into Humans (UK DHAGEX 1997) and worldwide developments in xenotransplantation, and in particular to advise:
  - on safety, efficacy and considerations of animal welfare in liaison with the Home Office, and any other preconditions for xenotransplantation for human use, and whether these have been met;
  - on research required to assess safety and efficacy factors in xenotransplantation procedures;
  - on the acceptability of specific applications to proceed with xenotransplantation in humans; and
  - to provide a focal point on xenotransplantation issues within government.

11 http://www.oecd.org/dsti/sti/s_t/biotech/xenosite/country.htm
Guidelines

The United Kingdom has not placed a moratorium on xenotransplantation research.

UKXIRA defines xenotransplantation as any procedure that involves the use of liver cells, tissues and organs from a nonhuman animal source, transplanted or implanted into a human or used for ex vivo perfusion.

On 30 July 1998, UKXIRA issued a set of guidelines to regulate xenotransplantation in human subjects: Guidance on Making Proposals to Conduct Xenotransplantation on Human Subjects (UKXIRA 1998). The document provides guidance for clinical procedures involving xenotransplantation. The guidelines provide the United Kingdom National Health Service with directions for the commissioning and provision of treatments involving xenotransplantation procedures. They also describe the arrangements under which clinical trials or procedures involving xenotransplantation may be undertaken, and the system for seeking approval to undertake such trials or procedures.

UKXIRA has now developed standards of tissue quality (including consideration of the biosecurity standards that animal facilities should maintain) and a nationwide surveillance system. UKXIRA guidelines and related documents can be found on the internet.12

Registries and archives

The United Kingdom has a national registry of electronic data on transplant recipients, participating centres, facilities supplying xenotransplantation products and so on. There are also local archives of biological samples from recipients and source animals.

The United Kingdom government is considering the establishment of a centralised government-managed facility (biobank) for collection and storage of all samples and associated information.

Clinical trials

There are currently no clinical trials of xenotransplantation in progress in the United Kingdom.

10.2.2 United States

Committees

In the United States, the primary regulatory agencies are the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS). Advisory committees include:

- the Xenotransplantation Subcommittee of the FDA Biological Response Modifiers Advisory Committee, which was formed in 1997 as an ongoing mechanism for open discussions of the scientific, medical, social and ethical issues and the public health concerns raised by xenotransplantation, as well as specific ongoing and proposed protocols. Open public meetings update the committee and the general public on the

12 http://www.open.gov.uk/doh/ukxira.htm
issues associated with xenotransplantation and the development of FDA policy regarding xenotransplantation products.

- the DHHS Secretary’s Advisory Committee on Xenotransplantation, which was established in 1999 and which discusses ongoing and proposed protocols, considers a full range of complex scientific, medical, social, ethical and public health concerns raised by xenotransplantation, and makes recommendations to the Secretary on policy and procedures.

- the DHHS Xenotransplantation Committee, which oversees departmental initiatives to address the public health issues raised by xenotransplantation. It has members from the FDA, Centers for Disease Control and Prevention, National Institutes of Health, and Health Resources and Services Administration and is administered through the Office of the Assistant Secretary for Planning and Evaluation and the Office of Science Policy.

The FDA Center for Biologics Evaluation and Research (CBER), which has been instrumental in understanding safety issues associated with xenotransplantation. CBER has issued a *Xenotransplantation Action Plan* (US CBER 2001), which is designed to provide a comprehensive approach to the regulation of xenotransplantation.

**Guidelines**

The United States has not placed a moratorium on xenotransplantation research. The FDA definition of xenotransplantation is the same as that given in Section 2.1.2.

Xenotransplantation products are subject to regulation by the FDA. Under statutory provisions governing premarket development, xenotransplantation products are subject to FDA review and approval. The FDA must review proposed xenotransplantation clinical trials before investigators can proceed.

The FDA has also announced the availability of a draft guidance document entitled *Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans* (US FDA 2001). This document is intended to provide guidance on the production, testing and evaluation of products intended for use in xenotransplantation. The draft guidance includes scientific questions that should be addressed by sponsors during protocol development and during the preparation of submissions to the FDA (eg investigational, or ‘biologics’ licence application). The topics in the draft guidance include regulatory responsibility; source animal and xenotransplantation products characterisation; microbiological testing of xenotransplantation products; manufacturing and process-related good manufacturing practice considerations for harvest and processing of xenotransplantation products; preclinical considerations for xenotransplantation products; and clinical issues in xenotransplantation.

Xenotransplantation products require premarket approval by FDA. Such products include live organs, tissues or cells from a nonhuman source, or xenotransplantation product materials used in encapsulated form or in which nonhuman live organs, tissues or cells have ex vivo contact with human body fluids, cells, tissues or organs that are subsequently given to a human recipient. If xenotransplantation products are to be used in clinical investigation, they require an appropriate investigational application to FDA.
Most xenotransplantation products will be regulated as biological products by the FDA CBER.

Some products may be combination products consisting of a biologic and a device. One example is xenogeneic cells contained in a device used for extracorporeal (ex vivo) haemoperfusion. Other products may be combinations of a biologic and a drug; for example, a novel immunosuppressive agent might be used only for a specific xenotransplantation product. The regulation of combination products is determined by the primary mode of action of the product.

These guidelines and other related FDA documents are available on the internet: 13

A second recent document released by the FDA is a proposed rule: Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation. The proposed rule is intended to allow disclosure of certain information about experimental clinical procedures in xenotransplantation and gene therapy, none of which should be conducted in the United States without FDA oversight. The rule has been put forward to allow the FDA to disclose to the public more information about proposed xenotransplant and gene therapy trials than is usually the case for investigational new drug (IND) trials. This rule has been proposed because clinical research trials for xenotransplantation and gene therapy have the potential to create unique public health risks or to modify the human genome.

The proposed rule would change relevant FDA regulations to allow the FDA to disclose the name and address of the sponsor, the clinical indications for the xenotransplant product, the protocol for each planned study, sample patient informed consent forms and the regulatory status of the IND. The biological products would be disclosed together with a general description of product features that may have safety implications, such as herd source, animal health maintenance and surveillance records and a description of the biological specimens to be archived. Product and patient safety data, results of product safety testing, including tests for infectious agents, and information on monitoring or prevention of health risks to the recipient, close contacts and health care workers would be disclosed. Trade secret information or patient identifiable information would not be disclosed. However, if accepted, the proposed rule would require sponsors of xenotransplantation and gene therapy trials to provide a version of their IND submissions for public access.

Registries and archives

Registries of electronic data on transplant recipients, participating centres, facilities supplying xenotransplantation products and so on are maintained by sponsors on a local basis. A national xenotransplantation database (NXD) is being developed; as at July 2001, it was still in pilot form. Archives of biological samples from recipients and source animals are also maintained locally.

13 http://www.fda.gov/cber/xap/xap.htm
The government is considering the establishment of a centralised facility (biobank) for collection and storage of all samples and associated information. The facility would be managed by the government.

**Trials**

In the United States limited clinical trials in xenotransplantation are now in progress under FDA regulation. These include the investigational use of ex vivo perfusion of blood through whole liver or isolated hepatocytes in patients with fulminant liver failure, and the transplantation of fetal pig neuronal cells into patients with refractory Parkinson’s disease and other neurological diseases.

**Designated central surveillance facility**

The United States does not have a designated central surveillance facility. The FDA and Centers for Disease Control and Prevention (CDC) both have a role in surveillance for all clinical trials and infectious outbreaks, respectively. There will not be a xenotransplantation-specific mechanism for surveillance until the NXD is operational.

**10.2.3 Canada**

Canada’s response to advances in xenotransplantation is similar to that of the United States. A National Forum on Xenotransplantation was held in November 1997. It was the first opportunity for Canadian health departments to consult broadly with stakeholders — health professionals, patient, animal care and consumer groups, ethicists, companies and research groups — on the clinical, ethical and regulatory issues for xenotransplantation.

In August 2000, the Canadian government funded the Canadian Public Health Association to form a Public Advisory Group on Xenotransplantation and conduct consultations across Canada. The report of the group has been submitted to the minister of health.

**National committee**

An expert advisory committee mandated by Health Canada advises on the regulation of xenotransplants.

**Guidelines**

Canada has not placed a moratorium on xenotransplantation research. Health Canada has chosen to develop a standards-based risk management (SBRM) regulatory framework for the safety of all organs and tissues used for transplantation. Key components of the SBRM approach are the Canadian General Standard on Safety of Organs and Tissues for Transplantation, and the development of specific subset standards for individual organ and tissue groups, including for xenotransplantation, which will be recognised under the National Standards System of Canada (see Health Canada 1999).

---

SBRM addresses the need to continually update and revise practices as science evolves. It can complement international activities and facilitate harmonisation of regulatory approaches. Under the Canadian *Food and Drugs Act*, xenotransplants are considered as therapeutics, and Health Canada therefore has the authority to regulate xenotransplantation as a new technology. More information can be found on the internet15

**Registries and archives**

As at July 2001, Canada did not have registries of electronic data or archives of biological samples, although the Proposed Canadian Standard for Xenotransplantation describes both as important issues to be addressed.

The government is considering the establishment of a centralised, government-managed facility (biobank) for collection and storage of all samples and associated information.

**Trials**

As at July 2001, no clinical trials involving xenotransplantation had been approved by Health Canada.

**Designated central surveillance facility**

Canada does not have a designated central surveillance facility.

### 10.2.4 New Zealand

New Zealand has not yet developed specific guidelines for xenotransplantation. Currently, xenotransplantation is regulated by the New Zealand Ministry of Health under the New Zealand *Medicines Act 1981*. Xenotransplantation clinical trials must meet the same requirements for safety as any other clinical trial.

New Zealand does not have any clinical trials of xenotransplantation in progress. A trial of xenotransplantation of encapsulated pig pancreatic islet cells for treatment of diabetes was conducted with six participants in the late 1990s, but in all cases the cells failed after several months (Elliot et al 2000). Subsequent applications for follow-up trials by the same investigators have been rejected in New Zealand because of concerns about porcine endogenous retrovirus (PERV) transmission but are proceeding in Mexico (see Section 5.5).

### 10.2.5 European Union (overall)

Xenotransplantation has recently been addressed at the Council of Europe by the Steering Committees on Health and Bioethics and by the Working Group on Organ Transplantation. The working group supported research on xenotransplantation on the basis that feasibility and risks can be evaluated. It also promoted the organisation of public debate at a European level, in cooperation with relevant international organisations, in order to achieve the broadest possible consensus on these issues.

15 [http://www.xeno.cpha.ca/english/index_e.htm](http://www.xeno.cpha.ca/english/index_e.htm)
The steering group adopted a series of recommendations, and in 1997 the Committee of Ministers of the Council of Europe adopted the ‘Recommendation on Xenotransplantation’.

This recommendation asked Member States to provide regulations to cover the potential risk of transmission of infectious disease from xenotransplantation. In 1999, however, the Parliament of the Council of Europe passed a different recommendation, which invoked a precautionary principle and proposed a moratorium on clinical trials in xenotransplantation. The Committee of Ministers did not approve the parliament’s decision but set up a Working Party on Xenotransplantation (WPX) under the joint responsibility of the Steering Committee on Bioethics and the European Health Committee.

The WPX was constituted to prepare a report on the state of the art of xenotransplantation and to prepare draft guidelines. A preliminary draft was developed in 2000 and the final document was expected at the end of 2001. The draft report strongly opposed the use of primates for xenotransplantation and considered issues such as animal welfare concerns where animals may be bred in conditions aimed at reducing the presence of microbiologic agents. The draft document focused heavily on the issues of informed consent and the social response to xenotransplantation. The WPX is of the view that it would be difficult to get informed consent because of the high level of restriction placed on the participant and because the normal pattern of freedom to withdraw from a trial may not be allowed. WPX also proposed that informed consent should be obtained from close family members as well as from the patient. Because of the unique potential risk to the community, WPX acknowledged that agreement of society at large as well as the patients would be required. The public response has been difficult to assess but at this stage surveys of public opinion indicate no public bias against xenotransplantation in Europe. Some member states are preparing guidelines to regulate xenotransplantation; others are not. The draft report notes this and calls for the development of European guidelines to harmonise existing laws and strengthen inadequate legislation.

The current situation in the United Kingdom is described in Section 10.2.1. Table 10.1 shows the situation in some other European countries.

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16 Recommendation No. R(97)15 of the Committee of Ministers to Member States on Xenotransplantation:

Considering that xenotransplantation, that is, the use of living organs, tissues and/or cells from animals, whether genetically modified or not, for transplantation into humans, may become a practicable therapeutic intervention in the very near future,

Aware that there is a risk of transmission of disease as a result of xenotransplantation procedures,

Recommend that Governments of Member States should establish a mechanism for the registration and regulation of the following aspects of xenotransplantation with a view to minimising the risk of transmission of known or unknown diseases and infections to either the human or animal population:

– basic research and clinical trials;
– the source and care of animals for use in xenotransplantation;
– xenotransplantation programmes;
– long-term follow-up and review of xenograft recipients and the xenograft source animals.
10.2.6 World Health Organization

In 1998, the Office of Zoonoses Prevention and Control, of the Division of Emerging and Other Communicable Diseases, Surveillance and Control, released a first guidance document for the prevention and management of xenozoonoses (WHO/EMC/ZOO/98.1, 1998). These guidelines deal with the assessment of the risk of transmission of contagious diseases from animal tissues to human recipients, considering known, as well as unknown, agents. The guidelines do not address other issues related to xenotransplantation such as ethics, animal welfare and socioeconomics. WHO held an expert meeting for the final review and endorsement of the guidelines in the northern autumn of 1997. During the meeting, ethical, social and religious issues were also discussed. Recommendations from the meeting were published in 1998 and recognised the need for further research on the safety and efficacy of xenotransplantation and the need to take account of diverse social, cultural and religious values (WHO/EMC/ZOO/98.2, 1998). The recommendations encouraged Member States to develop policies, regulations and guidance for the safe and ethical use of this technology and to provide a framework that can contribute to public health and safety at the national and international level.
### Table 10.1 Summary of xenotransplantation arrangements in various European countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Issue</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>National committee</td>
<td>Yes. German Working Group on Xenotransplantation (DAX) with broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td>representation, and the Xenotransplantation Commission of the German</td>
</tr>
<tr>
<td></td>
<td>Moratorium</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Guidelines</td>
<td>In preparation</td>
</tr>
<tr>
<td></td>
<td>Registry/archives/</td>
<td>No to all (under consideration)</td>
</tr>
<tr>
<td></td>
<td>biobank</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trials</td>
<td>Trials using ex vivo perfusion bioreactors have been initiated (but currently on hold</td>
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<tr>
<td></td>
<td></td>
<td>as the import licence for bioreactors has been suspended)</td>
</tr>
<tr>
<td></td>
<td>Designated central</td>
<td>No (under consideration)</td>
</tr>
<tr>
<td></td>
<td>surveillance facility</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>National committee</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Moratorium</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Guidelines</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Registry</td>
<td>Legal regulation and authorisation by Federal Office of Public Health</td>
</tr>
<tr>
<td></td>
<td>Archives</td>
<td>No</td>
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<tr>
<td></td>
<td>Biobank</td>
<td>Local</td>
</tr>
<tr>
<td></td>
<td>Trials</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Designated central</td>
<td>No (under consideration)</td>
</tr>
<tr>
<td></td>
<td>surveillance facility</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Yes (Federal Office of Public Health)</td>
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<tr>
<td>Belgium</td>
<td>National committee</td>
<td>No</td>
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<tr>
<td></td>
<td>Moratorium</td>
<td>No</td>
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<tr>
<td></td>
<td>Guidelines</td>
<td>No (under consideration)</td>
</tr>
<tr>
<td></td>
<td>Registry/archives/</td>
<td>No (responsibility of sponsor)</td>
</tr>
<tr>
<td></td>
<td>biobank</td>
<td></td>
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<tr>
<td></td>
<td>Trials</td>
<td>3T3-cells (autoderm on transferm) covering feeder layer (pig cells)</td>
</tr>
<tr>
<td></td>
<td>Designated central</td>
<td>No (but advised to inform the pharmaceutical inspection: ie treats cell therapy in the</td>
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<tr>
<td></td>
<td>surveillance facility</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>same way as pharmaceutical drugs )</td>
</tr>
<tr>
<td>Spain</td>
<td>National committee</td>
<td>Yes (since 1997)</td>
</tr>
<tr>
<td></td>
<td>Moratorium</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Guidelines</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Registry/archives/</td>
<td>Local registry and archives. Biobank managed by government</td>
</tr>
<tr>
<td></td>
<td>biobank</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trials</td>
<td>Yes (ex vivo perfusion device)</td>
</tr>
<tr>
<td></td>
<td>Designated central</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>surveillance facility</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>National committee</td>
<td>No (Finland does not conduct xenotransplantsations and has no plans to start them in</td>
</tr>
<tr>
<td></td>
<td>Moratorium</td>
<td>No ban</td>
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<td></td>
<td>Guidelines</td>
<td>No</td>
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<td></td>
<td>Registry/archives/</td>
<td>No</td>
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<td></td>
<td>biobank</td>
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<tr>
<td></td>
<td>Trials</td>
<td>No</td>
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<td></td>
<td>Designated central</td>
<td>No</td>
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<tr>
<td></td>
<td>surveillance facility</td>
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</table>

National committee = board of experts appointed by government whose authority, working methods and mandate is regulated (eg to advise on regulation of xenotransplantation, on the safety, efficacy and any other preconditions for xenotransplantation for human use and whether these have been met; on research required to assess safety and efficacy factors in xenotransplantation procedures; on the acceptability of specific applications to proceed with xenotransplantation trials in humans).
11 Options for regulation in Australia

OVERVIEW

This chapter outlines three models for regulating xenotransplantation research in Australia and discusses the strengths and weaknesses of each. All models would need to be underpinned by legislative changes.

Model 1—extension of the existing regulatory framework

Under this model, there would be no change to the regulatory controls for animal-to-animal (pre-clinical) xenotransplantation studies. However, the Gene and Related Therapies Research Advisory Panel (GTRAP) would have increased powers to oversee animal-to-human (clinical) trials. GTRAP has the scientific expertise to assess xenotransplantation research proposals, but would need additional members with animal welfare, veterinary and community expertise. Its terms of reference would be broadened to reflect the change from advisory panel to national decision-making organisation.

There would be a change in GTRAP’s relationship to human research ethics committees (HRECs). At present, GTRAP provides advice to HRECs, which make the final decision on whether or not to approve research at their institution. Under the proposed arrangements, HRECs could not approve research if it was not first approved by GTRAP. As animal ethics committees (AECs) and HRECs would be jointly involved in decisions about research at their institutions, there would need to be cross-membership between these committees.

This model would draw on GTRAP’s existing experience and knowledge of the issues involved and its links with the NHMRC, Therapeutic Goods Administration (TGA), Office of the Gene Technology Regulator, Australian Health Ethics Committee and HRECs. The model is cost-effective because there would be no need for a separate scientific advisory body.

Model 2 — formation of a national xenotransplantation committee

As for model 1, model 2 would not require any change to the current regulatory arrangements for animal-to-animal xenotransplantation research. For animal-to-human trials, a single national xenotransplantation committee established under the auspices of the NHMRC would approve and oversee all xenotransplantation research and development in Australia.

However, the proposed committee would not have the necessary expertise on all aspects of xenotransplantation safety and efficacy, so it would need the assistance of an expert advisory panel. GTRAP could fill this role, but the final decision about whether to approve or not approve a proposal would rest with the national xenotransplantation committee. As for model 1, institutional HRECs could only approve research at their institution if it was first approved by the national committee and there would require cross-membership between the AEC and HREC.

Separating the national decision-making committee from the scientific advisory group (GTRAP) should increase community confidence in the independence of the processes. However, there would be potential for delays and increased costs because some work may be duplicated while proposals are examined both GTRAP and the new national committee. The national committee would also require some scientific expertise, thus increasing the potential for duplication of resources and once again raising the issue of possible conflict of interest.

Model 3 — TGA as the sole regulatory agency

The working party briefly considered a third model, in which the entire process of assessment of xenotransplantation would be handled by the TGA, but does not support this idea because of the loss of the current close links between HRECs, researchers, AHEC, GTRAP and NHMRC.

Legislation requirements

Whichever model is ultimately followed to regulate xenotransplantation research will need to be underpinned by legislation. This may involve changes to the NHMRC Act 1992, the TG Act 1989, the GT Act 2001; or development of specific legislation for xenotransplantation.
11.1 **Introduction**

In this chapter, the working party outlines three possible models for the regulation of xenotransplantation research in Australia and requests comments on the models presented. As outlined in earlier chapters, xenotransplantation in humans raises scientific and ethical issues, especially in relation to safety and efficacy. These issues need to be considered in an ongoing way by an appropriate independent body, so that the Australian community is reassured that decisions to proceed to clinical trials are based on thorough assessment of safety, efficacy and ethical issues and that if trials do proceed they are properly monitored.

11.1.1 **Requirements for adequate regulation**

The working party recommends that the regulatory process chosen for 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 overseeing bodies in other countries; and
- the ability to regulate all xenotransplantation research in the public and private sector.

More specifically, a number of areas of expertise required to assess xenotransplantation research proposals have been identified in Chapters 5–8 of this discussion paper. These areas of expertise include:

- 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.

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 stand down if necessary.
11.1.2 Proposed models for regulation

The working party seeks comment on the following models that it has developed for the regulation of xenotransplantation in Australia.

- Model 1 — an extension and strengthening of the existing regulatory model based on the Gene and Related Therapies Research Advisory Panel (GTRAP; described in detail in Chapter 9 and in Appendix 5).

- Model 2 — formation of a separate xenotransplantation committee within the NHMRC but also linked to some of the existing mechanisms.

- Model 3 — direct oversight of xenotransplantation research by the Therapeutic Goods Administration (TGA).

For each of these models, legislative and/or regulatory changes will be required to underpin the process. Further details of these models and the legislative arrangements that will be required are given below.

11.2 Model 1 — extension of the existing regulatory framework

The current regulatory arrangements are described in Chapter 9. Figure 11.1 shows a flowchart of the proposed model 1.

11.2.1 Regulation of animal-to-animal studies

The current regulatory controls on animal experimentation will continue to apply for animal-to-animal (preclinical) xenotransplantation studies (ie those not involving any human research component). Research proposals will need to be consistent with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC 1997d) (Code of Practice) and must be approved by the animal ethics committee (AEC) of the institution in which the research will be conducted (see Section 9.2 for details of the current arrangements).

11.2.2 Regulation of animal-to-human trials

For animal-to-human (clinical) xenotransplantation trials, regulation currently involves a combination of initial review by the TGA and GTRAP, with local review and approval by the human research ethics committee (HREC) of the institution in which it is proposed that the research will be conducted (see Section 9.3).

Under model 1, the working party proposes continuing to use GTRAP as the central oversighting body for xenotransplantation research, but with significant changes to its powers and to the method of appointment of members and membership categories, and with a name that more accurately describes its role, such as the ‘National Xenotransplantation and Gene Therapy Committee’ (referred to here as NXGTC). The working party wishes to emphasise that, while building upon the expertise and breadth of membership already existing, this proposal significantly strengthens GTRAP’s membership and enhances its powers.
Terms of reference

The current terms of reference of GTRAP are shown in Appendix 5. These would need to be revised to better reflect the new role of the committee. The revised terms of reference would need to include the following terms specific to xenotransplantation (ie in addition to terms that relate to gene therapy):

- to advise on the data required to assess safety and efficacy in xenotransplantation procedures;
- to assess the safety, efficacy and any other preconditions for proceeding with animal-to-human xenotransplantation procedures after seeking expert advice from its scientific and technical expert subcommittee (GTRAP);
- to assess the acceptability of specific applications to proceed with xenotransplantation trials in humans;
- to authorise and monitor the conduct of xenotransplantation clinical trials, including the imposition of any conditions deemed necessary for their safe conduct;
- to maintain a register of all trials and all participants;
- to monitor overseas developments in xenotransplantation; and
- to liaise with the Animal Welfare Committee over the use of animals in preclinical studies and clinical trials.

Membership

The current membership of GTRAP is described in Appendix 5.

Its membership includes:
- persons coopted from the NHMRC Research Committee and Australian Health Ethics Committee (AHEC);
- a nominee of the TGA;
- persons coopted from the Gene Technology Technical Advisory Committee (an advisory committee of the Office of the Gene Technology Regulator; OGTR);
- a person with knowledge of ethics;
- a legal/consumer representative; and
- ‘other persons who bring relevant expertise’.

Thus, the existing panel currently includes most of the scientific, legal and ethical input necessary for the oversight of xenotransplantation and includes a member in common with AHEC as well as members from the TGA and OGTR. To fulfil the role proposed in this model, the committee would need additional membership categories to ensure that the desirable characteristics identified in Section 11.1 are fulfilled. Thus it is envisaged that the expanded membership would include:

- a member in common with the AWC;
- additional community member(s); and
- a person with veterinary expertise.
In addition, it would be desirable to clearly stipulate all the categories of membership and expertise that are deemed desirable for the expanded role of the committee.

**QUESTION**

*Is the suggested new membership of the proposed ‘National Xenotransplantation and Gene Therapy Committee’, based on GTRAP, suitable for assessment of human xenotransplantation research proposals?*

*If not, what other expertise would be required to provide a balanced input to decision making?*

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**Figure 11.1** Flowchart showing model 1 — extension of the existing regulatory framework

CTX = Clinical Trial Exemption Scheme; TGA = Therapeutic Goods Administration; OGTR = Office of the Gene Technology Regulator; NXGTC = [proposed] National Xenotransplantation and Gene Technology Committee (based on GTRAP); GTRAP = Gene and Related Therapies Advisory Panel; HREC = human research ethics committee; AEC = animal ethics committee
**Reporting relationships and method of appointment**

GTRAP is a subcommittee of the Research Committee of the NHMRC. Members of GTRAP are appointed by the NHMRC upon the recommendation of the Research Committee. To meet the requirements suggested by the working party, it is suggested that the proposed NXGTC report directly to the NHMRC, that its chairperson be appointed by the NHMRC Council, subject to the approval of the Minister of Health and Ageing, and that members be appointed by the NHMRC Council.

**Scientific advice**

Under this model, there would be no need for external expert advice, as the proposed NXGTC would already have the necessary scientific expertise to assess xenotransplantation research proposals. Hence, in this case, scientific advice and approval would be provided by the same group.

**Relationships with institutions wishing to undertake xenotransplant clinical trials**

Within the current NHMRC framework of regulation, GTRAP provides advice but not direction to institutional HRECs. The final decision on whether to approve a research proposal is made by the institutional HREC itself. In other words, it is possible under the present arrangements for HRECs to disregard GTRAP advice and, based on their own assessment, approve or disapprove specific proposals for their host institution. It should be noted however that this has not occurred in practice and, while it remains a possibility, there are a number of factors that reduce this risk, including the legal liability of the institution and of the clinical investigators.

However, to ensure consistent national regulation of xenotransplantation research, the working party is proposing a different arrangement for xenotransplantation (and for gene therapy research) under the proposed NXGTC. Under these arrangements, research could not proceed without the approval of the national committee. Local HRECs would still have the authority to refuse permission for the research to be undertaken at the institution but would not be able to approve research for their institution if the national committee had not approved it. HRECs would also have a key role in liaising with the modified GTRAP (if modification of any research protocol were sought at their institution) and would be involved in monitoring the research.

**Appeals process**

An issue requiring consideration is whether there is a need for an appeals process for the proposed NXGTC. Currently, decisions taken by the TGA can be appealed to the federal Administrative Appeals Tribunal. At the local level, decisions of HRECs are not formally open to appeal, but under the processes of the National Statement, institutions and their HRECs are expected to have a complaints process established. The *NHMRC Act 1992* establishes a Commissioner for Complaints, an office that has primarily dealt with complaints from research grant applicants. This pathway may need to be explored as an internal appeals or review pathway.
**QUESTIONS**

What sort of appeals/complaints/review process should be available to investigators and research sponsors who wish to have a decision of the proposed ‘National Xenotransplantation and Gene Therapy Committee’, based on GTRAP, reviewed?

How could such a process be best established?

**Relationship to animal ethics committees**

Under the proposed new arrangements for xenotransplantation research, AECs and HRECs will be jointly involved in decisions about whether an animal-to-human trial proposal that has been approved by the proposed NXGTC can proceed at the institution they represent. This decision process will require cross-membership between the AEC and the HREC at an institution (or at least the attendance of an AEC member when the HREC is considering a xenotransplant clinical trial proposal).

AECs will continue to be responsible for assessing proposals for animal-to-animal studies and for monitoring such research in their institution.

**Monitoring and follow-up of trials**

Under this model, it is proposed that the new NXGTC should be responsible for maintaining a centralised database or register of all xenotransplant clinical trials. The committee should also be responsible for advising local HRECs of the monitoring and reporting requirements of any trial that is approved. Consideration needs to be given as to whether the national committee should be given powers to audit clinical trials directly (including onsite visits) or whether this power is adequately addressed through the TGA legislation.

**QUESTIONS**

Should the proposed ‘National Xenotransplantation and Gene Therapy Committee’, based on GTRAP, oversee monitoring of xenotransplantation clinical trials by institutional human research ethics committees?

Does the proposed ‘National Xenotransplantation and Gene Therapy Committee’, based on GTRAP, require the power to audit such trials (including onsite visits) or is this power addressed by current Therapeutic Goods Administration legislation?

**Legislative framework/powers**

Model 1 derives most of its authority from the *Therapeutic Goods Act 1989* (with amendments). Chapter 9 describes the strengths and weaknesses of the TGA Act as it applies to the oversight of xenotransplantation, as well as the role of the OGTR as administrator of the *Gene Technology Act 2000*.

Legislative changes will therefore be required to underpin this model, if it is to have all the powers outlined above. Such changes may involve:

either

- amendments to the *NHMRC Act 1992*, the *Therapeutic Goods Act 1989* and possibly the *Gene Technology Act 2000*;

or

- development of specific legislation to regulate xenotransplantation research and clinical application, as has occurred with the establishment of the OGTR.
In drafting new legislation, it is very important that the links between the TGA, the OGTR and the proposed NXGTC (ie the reorganised GTRAP) are made clear. Particular attention is needed to ensure that the NXGTC has the necessary powers to assess and approve xenotransplantation research undertaken in both the public and private sectors.

Section 11.6 discusses some specific regulatory issues that will need to be addressed.

**Resourcing**

GTRAP is currently resourced by the NHMRC and it is proposed that this will continue for the new NXGTC (based on GTRAP). At present, there are relatively few trial proposals in the two fields, but if the workload increases, applicants making proposals for human xenotransplantation trials could be charged for the cost of reviewing the proposal, just as HRECs currently charge for the review of sponsored clinical trials.

**11.2.3 Arguments for and against model 1**

If given sufficient powers, this model can meet all the desired characteristics outlined in Section 11.1. GTRAP has already gained committee experience in reviewing a xenotransplantation proposal, and has also had seven years of experience advising on the introduction and conduct of human clinical trials involving gene therapy in Australia. The latter experience and expertise is directly relevant for the assessment of xenotransplantation research for two reasons. First, it is anticipated that genetically modified animals will be used for donor organs. Second, gene therapy research involves the use of viral vectors and this expertise overlaps with the assessment of the risks of retrovirus transmission in xenotransplantation. Additionally, it should be noted that to enable GTRAP to adequately consider xenotransplantation proposals, its terms of reference were previously broadened and its membership was expanded to include two experts in xenotransplantation and one with expertise in infectious diseases of relevance to xenotransplantation.

GTRAP already functions as a very cost-effective body and has the necessary links with the NHMRC, the TGA, AHEC and HRECs. It also has members with expertise in gene manipulation, which is likely to be a consideration for xenotransplantation research. As outlined above, the NHMRC can amend the membership of GTRAP to cover all the areas of expertise required (including animal welfare). It can therefore be argued that the use of GTRAP in this way will give additional efficiencies (compared to model 2, below), in that the required expert advice on safety and efficacy will be located within the committee, thereby removing the need for a separate scientific advisory group.

It could be argued that having active xenotransplantation investigators on the committee might create potential conflicts of interest. However, the NHMRC has well-developed processes for dealing with this concern. Such conflicts are likely to be raised in any such committee, because the number of people with the necessary expertise in Australia is limited and is likely to remain small for the foreseeable future.
11.3 Model 2 — a new committee

The second model differs from the first in two ways. First, it sets up a separate process for assessing xenotransplantation protocols to that for gene therapy protocols. Second, it would obtain its scientific and technical advice about xenotransplantation from a subcommittee (which could be the existing GTRAP).

Figure 11.2 shows a flowchart of the proposed model 2.

11.3.1 Regulation of animal-to-animal studies

As for model 1, no change is proposed to the current regulatory arrangements for animal studies (ie animal-to-animal xenotransplantation research).

11.3.2 Regulation of animal-to-human trials

Under this model, the working party proposes the option of a separate national xenotransplantation committee, which would be established under the auspices of the NHMRC with legislative backing to approve and oversee all animal-to-human (clinical) xenotransplantation research and development in Australia.

The following is an outline of the proposed terms of reference, membership, method of appointment of members, resourcing and other relevant matters for a national committee.

Terms of reference

The terms of reference of a new national xenotransplantation committee would include:

- to advise on the data required to assess safety and efficacy in xenotransplantation procedures;
- to assess the safety, efficacy and any other preconditions for proceeding with animal-to-human xenotransplantation procedures after seeking expert advice from its scientific and technical expert subcommittee (GTRAP);
- to assess the acceptability of specific applications to proceed with xenotransplantation trials in humans;
- to authorise and monitor the conduct of xenotransplantation clinical trials, including the imposition of any conditions deemed necessary for their safe conduct;
- to maintain a register of all trials and all participants;
- to monitor overseas developments in xenotransplantation; and
- to liaise with the AWC over the use of animals in preclinical and clinical studies.
Membership

It is proposed that the core membership of the national committee would include:

- an independent chairperson;
- member(s) with knowledge of research in or related to xenotransplantation;
- infectious diseases specialist(s);
- a member in common with the AWC with knowledge of animal ethics and welfare issues;
- a member in common with AHEC, with knowledge of ethics and related issues associated with xenotransplantation;

Figure 11.2 Flowchart showing model 2 — formation of a national xenotransplantation committee
• one representative each of the TGA and OGTR;
• a person with epidemiology and/or public health expertise;
• a person with legal training;
• one member who has knowledge of and current experience in the professional care, counselling or treatment of people with organ failure; and
• two members who are not involved currently in medical, scientific or legal work but who are actively involved in the consumer health movement or patient advocacy issues.

**Method of appointment**

The working party recommends that the committee should be appointed by the NHMRC, with the chairperson also approved by the Commonwealth Minister for Health and Ageing.

**Expert advice**

The proposed national xenotransplantation committee would not have the necessary expertise on all aspects of xenotransplantation safety and efficacy and it would therefore need an expert advisory panel to advise on scientific aspects of the procedures involved. Under this model, the working party proposes that GTRAP would fulfil the role of an expert advisory committee to the national committee but that the final decision to approve or not approve a proposal would rest with the national committee.

**Relationship to HRECs**

Under this model, as for model 1, if approval is granted by the national committee, institutional HRECs will decide whether to allow the research to proceed at their institution or not. HRECs will not, however, be able to approve research for their institution if the research has not been approved by the national committee. HRECs will also have a key role in seeking modification of any research protocol through the national xenotransplantation committee and in monitoring the research.

**Appeals**

The issue of an appeals process for the proposed national xenotransplantation committee needs to be considered as outlined for model 1.

**Relationship to animal ethics committees**

As for model 1, AECs and HRECs would be jointly involved in decisions about whether an animal-to-human trial proposal that has been approved by the national committee can go ahead at the institution they represent. This decision process will require cross-membership between the AEC and the HREC at an institution.

AECs will continue to be responsible for assessing proposals for animal-to-animal studies and monitoring such research in their institution.

**Monitoring and follow-up**

Under this model, it is proposed that the new national committee should be responsible for maintaining a centralised database or register of all xenotransplant clinical trials. The
committee should also be responsible for advising local HRECs of the monitoring and reporting requirements of any trial that is approved. Consideration needs to be given to whether the national committee should be given powers to audit clinical trials directly (including onsite visits) or whether this power is adequately addressed through the TGA legislation.

**Legislative powers**

As for model 1, this model derives most of its authority from the *Therapeutic Goods Act 1989* (with amendments) and the *Gene Technology Act 2000*.

Changes to these acts may therefore be required to underpin this model. Such legislative changes may involve:

- amendments to the *NHMRC Act 1992*, the *Therapeutic Goods Act 1989* and possibly the *Gene Technology Act 2000*;
- development of specific legislation to regulate xenotransplantation research and clinical application, as has occurred with the establishment of the OGTR.

In drafting new legislation, it is very important that the links between the national xenotransplantation committee, TGA, OGTR and GTRAP are made clear. Particular attention would be needed to ensure that the new national committee had the necessary powers to assess and approve xenotransplantation research in both the public and private sectors.

Some further specific regulatory issues that need to be addressed are discussed in Section 11.6.

**Resourcing**

The proposed national committee should be resourced by the NHMRC. In due course, however, applicants with proposals for human xenotransplantation trials would be charged for the cost of review of the proposal, just as HRECs currently charge for the review of sponsored clinical trials.

**11.3.2 Arguments for and against model 2**

Formation of a new national committee (with the existing GTRAP acting as an expert advisory body) would create a committee that has all the desired characteristics and yet maintains access to the existing expertise of GTRAP. Importantly, by separating the final decision-making committee from the scientific advisory group, community confidence in the independence of the processes should be enhanced. The new committee would be clearly seen to have only xenotransplantation as its focus.

However, this proposal also has its weaknesses, including the potential for delays and increased costs, because some work may be duplicated while proposals are being examined by GTRAP and the new national committee. The national committee will still need to have some scientific expertise, thus increasing the potential for duplication of
resources and once again bringing up the issue of possible conflict of interest. In addition, the separation of the assessment of gene therapy from xenotransplantation could be disadvantageous, as important input in the areas of genetic manipulation of animals, viral vectors and retrovirus risks would be lost or would have to be duplicated.

11.4 Model 3 — TGA as the sole regulatory agency

The working party gave brief consideration to the possibility that the process of assessment of xenotransplantation research proposals should be handled by the Therapeutic Goods Administration. For example, could the proposed national transplantation committee of Model 2 be sited in and resourced by the TGA, which has considerable experience in overseeing trials of pharmaceutical products and therapeutic devices? The working party does not support this idea, for reasons including the loss of the current close links between HRECs, researchers, AHEC and the NHMRC, and, in the case of Model 1 (the preferred model), the loss of the links with expertise in genetic modification and gene therapy expertise. However, comments on this possibility are welcome.

QUESTION
Which model do you favour and why?

11.5 Other options

The regulatory frameworks in place or being developed in other countries have been summarised in Chapter 10. While these frameworks may not be readily adapted to the existing regulatory framework for human research in Australia, community comment is also sought on this possibility.

11.6 The view of the working party

The working party unanimously considers that model 1 (ie a modified GTRAP) appears to be the best and most practical means of meeting all the desired attributes for effective regulation of xenotransplantation in Australia.

11.7 Legislative underpinning of models

Both models 1 and 2 rely for most of their authority on the Therapeutic Goods Act 1989 (with amendments). The strengths and weaknesses of the TG Act as it applies to the oversight of xenotransplantation are described in Chapter 9, as well as the role of the OGTR as administrator of the Gene Technology Act 2000.

Legislative changes may therefore be required to underpin either of the proposed models, including either amendments to existing legislation or development of specific legislation to regulate xenotransplantation research and clinical application, as has occurred with the establishment of the OGTR.

There are some core requirements for legislative underpinning:

• ‘xenotransplantation products’ need to be securely covered under TGA legislation;
• all xenotransplantation products need to come under the CTX scheme or a modification of it designed to achieve centralised review;

• xenotransplantation in the public and private spheres must be regulated by the same mechanism;

• there should be no possibility that the Special Access Scheme can be used for xenotransplantation research;

• there should be no access to personal importation arrangements or to the authorised prescriber scheme; and

• links between the TGA, OGTR and the national xenotransplantation committee must be clear.
### Appendix 1

**Xenotransplantation Working Party membership**

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<thead>
<tr>
<th>Member</th>
<th>Nominee of:</th>
<th>Expertise</th>
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<tr>
<td>Dr Kerry Breen</td>
<td>AHEC</td>
<td>Medicine, Chair of AHEC</td>
</tr>
<tr>
<td>Associate Professor Bernadette Tobin</td>
<td>AHEC</td>
<td>Philosophy, previously chair of Transplantation Ethics Working Party (1994–96)</td>
</tr>
<tr>
<td>Dr Dominic Dwyer</td>
<td>Research Committee</td>
<td>Clinical virology and infectious diseases</td>
</tr>
<tr>
<td>Associate Professor Philip O’Connell</td>
<td>Research Committee</td>
<td>Clinical and experimental transplantation</td>
</tr>
<tr>
<td>Ms Elizabeth Grant</td>
<td>Research Committee</td>
<td>Chair of Animal Welfare Committee</td>
</tr>
<tr>
<td>Ms Michele Kosky</td>
<td>NHMRC</td>
<td>NHMRC member with expertise in consumer issues</td>
</tr>
<tr>
<td>Mr Twanny Farrugia</td>
<td>Consumer representative</td>
<td>Counsellor (general, loss and grief), long-term transplant recipient</td>
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**Secretariat (Office of NHMRC)**

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<th></th>
<th>Director, Health Ethics Section</th>
<th>Project officer (December 2000 to July 2001)</th>
<th>Project officer (July 2001 to January 2002)</th>
<th>Project officer (from February 2002)</th>
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<tr>
<td>Ms Cathy Clutton</td>
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<td>Mr Ben Battison</td>
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<td>Ms Helen Willimott</td>
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<td>Ms Milly Betteridge</td>
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**Consultants**

| Dr Janet Salisbury | Technical writer |
| (Biotext, Canberra)|                |
Appendix 2

Process of guideline development

TO BE ADDED AFTER THE CONSULTATION PROCESS
Appendix 3
Membership and role of human research ethics committees

[Extract from the National Statement on Ethical Conduct in Research Involving Humans (NHMRC 1999), Section 2: pp 15–18]

Research proposals involving human participants must be reviewed and approved by a human research ethics committee (HREC) which is established by and advises an institution or organisation regarding ethical approval for research projects. Requirements are set out for:

- institutions or organisations in establishing HRECs
- researchers in submitting research proposals to HRECs and
- HRECs in considering and reaching decisions regarding those proposals and in monitoring the conduct of approved research.

2.1 Institutions and organisations in which research involving humans is undertaken must individually or jointly establish, adequately resource, and maintain an HREC composed and functioning in accordance with this Statement.

2.2 The institution or organisation must, when establishing an HREC, set out its terms of reference including the scope of its responsibilities, relationship to non-affiliated researchers, accountability, mechanisms of reporting, and remuneration, if any, for members.

2.3 The institution or organisation (individually or jointly) must accept legal responsibility for decisions and advice received from the HREC and indemnify its members.

2.4 Researchers without affiliation to an institution or organisation with an HREC must ensure that the project is approved by an established HREC. There should be an agreement between the institution or organisation and researchers that defines the approval, conduct and monitoring of research, and who carries legal responsibility for it.

2.5 The primary role of an HREC is to protect the welfare and the rights of participants in research and the primary responsibility of each member is to decide, independently, whether, in his or her opinion, the conduct of each research proposal submitted to the HREC will so protect participants.

COMPOSITION

2.6 The minimum membership of an HREC is seven members, being men and women, comprising:

(a) a chairperson;

(b) at least two members who are lay people, one man and one woman, who have no affiliation with the institution or organisation, are not currently involved in medical, scientific, or legal work, and who are preferably from the community in which the institution or organisation is located;
(c) at least one member with knowledge of, and current experience in, the areas of research that are regularly considered by the HREC (eg. health, medical, social, psychological, epidemiological, as appropriate);

(d) at least one member with knowledge of, and current experience in, the professional care, counselling or treatment of people (eg. medical practitioner, clinical psychologist, social worker, nurse, as appropriate);

(e) at least one member who is a minister of religion, or a person who performs a similar role in a community such as an Aboriginal elder; and

(f) at least one member who is a lawyer.

2.7 The institution or organisation must ensure that the membership will equip the HREC to address all relevant considerations arising from the categories of research likely to be submitted to the HREC. For example, an experienced medical practitioner should be included if the HREC considers research protocols which involve any physically invasive procedures or medical interventions (eg. surgical, pharmacological, physiological, technological, or nutritional intervention).

2.8 An HREC must ensure that it is sufficiently informed on all aspects of a research protocol, including its scientific and statistical validity, that are relevant to deciding whether the protocol is both acceptable on ethical grounds and conforms with this Statement. This may necessitate appointment of additional members with specific expertise.

2.9 If an institution or organisation appoints additional members it should ensure that the membership continues to reflect both the diversity of the categories of members listed in paragraph 2.6, including gender, and the relative proportion of institutional to non-institutional members.

APPOINTMENT OF MEMBERS

2.10 The institution or organisation may recruit members for an HREC in such a manner and shall appoint them for such a period and on such terms and conditions as it determines.

2.11 Members are to be appointed for their expertise and not in a representative capacity.

2.12 Members must receive a formal notice of appointment and assurance that the institution or organisation will provide legal protection in respect of liabilities that may arise in the course of bona fide conduct of their duties as committee members.

PROCEDURES

2.13 Institutions and organisations and their HRECs must establish working procedures concerning:

- frequency of meetings;
- preparation of agendas and minutes;
- distribution of papers prior to meetings;
- presentation of research protocols;
- timely consideration and review of research protocols;
- methods of decision making;
- prompt notification of decisions;
- reporting of adverse occurrences;
- appropriate monitoring;
- receiving complaints;
- advising institution(s) or organisation(s) to discontinue a research project;
- fees, if any, to be charged; and
• confidentiality of the content of protocols and of committee proceedings.

2.14 An HREC may approve, require amendment of, or reject a research proposal on ethical grounds. The HREC must record decisions in writing and should include reasons for rejection.

2.15 Meetings of an HREC must be so arranged as to allow, wherever possible, all members to be fully informed by receipt of all relevant papers and the opportunity to attend.

2.16 Where there is less than full attendance at a meeting, the Chairperson must be satisfied, before a decision is reached, that the minimum membership listed in paragraph 2.6 have received all papers and have had an opportunity to contribute their views and that these have been recorded and considered.

2.17 An HREC should endeavour to reach decisions by general agreement. This need not involve unanimity, but failure to agree may require an extension of time to reconsider the research protocol and its possible amendment, especially when any member is not satisfied that the welfare and rights of participants are protected.

2.18 An HREC may invite the researcher(s) to be present for discussions of the research and may request amendments to the research protocol.

2.19 An HREC may seek advice and assistance from experts to assist with consideration of a research protocol, but must be satisfied that such experts have no conflicts of interest in relation to the research project under consideration arising from any personal involvement or participation in the research, any financial interest in the outcome or any involvement in competing research.

2.20 An HREC shall ensure that no member of the committee adjudicates on research in which that member has any conflict of interest including any personal involvement or participation in the research, any financial interest in the outcome or any involvement in competing research.

2.21 A researcher must disclose to the HREC the amount and sources or potential sources of funding for the research and must declare any affiliation or financial interest when proposing and when reporting the research. The HREC must consider the extent to which it should disclose that information about funding sources.

2.22 A researcher must include, in the research proposal, a statement of the ethical considerations involved in the proposed research and an HREC must be satisfied that the research protocol gives adequate consideration to participants' welfare, rights, beliefs, perceptions, customs and cultural heritage both individual and collective.

2.23 An HREC should not communicate directly with a research sponsor on matters relating to the protocol or ethics of a project, but the institution or organisation and the sponsor may have direct communication on matters relating to administration, indemnity and insurance.

2.24 All documents and other material used to inform potential research participants should be approved by the HREC including plain language information sheets, consent forms, questionnaires, advertisements and letters of invitation.
Appendix 4
Membership and role of animal ethics committees


2.2 Responsibilities and operation of AECs
AECs must ensure that all animal care and use within the institution is conducted in compliance with this Code and incorporates the principles of Replacement, Reduction and Refinement.

Terms of Reference
2.2.1 AECs must have terms of reference which include provisions to:

(i) monitor the acquisition, transport, production, housing, care, use and disposal of animals;

(ii) recommend to the institution any measures needed to ensure that the standards of this Code are maintained;

(iii) examine and approve, subject to modification, or reject written proposals relevant to the use of animals in scientific and teaching activities. Also to approve only those studies for which animals are essential and which conform to the requirements of this Code, taking into consideration ethical and welfare aspects as well as scientific or educational value;

(iv) formally withdraw approval for any project or authorise the treatment or humane killing of any animal;

(v) examine and comment on all institutional plans and policies which may affect animal welfare;

(vi) maintain a register of approved projects; and

(vii) perform all other duties required by this Code.

Membership
2.2.2 An AEC must have a membership which will allow it to fulfil its terms of reference. It must comprise at least four persons, including a separate person appointed to each of the following categories:

Category A. A person with qualifications in veterinary science, with experience relevant to the activities of the institution or, in special circumstances, a person with qualifications and experience to provide comparable expertise;

Category B. A person with substantial recent experience in the use of animals in scientific or teaching activities;

Category C. A person with demonstrable commitment to, and established experience in, furthering the welfare of animals, who is not employed by or otherwise associated with the institution, and who is not involved in the care and use of animals for
scientific purposes. The person should where possible be selected on the basis of active membership of, and nomination by, an animal welfare organisation; and

*Category D.* An independent person who does not currently and has not previously conducted scientific or teaching activities using animals, and who is not an employee of the institution, except under defined circumstances.

2.2.3 A person responsible for the daily care of animals within the institution should have membership of the AEC.

2.2.4 The AEC may include additional members to ensure that it can function effectively.

2.2.5 The Chairperson should hold a senior position in the institution.

2.2.6 If the committee has more than four members, Categories C plus D should represent no less than one third of the members.

2.2.7 The composition of the AEC also must comply with any relevant legislation.

2.2.8 Before appointment, all members of the AEC should acknowledge in writing their acceptance of the terms of reference of the committee and any requirements for confidentiality required by the institution. The committee should reach agreement on how advice may be sought without breaching confidentiality.
Appendix 5
Gene and Related Therapies Research Advisory Panel

[Edited extract from the GTRAP website:

A novel form of treatment arrives

In anticipation that gene therapy would become a mode of treatment in medicine, the Research Committee of the National Health and Medical Research Council (NHMRC) in the 1994–96 triennium formed a subcommittee known as the Gene and Related Therapies Research Advisory Panel (GTRAP) to provide the NHMRC and human research ethics committees (HRECs) with advice on matters pertaining to human gene therapy trials, and to assist researchers in the establishment of best practice standards.

Extended approval process

The requirement for an additional step in the Australian system for review and monitoring of human clinical research studies was unusual, since HRECs (with guidance from the Australian Health Ethics Committee, AHEC) usually undertook this work independently. However, it was considered that HRECs would need specialised advice when it came to gene therapy because best practices had yet to be defined. Since this technology involved novel approaches to treatment, the short or long-term potential for harm was still undetermined, and it would be difficult for HRECs to gain expertise as the number of research studies would be small. Although the public has strongly supported medical research, it was essential that the community was comfortable with the review and monitoring process for this particular therapy since it involved manipulation of genes.

Relationship between GTRAP and HRECs

GTRAP was required to provide the NHMRC with advice on gene therapy matters, and to assess protocols involving human gene therapy trials so that HRECs had expert independent advice for each trial when they undertook the final review. GTRAP assessment would cover medical, scientific, ethical, safety and other matters related to a gene therapy trial in humans. Although GTRAP is an advisory body, AHEC in its ‘Information Sheet for HRECs #2’ (revised May 2001) has clearly defined the role to be played by GTRAP and HRECs in the approval process for clinical trials involving human gene therapy. In this framework, the HREC should not approve research that involves gene therapy without the prior approval of both the Institutional Biosafety Committee and GTRAP.

Gene therapy register

Another of GTRAP’s functions was to develop and maintain a register of patients who had undergone gene therapy so that in the unlikely scenario that gene therapy was
associated with long-term untoward side effects, patients and their families could be followed up, or contacted at some future time.

**Expanded terms of reference for GTRAP**

Late in 1999, the NHMRC’s Research Committee changed the terms of reference for GTRAP to include provision of advice about, and monitoring of, xenotransplantation trials and whether these should be undertaken in Australia. It was considered that, as for gene therapy, HRECs would need expert advice to assist them in assessing xenotransplantation proposals, and some of the expertise required was already available within the existing GTRAP. Just as for gene therapy, the public needed to be reassured that an additional safeguard, in the form of GTRAP, was in place to monitor human xenotransplantation clinical trials. The provision of advice to NHMRC about cell therapies was also added to GTRAP’s brief.

**GTRAP’s composition**

To cover its broad brief, the composition of GTRAP includes:

1. A core group of individuals with expertise in research, clinical medicine, the law and ethics as well as representatives from the Therapeutic Goods Administration, Genetic Manipulation Advisory Committee (GMAC) and the Australian Health Ethics Committee (AHEC),

2. A gene therapy specialty group,

3. A xenotransplantation specialty group, and

4. A cell therapy specialty group.

Under the new regulatory regime, administered by the *Gene Technology Act 2000*, that came into being in June 2000, GMAC will no longer exist. The Gene Technology Technical Advisory Committee (GTTAC) will advise the Gene Technology Regulator and arrangements are put in place regarding representation from GTTAC on GTRAP.

**GTRAP and the public**

From its inception GTRAP has provided HRECs, the NHMRC and individual investigators with advice on gene therapy matters, but has not made available to the public a source of information about gene therapy trials in Australia. GTRAP is aware that its contact with the public has been limited, and late in 2000 moved to develop its pages on the NHRMC web site to provide information about gene therapy in Australia and overseas, including a list of gene therapy studies approved by GTRAP.

**GTRAP’s terms of reference**

GTRAP is a subcommittee of the Research Committee, a principal committee of the NHMRC. GTRAP reports directly to the Research Committee although it maintains an active link with AHEC through the NHMRC secretariat and a member in common.
Through the NHMRC Research Committee, GTRAP:

- provides advice to Council on scientific, medical and technical issues related to gene therapy and related technologies;
- provides scientific, medical and technical advice to HRECs, scientists and other interested parties during the formulation and ethical review of research using gene therapy and related technologies;
- functions as a source of information on gene therapy and related technologies to the public and other interested parties; and
- maintains a register of research trials in which gene therapy or a related technology has been used.

**Membership of GTRAP**

GTRAP comprises a core group with general expertise relevant to gene therapy and xenotransplantation, and three specialty expert groups (gene therapy, xenotransplantation, and cell therapy). When dealing with gene therapy matters, the core and the gene therapy specialist group meet. The core and the xenotransplantation group meet to discuss xenotransplantation-related issues. The role of the cell therapy group is to provide the NHMRC with advice on matters relating to human ‘cloning’ and cell therapy. The latter is meant to cover a broad range of gene technologies that predominantly involve cell therapies.

**Core Group**

Prof R J A Trent (Chair)
A/Prof E Haan (Deputy Chair)
Prof J Pittard (GMAC nominee)
Prof J Mathews
Sister R Dunne RSM
Prof C Thomson (AHEC nominee)
Dr G Dickson (TGA nominee)
A/Prof L Skene

**Gene Therapy Expert Group**

Dr I Alexander
Prof A Dunn
A/Prof G Symonds

**Xenotransplantation Expert Group**

Dr A d’Apice
Dr D Dwyer
A/Prof Phillip O’Connell
Cloning (Cell Therapies) Expert Group  
Prof G Begley  

NHMRC Secretariat  
Ms Helen Willimott  

Conflicts of interest  

Members of GTRAP are bound by conflict-of-interest requirements outlined in the legislation under which the NHMRC operates. Because the gene therapy and xenotransplantation research communities are relatively small within Australia, conflicts of interest or perceived conflicts of interest can arise. Members are asked to disclose, at the start of each meeting, whether they have a conflict of interest with respect to any agenda item for that meeting. Commercial-in-confidence issues are dealt with in the same manner.  

Xenotransplantation  

Although xenotransplantation per se does not constitute gene therapy, it is likely that there will be overlap with gene therapy when a xenotransplanted tissue or organ has been genetically modified by the insertion of human genes to make the xenotransplanted material less likely to be rejected by the recipient.  

The NHMRC Council in 2000 requested AHEC and the Research Committee to form a committee to consider the future role of xenotransplantation within Australia. This committee is to report to Council via AHEC and the Research Committee by mid 2001. Particular issues to be reviewed by the xenotransplantation committee will include safety guidelines, and the role to be played by GTRAP in the approval and monitoring process. Until this committee provides its report, HRECs were advised in a combined letter from AHEC and the NHMRC’s Research Committee that they should not approve xenotransplantation studies without consulting GTRAP.  

Sources of information  

The above information has been abridged and modified from the GTRAP web site at http://www.health.gov.au/nhmrc/research/gtrap.htm
Appendix 6  Definition of a therapeutic good

The *Therapeutic Goods Act 1989* defines therapeutic goods as follows:

‘*Therapeutic goods*’ means goods:

(a)  that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be:

(i) for therapeutic use; or

(ii) for use as an ingredient or component in the manufacture of therapeutic goods; or

(iii) for use as a container or part of a container for goods of the kind referred to in subparagraph (i) or (ii); or

(b) included in a class of goods the sole or principal use of which is, or ordinarily is, a therapeutic use or a use of a kind referred to in subparagraph (a) (ii) or (iii); and includes goods declared to be therapeutic goods under an order in force under section 7, but does not include:

(c) goods declared not to be therapeutic goods under an order of force under section 7; or

(d) goods in respect of which an order is in force, being an order that declares the goods not to be therapeutic goods when used, advertised or presented for supply in the way specified in the order where the goods are used, advertised or presented for supply in that way; or

(e) goods for which there is a prescribed standard in the Australia New Zealand Food Standards Code as defined in subsection 3(1) of the *Australia New Zealand Food Authority Act 1991*; or

(f) goods which, in Australia or New Zealand, have a tradition of use as foods for humans in the form in which they are presented.
Glossary

adaptive, or acquired, immune response: relatively slow immune response to a foreign substance, involving cell-mediated (T cell) and humoral (B cell) components, that ultimately gives long-term immunity (cf innate immune response)

allo-: Greek prefix meaning 'the same' (see allotransplantation)
allogeneic: tissues from individuals of the same species

allotransplantation: transplantation of tissue or organs between individuals of the same species (usually matched humans)

animal-to-animal studies: preclinical xenotransplantation research studies in which organs, cells or tissues are transferred from one animal species (eg pig) to another (eg baboon) (see also preclinical study)

animal-to-human trials: clinical xenotransplantation research in which organs, cells or tissues are transferred from an animal species (eg pig) to a human (see also clinical trial)

antibody: a protein produced by the immune system in response to a foreign substance (eg microorganism, previous transplant, blood transfusion)

antigen: a foreign molecule or substance that triggers an immune response

auto-: Greek prefix meaning ‘self’ (see autotransplantation)

autotransplantation: transplantation of tissue or organs from and to the same individual (eg relocation of skin from the thigh to the arm to repair burn damage)

B cell: a lymphocyte (white blood cell), produced in the bone marrow, that makes antibodies

benefit: that which positively affects the interests or welfare of an individual or group

bioartificial liver: term used to describe an external piece of equipment containing isolated (usually pig) liver cells. The cells are physically separated from the patient’s circulation by a semipermeable barrier that allows essential liver functions to occur through diffusion (see also bioreactor)

bioreactor: term used for an ex vivo perfusion device containing cells (see bioartificial liver)

biotechnology: the use of molecular biological techniques to develop new products used in medicine and industry; often involves altering genes or transferring genes from one species to another (see gene technology)

cadaveric graft: a grafted organ, tissue or cells from a person who has died

cell-mediated immunity: an adaptive immune response in which antigen-specific T cells play the main role (cf humoral immunity)

clinical trial: a preplanned clinical study of the safety, efficacy or optimum conditions of use of one or more diagnostic, therapeutic or prophylactic interventions in humans selected according to predetermined criteria of eligibility and observed for predefined evidence of favourable and unfavourable effects (see animal-to-human trials)

clones: individuals that have the same genotype
complement a series of serum proteins involved in the mediation of immune reactions. The activation of complement (complement cascade) is usually triggered by interaction of antibody with specific antigens but it can be triggered by transplanted tissues even in the absence of antibody

complement regulator inhibitory and regulatory molecules on the surface of endothelial cells that prevent complement activation

consent the voluntary agreement of a person or group, based on adequate knowledge and understanding of relevant material, to participate in research. Consent is one possible result of the informed choice process; the other possible result is refusal.

delayed xenotransplantation rejection (DXR) an immune reaction that occurs within a few days, involving coagulation of white blood cells; in xenotransplantation, DXR can occur after hyperacute rejection and will lead to further clotting and death of the graft (see also hyperacute rejection)

domogeneous retrovirus partial or complete virus that is integrated into the genome of its host, only replicates with the genome and is passed vertically from generation to generation as an inactive provirus. In some circumstances ERVs can become activated and produce infectious virus particles that can spread horizontally and cause disease.

endothelial lining/ endothelium the layer of cells lining the heart, blood vessels and lymphatic vessels

erthropoietin (EPO) a hormone essential for regulating the production of red blood cells

ethics the study of morals and values; that is, the study of right and wrong, justice and injustice, virtue and vice, good and bad, and related concepts and principles

ethical right or morally acceptable (see also unethical)

ex vivo term meaning ‘outside the body’, used for procedures in which cells or fluids from a patient are cultured with or perfused through animal cells before being returned to the patient

ex vivo transplantation procedure in which human body fluids, cells, tissues or organs that have had contact outside the body with live nonhuman cells, tissues or organs are transplanted, implanted or infused into a human recipient (cf in vivo transplantation)

galactose-α1,3-galactose (αGal) a carbohydrate (sugar) found on the cell surface of microorganisms and mammals below apes and Old World monkeys. Humans have preformed antibodies to αGal because of previous exposure to microorganisms that carry it

gene technology the process of manipulating genetic material in a cell or organism to produce desired traits (eg inserting genes from one plant or animal species into another so as to modify growth or other characteristics) (see also biotechnology)

genetic material any source of DNA or RNA that can be tested to obtain genetic information. It thus includes cells, whether as single cells or as part of tissues, and extracted DNA and RNA.
genetically modified animal
an animal strain which has had genes inserted or deleted into its genome to produce desired characteristics (also called transgenic animal)

germ cell
reproductive cell (sperm or ova) (cf somatic cell)

haemodialysis
a procedure in which the blood is cleaned outside the body in a machine that contains a filter called the dialyser or artificial kidney

harm
that which adversely affects the interests or welfare of an individual or a group. Harm extends to physical harm, discomfort, anxiety, pain, psychological disturbance and social disadvantage

hazard
a biological, chemical or physical agent that may have an adverse health effect

hepatocytes
liver cells

heterotopic transplant
a transplant procedure in which the equivalent organ of the recipient is also left in place and the transplant is therefore not life supporting (see also orthotopic transplant)

histocompatibility antigens
genetically determined complex of antigens that determine the compatibility of tissues from different individuals for transplantation; in humans the human leucocyte antigens (HLAs) determine the compatibility of tissues for transplantation from one individual to another

humoral immunity
an adaptive immune response mediated by antibodies produced by antigen-specific B cells (cf cell-mediated immunity)

hyperacute rejection (HAR)
an immune reaction that occurs within minutes or hours; in xenotransplantation, it causes blood clotting and death of the transplant or can be followed by delayed transplant rejection (see also delayed xenotransplantation rejection)

immune response
mechanism for distinguishing ‘self’ from ‘nonself’ and eliminating invading microorganisms or other foreign materials from the body; in transplantation it can lead to rejection of the transplanted organ, tissue or cells (see also innate immune response, adaptive immune response)

immunoglobulin
One of a group of proteins (globulins) in the body that act as antibodies. They are produced by B cells and are present in blood serum and other body fluids.

immunosuppression
preventing or reducing an immune response, either by disease or drugs; immunosuppressive drugs are required after an organ is transplanted from another individual to prevent rejection of the organ

innate immune response
rapid, first line of defence against many common infectious foreign materials (cf adaptive or acquired immune response)

in vivo transplantation
a procedure in which live cells, tissues or organs from a nonhuman animal source are transplanted, implanted or infused into a human recipient (cf ex vivo transplantation)

lymphocytes
type of white blood cells responsible for immune response; subdivided into T lymphocytes (T cells) and B lymphocytes (B cells) (see also T cells, B cells)
macrophages | large, white blood cells that ingest foreign substances and display on their surfaces antigens produced from the foreign substances, to be recognised by other cells of the immune system

microchimerism | existence of cells of two or more gene types within the same individual

minimal risk | risk experienced when the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life

monitoring (of research) | the review by a committee of ongoing research. Such monitoring can take a variety of forms including review of annual reports, formal review of the informed consent process, establishment of a safety monitoring committee, a periodic review by a third party of the documents generated by the study, a review of the impact of the research on a collectivity, a review of reports of adverse events, or a random audit of the particular processes

natural killer (NK) cells | non-T, non-B lymphocytes that kill cells expressing foreign antigens. They are also important in innate immunity to viruses and other intracellular pathogens.

nontherapeutic | not directed towards the benefit of the individual but rather towards improving scientific knowledge or technical application (see also therapeutic)

orthotopic transplant | a transplant procedure in which the donor organ replaces the equivalent organ of the recipient and is therefore life supporting (see also heterotopic transplant)

pancreatic islet cells | cells of the islets of Langerhans in the pancreas that secrete the hormones insulin and glucagon

pathogen | an organism that causes disease

phagocytic cells | immune system cells that ingest and destroy viruses, bacteria, fungi and other foreign substances or cells

preclinical study | a study carried out using animals or laboratory methods to test the efficacy or safety of a procedure before clinical trials are carried out on human patients (see animal-to-animal studies)

prion | ‘proteinaceous infectious particle’ implicated as the causative agent in the degenerative neurological diseases called ‘transmissible spongiform encephalopathies’ (eg CJD, kuru)

protocol | a document that provides the background, rationale and objectives of the research and describes its design, methodology, organisation and the conditions under which it is to be performed and managed

research participant | living individual (or groups of living individuals) about whom a researcher obtains data through intervention or interaction with the person or identifiable private information

retrovirus | virus whose genetic material is made up of ribonucleic acid (RNA) instead of deoxyribonucleic acid (DNA)

risk | the function of the magnitude of a hazard and the probability of its occurrence (see also hazard, minimal risk)
semipermeable membrane: membrane that allows the passage of some molecules but not others
somatic cell: nonreproductive cell (cf germ cell)
stem cells: early unspecialised cell that can, under certain conditions, be induced to mature into specialised cell types (eg heart muscle cells, liver cells)
syngeneic: donor and recipient are genetically identical
therapeutic research: interventions directed towards the wellbeing of the individual involved (see also nontherapeutic research)
thrombomodulin: an anticoagulant consisting of a glycoprotein bound by the cell membrane and lining the vascular endothelium
thrombosis: process in which a clot is formed in a blood vessel
tissue typing: a process used to assess the compatibility of tissues for transplantation and other purposes by identifying human leucocyte antigen profiles (see also histocompatibility antigens)
T cell: commonly used name for T lymphocytes, which are the lymphocytes associated with cellular immunity (see also lymphocyte, B cell)
transgenic animal: see genetically modified animal
unethical: wrong or morally unacceptable (see also ethical)
vascularised: having a direct blood supply via blood vessels
xeno-: Greek term for ‘foreign’ (see xenotransplantation)
xenoantigen: an antigen from a different species
xenogeneic: tissues from individuals of different species
xenotransplantation: transplantation of organs, tissue or cells from another species (eg pigs to humans)
xenozoonosis: an animal disease specifically transmitted by xenotransplantation (see zoonosis)
zoonosis: an animal disease that can be communicated to humans (see xenozoonosis)
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AEC</td>
<td>animal ethics committee</td>
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<tr>
<td>AFFA</td>
<td>Department of Agriculture, Fisheries and Forestry — Australia</td>
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<tr>
<td>AHEC</td>
<td>Australian Health Ethics Committee (NHMRC)</td>
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<td>AQIS</td>
<td>Australian Quarantine and Inspection Service</td>
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<td>ARC</td>
<td>Australian Research Council</td>
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<tr>
<td>ARMCANZ</td>
<td>Agriculture and Resource Management Council of Australia and New Zealand</td>
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<tr>
<td>ARTG</td>
<td>Australian Register of Therapeutic Goods</td>
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<td>AVCC</td>
<td>Australian Vice-Chancellors’ Committee</td>
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<tr>
<td>AWC</td>
<td>Animal Welfare Committee (NHMRC)</td>
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<tr>
<td>BSE</td>
<td>bovine spongiform encephalopathy</td>
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<tr>
<td>CBER</td>
<td>Center for Biologics Evaluation and Research (US)</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention (US)</td>
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<tr>
<td>CJD</td>
<td>Creutzfeldt–Jakob disease</td>
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<tr>
<td>CSIRO</td>
<td>Commonwealth Scientific and Industrial Research Organisation</td>
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<tr>
<td>CTN</td>
<td>Clinical Trial Notification Scheme (of the TGA)</td>
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<td>CTX</td>
<td>Clinical Trial Exemption Scheme (of the TGA)</td>
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<tr>
<td>DHHS</td>
<td>Department of Health and Human Services (US)</td>
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<td>DIC</td>
<td>disseminated intravascular coagulation</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<td>DXR</td>
<td>delayed xenotransplant rejection</td>
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<td>EPO</td>
<td>erythropoietin</td>
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<td>ERV</td>
<td>endogenous retrovirus</td>
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<td>FAO</td>
<td>Food and Agriculture Organization</td>
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<td>FDA</td>
<td>Food and Drug Administration (US)</td>
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<td>GM</td>
<td>genetically modified</td>
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<td>GMO</td>
<td>genetically modified organism</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<td>GTRAP</td>
<td>Gene and Related Therapies Research Advisory Panel</td>
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<td>HAR</td>
<td>hyperacute rejection</td>
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<tr>
<td>HERV</td>
<td>human endogenous retrovirus</td>
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<tr>
<td>HIV/AIDS</td>
<td>human immunodeficiency virus /acquired immunodeficiency syndrome</td>
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<tr>
<td>HREC</td>
<td>human research ethics committee</td>
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<td>HSV</td>
<td>herpes simplex virus</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>HTLV</td>
<td>human T-cell lymphotrophic virus</td>
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<td>IND</td>
<td>investigational new drug</td>
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<td>MHC</td>
<td>major histocompatibility complex</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<td>NHP</td>
<td>nonhuman primate</td>
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<td>NK cell</td>
<td>natural killer cell</td>
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<tr>
<td>NLRD</td>
<td>notifiable low-risk dealing</td>
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<td>NXD</td>
<td>national xenotransplantation database (US)</td>
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<tr>
<td>NXGTC</td>
<td>National Xenotransplantation and Gene Therapy Committee (proposed)</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<tr>
<td>OGTR</td>
<td>Office of the Gene Technology Regulator</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>PERV</td>
<td>porcine endogenous retrovirus</td>
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<td>SAS</td>
<td>Special Access Scheme</td>
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<tr>
<td>SBRM</td>
<td>standards-based risk management (Canada)</td>
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<tr>
<td>SIV</td>
<td>simian immunodeficiency virus</td>
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<tr>
<td>STLV</td>
<td>simian T-cell lymphotrophic virus</td>
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<tr>
<td>TFPI</td>
<td>tissue factor pathway inhibitor</td>
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<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<tr>
<td>TK</td>
<td>thymidine kinase</td>
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<tr>
<td>UKXIRA</td>
<td>United Kingdom Xenotransplantation Interim Regulatory Authority</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WPX</td>
<td>Working Party on Xenotransplantation (European Union)</td>
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</tbody>
</table>
References


Friedlaender MM (2002). The right to sell or buy a kidney: are we failing our patients? *The Lancet* 359:971–973.


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**Further reading**


ATTACHMENT:
NHMRC procedures for making submissions
**Public Consultation – Procedures for Making Submissions**

**The NHMRC in Brief**

The National Health and Medical Research Council (NHMRC) consolidates within a single national organisation the often independent functions of research funding and development of advice. One of its strengths is that it brings together and draws upon the resources of all components of the health system, including governments, medical practitioners, nurses and allied health professionals, researchers, teaching and research institutions, public and private program managers, service administrators, community health organisations, social health researchers and consumers. The functions of NHMRC come from the statutory obligations conferred by the National Health and Medical Research Council Act 1992 (the Act).

The Act sets down four statutory obligations on the directions taken by NHMRC. These obligations are:

- to raise the standard of individual and public health throughout Australia;
- to foster the development of consistent health standards between the various States and Territories;
- to foster medical research and training and public health research and training throughout Australia; and
- to foster consideration of ethical issues relating to health.

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

**Approach to Consultation by Council**

The Council undertakes its advisory role with the assistance of an extensive structure of committees, working parties and expert panels. The substantial networks represented in this structure are used both to disseminate information about the Council’s activities and to assist the Council to gain a full appreciation of the range of views in the community. This networking complements the public consultation processes.

The Council is keen to ensure that the Australian community has the best opportunity to participate in developing Council reports. For this reason a consultation strategy is an important part of any recommendation or guideline development process. The strategy will identify individuals and organisations who have a special interest in the topic under consideration and who will receive direct contact from Council. In developing the timetable for consultations the need to allow adequate time for participants to undertake their own processes is taken into account. Other current consultative activities relevant to the issues are also taken into consideration.

Participants involved in consultations will be provided with:

- information about the reasons for the consultation;
- any other available background information; and
- a contact name.

The Act sets out steps to be followed by the Council in consulting people and bodies when it intends to:

- make a regulatory recommendation;
  - that is, a recommendation of the Council that is intended to be given legal effect in a State or Territory by legislation of that State or Territory;
- issue guidelines;
- approve guidelines developed by other organisations; or
- engage in other activity prescribed in regulations to the Act;
  - the Council’s present plans do not include any activities that will need to be prescribed.

**The Consultation Process**

Council now has two separate consultation processes as follows.

**Regulatory recommendations and prescribed activities**

Council follows a two stage consultation process. Firstly, Council will advertise its intention to develop a regulatory recommendation or engage in a prescribed activity. At this stage Council will seek comment on its intentions.

Once comments have been received and considered, Council will draft the regulatory recommendation or refine its prescribed activity and will then publish a second notice asking for comment on the actual draft.

Notices for both these stages of consultation will be published in the Commonwealth Gazette and on the NHMRC website. Copies of draft documents and supporting information will be available free of charge from the Office of NHMRC and on the NHMRC website. In addition, notices may be included in other publications and media such as newspapers and radio, and will be circulated to bodies that are expected to be interested.
The notices will state:

• that submissions should normally be in writing but would also be acceptable on audio tape;
• details of where, and by when, the submissions are to be lodged; and
• whether it is intended to conduct other forms of consultation.

Development of guidelines

Council undertakes a single stage of consultation. When Council has determined a need for a guideline, undertaken the initial research and developed a draft of the guideline, a notice inviting submissions will be published in the Commonwealth Gazette and on the NHMRC website. The notice will give the same information referred to above.

In addition, notices may be included in other publications and media, such as newspapers, and the draft guideline will be circulated to bodies that are expected to be interested.

Consideration of submissions

All submissions will be acknowledged upon receipt. All submissions will be considered. The committees are obliged to report to Council on the consultation process, including showing how they have addressed the comments that submitters have made.

Variations to standard consultation arrangements

On occasions it is necessary for Council to modify the consultation process, for example in an emergency situation or where proposed recommendations or guidelines are of minor significance. The Act allows Council to take this course of action.

If this happens, Council will advertise its reasons for making such a decision. In the case of an emergency situation, Council will also consult formally with interested individuals and organisations before confirming its original decision. The Act sets out strict timeframes for this type of consultation.

HOW TO WRITE A SUBMISSION

Submissions should be clear and concise, preferably typewritten and submitted as an original by mail or email. Facsimile copies will be accepted, but are sometimes difficult to read. Audio tapes will also be accepted.

Each submission should include:

• the submitter’s name and address;
• names of any additional contributors to the submission who may wish to be acknowledged;
• contact telephone numbers in case Council needs to clarify any points, obtain additional information, or advise if the submission appears incomplete (e.g., pages missing); and
• fax and email address where possible.

Submissions to Council need to include specific information that will help Council to consider the point(s) being made. Evidence that supports the point(s) being made should include full references and copies of material referred to. If it is not possible to include such references, please include as much detail as possible.

Information in the submission should be in a logical order, preferably following the layout of the consultation document (for instance, use the same chapter headings and subheadings). Quote the page number relevant to the point(s) being made.

There is no set length for a submission and, in fact, the length will vary depending on the complexity of the issue and the number of comments a submitter wants to make. However, submissions should balance the need to provide as much information as possible with a need to be concise. If particular length restrictions are set, they will be specified in the notice inviting submissions.

GENERAL INFORMATION ON COUNCIL’S ACTIVITIES

Information on the activities of the Council can be obtained from its secretariat by phoning (02) 6289 9184, faxing (02) 6289 9197 or writing to:

The Executive Secretary
National Health and Medical Research Council
Office of NHMRC (MDP 100)
GPO Box 9848
Canberra ACT 2601

The Council’s Secretariat circulates periodically a catalogue of Council publications and is able to provide synopses of publications upon request. Most of Council’s publications are available through AusInfo (contact details on back page). There are also many NHMRC publications available on the NHMRC website, including synopses.
How to Contact Us

General
Postal: The Executive Secretary
National Health and Medical Research Council
Office of NHMRC
(MDP 100)
GPO Box 9848
Canberra ACT 2601

Physical: The Executive Secretary
National Health and Medical Research Council
Office of NHMRC
32 Corinna Street
Woden ACT 2606

Phone: +61 2 6289 9184
Fax: +61 2 6289 9197
Email: exec.sec@health.gov.au

Research Program
NHMRC Centre for Research Management
Office of NHMRC
(MDP 33)
GPO Box 9848
Canberra ACT 2601

Phone: +61 2 6289 9167
Fax: +61 2 6289 9132
Email: nhmrc.research@health.gov.au

Advisory Program
Health Advisory Section
Office of NHMRC
(MDP 100)
GPO Box 9848
Canberra ACT 2601

Phone: +61 2 6289 9188
Fax: +61 2 6289 9180
Email: health.advisory.ctee.nhmrc@health.gov.au

Ethics Program
Health Ethics Section
Office of NHMRC
(MDP 70)
GPO Box 9848
Canberra ACT 2601

Phone: +61 2 6289 9154
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Email: ahec.nhmrc@health.gov.au

Publications
The Publications Officer
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