Guidelines for Preparation of Applications Involving Clinical Trials of Xenotransplantation in New Zealand

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HRC Gene Technology Advisory Committee

Introduction

Overview of Application Process for Clinical Trials Involving Xenotransplantation

Investigators who wish to conduct a clinical trial of an unapproved medicine must apply to Medsafe for an exemption under Section 30 of the Medicines Act (1981). Xenotransplantation is listed as a "restricted procedure" in Part 7A of the Medicines Act, and can only be authorised by the Minister of Health. To be approved, clinical trials of xenotransplantation must not pose an unacceptable risk to the health and safety of the public, and any ethical, cultural, and spiritual issues associated with the procedure must have been adequately addressed.

Applications for clinical trials involving xenotransplantation in humans are required to go through three assessment steps. The first step is scientific assessment by the Gene Technology Advisory Committee (GTAC), a standing committee of the Health Research Council of New Zealand (HRC). If GTAC approval is achieved, investigators may proceed to the next step and apply to a Regional Health and Disability Ethics Committee for assessment. After completion of the ethics committee review, Medsafe and the Ministry of Health will provide advice to the Minister of Health, who will make a final decision based on all of the assessments of the application.

Process for GTAC Approval

The process for application to GTAC is outlined in Section A of the GTAC document *Process and Guidelines for Application for Approval of Proposals Involving Administration of Gene Products to Human Subjects in New Zealand,* available from the HRC website (www.hrc.govt.nz). Applications to Medsafe for GTAC approval of clinical trials involving xenotransplantation should be made by letter using the guidelines set out in the following pages, rather than general Guidelines for Preparation of Applications for GTAC Review (Section B of the Process and Guidelines document). Each step of a xenotransplantation clinical trial programme (phase I through to phase IV) will need to be reviewed by GTAC. GTAC will recruit additional experts in disciplines such as infectious disease, veterinary medicine, virology and immunology as needed for adequate assessment of proposals. Selected members of the HRC's Standing Committee for Therapeutic Trials (SCOTT) may be asked to review the application where necessary.

Development and Use of Guidelines

The development of the following GTAC guidelines builds upon advice provided by the Bioethics Council on the cultural, ethical and spiritual aspects of xenotransplantation.[1] The use of guidelines as a national standard is only one of a series of controls required for regulation of clinical trials involving xenotransplantation in New Zealand. Other controls include use of patient registries, centralised patient and researcher databases, and government-owned tissue storage facilities.

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[1] The Cultural, Ethical and Spiritual Aspects of Animal-to-Human Transplantation
A report on xenotransplantation by Toi te Taiao: the Bioethics Council. Available from www.bioethics.org.nz

The following guidelines have been developed to assist investigators wishing to submit proposals for assessment, and to guide GTAC and/or future national animal-to-human transplantation advisory committees in their assessment of these proposals. They draw heavily on the U.S. Food and Drug Administration (FDA) *Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans*, and GTAC will draw upon the detailed recommendations of that document to assess applications that involve xenotransplantation. Researchers are referred to the FDA's recommendations[2] for more advice on how to design a strong preclinical programme. Investigators may request for GTAC to assess preclinical data prior to design of a clinical programme.

Investigators may wish to format applications as specified in the ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (http//www.ich.org). This includes the preparation of a Clinical Trial Protocol (section 6) documenting the design and conduct of the proposed trial, and an Investigator's Brochure (section 7) documenting the nonclinical and clinical data on the investigational product relevant to its study in human subjects. Investigators who submit their applications using this format should include a separate checklist to indicate precisely where reviewers can locate the information requirements set out in the 9 individual sections of the GTAC xenotransplantation guidelines.

Key Features of the Guidelines

Animal-to-human transplant research has unique safety and ethical considerations that require controls additional to those used for clinical trials that do not involve xenotransplantation. A primary concern is the cross-species infectious potential of animal pathogens. The risk must be minimised through appropriate control of animal sources and husbandry in addition to testing of the final product for infectious agents. There is a need to consider the safety of the recipient, close contacts and the public. Sponsors have important responsibilities in terms of documenting information relating to the xenotransplantation product and procedure, for recipient monitoring and follow-up, and for collection and storage of archival tissue samples from animal source and recipient.

Assessment of proposed clinical trials involving xenotransplantation requires GTAC to assess data on source animal and xenotransplantation product characterisation, preclinical data, patient selection, medical procedures to be undertaken, plans for post-transplant patient monitoring, and the qualifications and experience of professionals involved in patient care, the animal facility and animal-testing laboratories.

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[2] Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans. Available from www.fda.gov/cber/guidelines.htm

Definition of Xenotransplantation

For the purposes of this document, the FDA definition of xenotransplantation will be used: any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a non-human animal source, or (b) human body fluids, cells tissues or organs that have had ex vivo contact with live non-human animal cells, tissues or organs. Xenotransplantation products include live cells, tissues or organs.

Summary of Guidelines Sections

1. **Executive Summary**
    - A 1-2 page summary of the proposed xenotransplantation trial
2. **Objectives and Rationale**
    - Introductory statements of the objectives and rationale of the proposed research
3. **Source, Characterisation and Safety of Xenotransplantation Product**
    - Rationale for using the selected source animal, and programmes for prevention and screening for infectious agents
    - Details on how the product will be harvested, processed and assessed for safety, purity, identity and potency
4. **Preclinical Studies**
    - Preclinical evidence from animal models relating to the safety and possible efficacy of the transplantation procedure
    - How the preclinical program has been designed to ensure compatibility of preclinical to clinical study design
    - Preclinical studies must use the xenotransplantation product to be tested in the proposed clinical trial
5. **Design of Clinical Study**
    - Patient selection, the transplantation procedure, clinical endpoints, clinical resources available for the study, prior clinical trials of relevance
6. **Risk Assessment**
    - A detailed and comprehensive evaluation of safety, risks and benefits relating to the xenotransplantation procedure that addresses both recipient and public health concerns
7. **Post-Xenotransplantation Patient Monitoring**
    - A screening programme to monitor infectious disease in the recipients and their intimate contacts
    - A programme for life-long follow-up of clinical outcome measures
8. **Informed Consent**
    - A plan for how consent will be obtained from candidates for the proposed treatment, and a clear, plain-language statement designed to allow candidates and their families to make an informed decision
9. **Additional Documents**
    - Include with your application all relevant curricula vitae and reprints, and contact details for potential referees

1. Executive Summary

1.1. Provide a 1-2 page summary of the proposed xenotransplantation trial highlighting the clinical need, preclinical data, and the nature of the transplant.

2. Objectives and Rationale

Provide introductory statements of the objectives and rationale of the proposed research. Note that non-therapeutic trials will not be permitted.

2.1. Details of disease to be treated with reference to prevalence, aetiology, clinical features, staging (where relevant), phenotypic variability, range of cells/tissues affected, severity and natural history.
2.2. Current therapy: provide details of alternative forms of treatment. Discuss the strengths and limitations of each treatment regimen in the short- and long-term. What is the prognosis associated with conventional treatment?
2.3. Why is the proposed strategy appropriate for this disease? Put the proposed therapy in the context of emerging therapies. Describe new therapies for the disease either currently in trials or where trials are being considered.
2.4. What is the anticipated quality of life for patients following treatment?
2.5. Is the clinical course of the disease sufficiently well understood to allow outcomes of the treatment to be assessed? What measures of disease progression/severity are available?
2.6. What promise does the proposed strategy hold for reversing the disorder or bringing about a remission in both the short- and long-term?
2.7. Define the group(s) of patients to be offered the proposed treatment. Which other treatment regimens have been used on subjects recruited to this study?
2.8. Indicate whether this study requires the approval of any other body especially if patients or collaborators normally reside in another country. Describe and document the approvals obtained, or to be obtained, from all other relevant regulatory bodies.

3. Source, Characterisation and Safety of Product Proposed for Xenotransplantation

3.1. Characterisation of the Source Animal

In this section, describe the rationale for using the selected source animal. Provide appropriate information about the source animal, including herd management protocols and programmes for prevention and screening for infectious agents by qualified experts.

Recommendations for Source Animal

In general, use of non-human primates as source animal is not permitted. You should use closed herds with documented health screening programmes only. Do not use as source animal those that are raised under free-ranging conditions, or those obtained from slaughterhouses or abattoirs. Production of source animals should involve an adequately designed facility and a program for the operation of the facility to minimise the animals' exposure to infectious agents. See FDA Guidance to Industry on the housing and husbandry of source animals for xenotransplantation.

3.1.1. What source animal species will be used and why? What anatomic and physiologic considerations (including immunological concerns) have been addressed by the selection of the source animal species?

3.1.2. Document any form of genetic modification of the source animals. Attach all relevant documents (e.g. Environmental Risk Management Authority approval, animal ethics approval).

3.1.3. Document the geographic origin, species, strain, and genealogy of the source animal(s) and herd(s). Describe any factors relating to origin that may pose risks to recipients.

3.1.4. Provide evidence that procedures for animal husbandry, tissue harvesting and termination of source animals comply with the Animal Welfare Act 1999.

3.1.5. Describe a detailed plan for maintaining source animals. Include standard operating procedures (SOP) detailing containment and housing, feeding and obtaining feed, water and bedding, performance and monitoring of health screenings, removal from production and disposal of the animals and their by-products, and identifying individual animals and recording their movements through and out of the facility.

3.1.6. Describe the procedures and physical facilities used for harvesting of live cells, tissues or organs from source animals.

3.1.7. Track the location of the source animal cells, tissues or organs from harvesting through product development to proposed site of clinical use. Describe how the animal material will be transported for each translocation.

3.1.8. Detail plans for obtaining and storing archive samples taken at the time of harvesting, and plans for full necroscopy when source animals die or are euthanized. Make provisions for all records and archived samples to be maintained for 50 years in the event that the establishment ceases operation. Who is responsible for the archives and access to the specimens? Who will be responsible for archival samples when the applicant's company or research group, ceases to exist, is sold or dissolved for any reason? Discuss quality control, authentication of cell lines used, pathogen testing.

3.1.9. Where cell lines from animals have been established and used in the production of xenotransplantation products, describe the history of the cell line. For established cell lines, note the species, tissue of derivation, age and sex of source animal, laboratory of derivation and immediate provider of cell line. For primary cultures also include description of the husbandry and health status of the particular source animal or herd or colony.

3.1.10. Human embryonic stem (hES) cell lines that have been cultured with murine feeder cells fit the definition of xenotransplantation products. If investigating a stem cell product derived from an existing hES cell line in clinical trial, demonstrate that the hES cell line is free from infectious agents. (Applies to other xenotransplantation products that contain human cells with a history of co-culture with non-human animal cells).

3.2. Characterisation of Xenotransplantation Product

3.2.1. What is the nature of the animal material to be introduced (e.g. organ, tissue, cells)?

3.2.2. Will the product be treated in any way after harvesting (e.g. encapsulated, cultured, stored)? If the product is used immediately after harvesting, will you perform tests to characterise the product, a biopsy of the organ or a relevant surrogate sample? Will the results of these tests be available before use of the product?

3.2.3. How will the xenotransplantation product be assessed for:

- **safety** (see microbial testing below)
- **identity** of active component (e.g. by identifying relevant cell types using immunological, immunohistological or biochemical cell markers)
- **purity** (i.e. quantify the presence of the putatively active cell type(s) as well as contaminating cell types)
- **potency** (i.e. measure the intended biological activity of the final xenotransplantation product, such as secretion of cytokines, hormones, or neurotransmitters)

3.2.4. In certain xenotransplantation product/device combination products, physical barriers may separate the animal xenogeneic component from human fluids or tissue and might prevent or reduce the transmission of certain infectious agents. If such claims are made or are implicit, provide data from validation studies that demonstrate the inhibition of transmission of specific infectious agents and the longevity of device/barrier integrity.

3.3. Microbial Testing of Source Animals and Xenotransplantation Product

3.3.1. Describe the cross-species infectious potential of specific animal pathogens from your source animal. Describe and justify frequency of screening for pathogens, method of assay, and the method of identifying which and what proportion of animals are sampled.

3.3.2. Describe assay design for detection of infectious agents in the xenotransplantation product. Provide scientific rationale to support selection of tests performed, and the time intervals at which they are performed during culture period. How is the choice of tests for the xenotransplantation product appropriate for the specific animal source? Testing of the product should be conducted by an independent group or company with a SOP and QA/QC for relevant assays in place if possible (applies also to sections 3.3.6 and 7.1).

3.3.3. Indicate whether the test procedures used are standard or specialised with respect to international best practice. Provide data to support the specificity, sensitivity, and reproducibility of procedures to detect infectious agents, particularly if the test is novel.

3.3.4. What type of assays will be used to measure levels of endotoxin or pyrogen during product development phase?

3.3.5. What tests will be used to monitor animals and non-human cells for potential viral contaminants, including latent viruses?

3.3.6. If the xenotransplantation product is porcine-derived, provide evidence that products and source animals will be evaluated using appropriate assays for the expression and transmission of porcine endogenous retrovirus (PERV).

3.3.7. Does the protocol take account of all relevant Good Manufacturing Practices (GMP) and QC considerations for the xenotransplantation product?

3.3.8. Outline plans to cryopreserve and archive for further testing, as needed, samples of all final xenotransplantation products (i.e. cells or tissues, or biopsies of organs).

4. Preclinical Studies

Describe the preclinical evidence relating to the possible safety and efficacy of the transplantation procedure, and explain why the strategy chosen is the most appropriate. In general, studies should focus on activity (the intended alteration to the human pathophysiologic state) and toxicity (unintended effects to the host system). Preclinical studies should be conducted usually in a minimum of 2 animal models (including 1 non-human primate model). In general, studies should apply a framework as set forth in the document generated by the ICH on the safety of biotech-derived pharmaceuticals to these studies. Describe how the preclinical program has been designed to ensure compatibility with the clinical study design. Preclinical studies must use the xenotransplantation product that will be tested in the proposed clinical trial. GTAC will require rigorous analysis of preclinical data. It may be presented in summary form with appropriate statistical analysis, but will be expected to meet most standards required for publication in a peer reviewed scientific journal. GTAC reserve the right to request raw study data. Data presented should include the following:

4.1. What specific considerations in design of the preclinical studies are intended to support the safety of the xenotransplantation product?

4.2. Give details of the animal recipient(s) used in preclinical studies. How were similarities maximised between the animal and human testing strategies in test substance, route of administration, dosing regimen? Describe the limitations of these animal models of disease for assessing efficacy and safety of the xenotransplantation product (including transmission of infectious agents).

4.3. What immunosuppressive regimens were used in the animal model, and were they clinically relevant?

4.4. What veterinary monitoring of animals was used to detect any early signs of infection? What assays were used to detect infectious agents? Where applicable, what procedures were used to assign a cause of recipient animal mortality? What precautions were used to prevent the spread of demonstrable or potential infectious agents from the recipient animal?

4.5. What methods were used to assess survival of the xenogenic cells and for evidence of immunological rejection?

4.6. Have you evaluated in animals the potential for migration of xenogeneic cells within the host? (e.g. by histopathology)

4.7. For xenotransplantation products that are intended to synthesise and provide bioactive molecules such as cytokines or hormones, what experiments were conducted to support that the molecules produced will be active in humans? Provide data to show a concentration-response curve. What means have been used to evaluate the outcome measures in animals?

4.8. What is the potential of the xenotransplantation product to secrete unintended molecules that could alter host physiology?

4.9. For heterogenous xenotransplantation products, has the product tested in preclinical studies been characterised for constituent cell types in the same way as the proposed clinical xenotransplantation product? Provide data from experiments used to identify released, bioactive substances appropriate to the particular xenotransplantation product, whether by intended or extraneous cell types in the xenotransplantation product.

4.10. For xenotransplantation product/device combination products, is the device intended for short-term, extended or permanent residence in the body? Describe tests to characterise the bioreactivity and biocompatibility of device components, and tests to evaluate activity, integrity and tissue viability after various periods of time in animal models. Discuss any device toxicity issues. Attach Medsafe approval for the device if obtained.

4.11. Certain xenotransplantation products may be tumourigenic in a new species because of various factors, such as transgenic manipulations, endogenous viruses, ex vivo culture, and immunosuppression of the host. Describe the risk of tumourigenicity for the xenotransplantation product proposed for clinical use. Justify and provide data to support this analysis of risk.

5. Design of Clinical Study

Because of the potentially serious public health risks you should limit xenotransplantation to patients for whom the following can be demonstrated:

- a serious or life-threatening disease for which adequately safe and effective alternative therapies are not available, except when very high assurance of safety can be demonstrated
- the potential for clinically significant improvement with increased quality of life following the procedure
- the ability to comply with public health measures, including long-term monitoring.

Note that phase 1 clinical studies in children will not usually be approved until safety and efficacy of the procedure has been demonstrated in adults. (There may be exceptions for childhood-specific diseases).

Include the following information:

5.1. Have there been any prior clinical trials using a similar strategy for the disorder in question? If applicable, provide full details of the results, including biochemical, physiological, pathological, and/or clinical endpoints.

5.2. Put the proposed study in the context of previous work and ongoing work in New Zealand and overseas by your group and others in the field. What makes the proposed xenotransplantation study competitive?

5.3. Eligibility and exclusion criteria for patient selection. Indicate if a particular disease stage is being selected.

5.4. Number of subjects to be entered into the study including the statistical basis for selecting this number. Emphasise whether procedures and requirements for selection are fair and equitable; if not, explain why.

5.5. Will the tests used to characterise the xenotransplantation product prior to implantation in humans be the same as those used during product development and preclinical testing?

5.6. Describe the study methods, including the procedure for transplantation of animal cells, tissue, or organs into the human recipients. Will patients receive a single dose or be required to undergo repeat procedures?

5.7. Document the levels of immunosuppression if applicable. How will the levels of immunosuppression differ from an equivalent allotransplantation procedure? What are the implications for contracting other diseases?

5.8. How will you demonstrate the efficacy of transfer, expression and survival? Provide details of the biochemical, physiological, pathological or clinical outcome measures of the study and how assessments will be made. Indicate the frequency of monitoring, and the nature of the statistical evaluation.

5.9. In what setting will the clinical procedures be performed?

5.10. Provide details of the facilities and services that will be made available for the conduct of the trial.

5.11. Detail the expertise of staff administering and monitoring therapy, and provide details of the training these staff will receive.
5.12. If relevant, indicate the containment procedures (including waste disposal) to be followed with respect to all products being administered.
5.13. Provide a simplified version of the protocol which will assist health professionals (e.g. GPs or nurses) who may come into contact with treated patients to understand what is being done.
5.14. Does the study follow the Interim New Zealand Guidelines for Good Clinical Research Practice, August 1998? (http://www.medsafe.govt.nz)

6. Risk Assessment

Risk assessment should be considered from the perspective of the patient, health professionals, and the community.

6.1. Provide a detailed and comprehensive evaluation of safety, risks and benefits relating to the xenotransplantation procedure that addresses both recipient and public health concerns. Examine the likelihood of, and uncertainties associated with, any potential consequences for recipients and/or public health of each of the following events:

- transmission of microbial agents from xenotransplantation product to recipient (which could potentially lead to failure of product, systemic disease in recipient, outbreak of zoonotic disease, silent transmission of latent viruses, or emergence of new pathogens)
- immunological risk including rejection of the xenotransplantation product and, in some cases, graft versus host disease
- any other adverse event(s) arising from the xenotransplantation procedure.

6.2. Are there risks to individuals working in the laboratory with the source animal material? How will these be controlled and minimised?

6.3. Where the same xenotransplantation procedure has been employed in other studies in human subjects, provide details, including relevant papers. Include details of precautions taken and the criteria used to assess safety.

6.4. Comment on the standard of the laboratory in which products to be administered are prepared with reference to compliance with GMP.

7. Post-Xenotransplant Patient Monitoring

This section should contain a detailed description of clinical and laboratory assessment during and following therapy, including a screening programme for infectious agents in recipients and their close contacts.

7.1. Describe testing and scheduling of testing of clinical specimens from recipients for specific infectious agents of concern. Describe how selected tests for infectious agents relate to the specific xenotransplantation product in question. Data should be available to demonstrate specificity, sensitivity and reproducibility for all tests not in widespread use, or for newly developed tests. A particular concern is the potential transmission of xenogeneic retroviruses, such as PERV in the case of recipients of porcine products. Where such transmission may potentially occur, develop a plan to address the possibility that a recipient tests positive for the presence of PERV or other similar xenotransplantation infectious agents.

7.2. Provide a plan for life-long clinical follow-up of recipients in a xenotransplant protocol, including a screening programme for infectious agents (see recommendations in box below).

7.3. Provide a back-up plan (e.g. removal of the device holding the cells) in case of an adverse event in the patient.

7.4. Describe plans for keeping information relating to recipients' health and the xenotransplantation product and procedure on recipients' medical record for at least 50 years beyond the date of transplantation (see box below for information required). What safeguards and procedures are set in place to ensure that monitoring continues and records are maintained? Indicate where records relating to the study will be kept, for how long and in what form.

7.5. Describe a tracking system for all recipients in case they require notification in the event of a serious adverse event related to a xenotransplantation product.

7.6. Indicate how biopsy material, blood samples and cell samples, from both animal source and recipients, if appropriate, will be stored and the proposed duration of such storage. Describe protocols/SOPs for archiving all samples of patient tissues and fluids (including post-mortem samples).

7.7. Describe provisions for all records and samples (from animal source and recipients; including post-mortem samples) to be maintained for 50 years in the event that the sponsor's establishment ceases operation.

7.8. In the event of a recipient's death, what special arrangements have been made for autopsy and what special studies will be requested? How will this information be used?

7.9. During the initial conduct of the study, six-monthly progress reports will be required by GTAC. This should be noted in the protocol.

7.10. Immediate written notification to GTAC will be required if adverse reactions occur during treatment and these are considered to be the result of the treatment rather than the disease process itself. How this will be undertaken should be detailed in the protocol.

7.11. Provide evidence of a programme to educate and monitor health care providers and to monitor other intimate contacts of recipients (e.g. persons with whom recipients repeatedly engage in activities that could result in intimate exchange of body fluids). Will you employ a passive screening programme including pre-exposure serum and blood cells of staff and close associates of patients?

Recommendations for Screening Programmes for Infectious Agents in Xenotransplant Recipients

Screening programmes should take into consideration the source animal species, and type(s) of cell, tissue or organ used. The programme should involve diagnostic testing plus ongoing recipient screening programmes for clinically inapparent infections and seroconversions. Include tests for latent agents known to be in the source animal species. The programme should extend for the life of the patient, although frequency of follow-up will decrease with time post-procedure.

Recommendations for testing of clinical samples from transplant patient for infectious agents:

1) Diagnostic testing - for both acute and chronic infections when a recipient appears ill.
2) Passive screening programme - in which appropriate clinical samples are obtained periodically and archived for possible future testing.
3) Active screening programme – to screen prospectively for evidence of infection in the absence of symptoms. In particular, if a xenotransplantation product known to harbour an infectious agent is used, active screening for that infectious agent should be implemented (e.g. assess all recipients of xenotransplantation products involving the use of porcine products for evidence of infection by PERV).
4) Provide a plan for post-mortem detection of infectious agents and archiving of autopsy samples.

Recommendations for Health Records and Data Management

Each recipient's medical record should contain information on the recipient's health, and all xenotransplantation-related information including procedures, a description of the xenotransplantation product, and any xenotransplantation product-related adverse events. Reporting forms should be uniform and include information relevant to the recipient. Information to be collected and tracked should include, at a minimum, the following:

1) **Facility information** - Sponsors should record information regarding their animal facilities, manufacturing facilities, and clinical centres associated with each source animal, xenotransplantation product, and recipient.
2) **Recipient information –** Sponsors should identify recipients by code number or other identifier to link the recipient to relevant information in the tracking system.
3) **Procedure information** - Sponsors should record information about each xenotransplantation procedure. This information should include, but is not limited to:
   a) recipient identifiers,
   b) the date of the procedure,
   c) the clinical centre where the procedure was performed,
   d) the physician or investigator who performed the procedure,
   e) the clinical indication for the xenotransplantation procedure,
   f) medications and therapies administered at the time of the procedure,
   g) a description of the xenotransplantation product(s),
   h) identification of the animal source(s),
   i) animal facilities for each animal source,
   j) xenotransplantation product manufacturing facilities, and
   k) other pertinent clinical information
4) **Adverse Event Reports** - A sponsor must record adverse events and report the events according to the Interim Good Clinical Research Practice Guideline. The sponsor of the trial should report all serious adverse events to Medsafe within 72 hours of being informed of the adverse event(s). Sponsors should keep detailed records of each event.
5) **Recipient clinical follow-up examinations –** Sponsors should periodically collect clinical status information for recipients of xenotransplantation products. This information should include, but is not limited to:
   a) the date of the clinical follow-up examination,
   b) the location of the clinical follow-up examination,
   c) the status of the xenotransplantation product in the recipient,
   d) any new significant co-morbidities or inter-current conditions, and
   e) any hospitalizations since the recipients' last clinical follow-up examination.

6) **Animal Health Events** - Animal facilities should record animal health events. These events include, but are not limited to:
   a) breaks in the environmental barriers of the secured animal facility,
   b) disease outbreaks, and
   c) sudden, unexplained, or unexpected animal deaths.

   The animal facility should report animal health events to the sponsor. The sponsor should include this information in its tracking system for recipients and in reports to the Ministry of Health.
7) **Recipient Death Reports** - Sponsors should maintain death reports on recipients. This information should include recipient identifying information, the date of death, and the cause of death. Sponsors should record death certificate and autopsy information, if available, and report deaths to the Ministry of Health.

8. Informed Consent

The following section provides some points for consideration that have been derived from FDA documents, but this list should not be regarded as a comprehensive summary of issues that need to be considered for Ethics Committee approval.

8.1. How will consent be obtained from candidates for the proposed treatment? It is essential that all participants are given the opportunity to receive information and advice from an independent relevant specialist before consent is sought. Will there be an independent person who patients could approach to express concerns, or to obtain information? Procedures for obtaining consent should include the following:

- Collection of signed information sheets (or equivalent) from intimate contacts of research participants.
- Agreement to provide information sheets (or equivalent) to any future intimate contacts and to provide contact details for the intimate contacts to the research group.
- A request for autopsy to be signed by the intended recipient or his/her appropriate representative.

8.2. What safeguards have been set in place to protect the privacy and identity of subjects in the trial?

8.3. Include with your application a clear, plain-language statement designed for patients and their families to allow potential participants to make an informed decision. The plain-language statement should be written in a non-technical way and include certain information:

Information required for a plain-language statement

1) A brief review of the disease and the nature and impact of conventional treatment.
2) The rationale behind the study and the likelihood of providing benefit.
3) A full explanation of the procedure.
4) The potential benefits to the subject in the short- and long-term. Convey the specific desired benefits (e.g. limited prolongation of survival, improved specific organ function, or xenotransplantation product support until allograft becomes available). Clarify whether xenotransplantation is being studied as a first-line, second-line, or salvage therapy.
5) Explain, to the extent possible, subsequent treatment options should the product fail or undergo irreversible rejection, including clear and unambiguous statements about the options that may not be possible after rejection of the xenotransplantation product.
6) Potential risk to the recipient and to intimate contacts and third parties. This should cover:
   a) The recipient's potential to transmit zoonotic or opportunistic infections and the possibly increased risk of such transmission to individuals who may be susceptible to zoonotic or opportunistic pathogens such as infants, pregnant women, the elderly, chronically ill or immunosuppressed individuals.

b) The specific and known risks of all protocol-related activities not directly associated with source animal issues as well as the known and unknown zoonoses that may be associated with the source species. It should mention the uncertainty of the risk of infection or its transmission, and of the risk of tumourigenesis. It should mention the possibility of a long latency period before detection of possible adverse effects. It should specify the need for, and risks from, prophylactic antimicrobial, antiviral, or other chemo- or immunotherapy. It should provide in an attachment for the recipient and the recipient's family the reasoning behind the use of any prophylactic treatments.

c) The possible need for confinement, reverse isolation or other specialised medical housing, including the estimated duration of such confinement. Describe any specialised dietary, travel or other precautions in as much detail as possible.

d) Include any known time course for the risks of disease development and transmission. Discuss infectious diseases with protracted incubation periods such as transmissible spongioform encephalopathy (TSE) and other unusual pathogens.

e) In the specific case of xenotransplantation products from porcine sources, the informed consent document should include specific, updated information about the potential risk for PERV transmission from pig cells to human cells in vivo and in vitro and the clinical significance of PERV transmission.

f) Inform patients of the necessity for behavioural modifications including deferral from donation of whole blood, blood components (including source plasma and source leukocytes), tissues, breast milk, ova, sperm, or any other body parts for use in humans. Provide advice on the use of barriers to transmission of infectious agents during sexual activity and the use of appropriate precautions for nonsexual contacts.

g) The patient should consent to inform his or her current and future intimate contacts of their potential risks from the source animal species, and of their deferral from blood donation.

7) Inform patients of the need for life-long follow-up with clinical and laboratory monitoring, and the importance of autopsy. Include:
   - the schedule for clinical and laboratory monitoring (to the extent possible)
   - the responsibility to inform the investigator and Ministry of Health of any change in address or telephone number
   - the need for archiving plasma and tissue specimens from the source animal and the recipient. Explain that such specimens may be tested in the future by the sponsor or Ministry of Health as needed to evaluate concerns regarding xenogeneic infections.

8) Subjects should be told that all information relating to their therapy, including data collected during the follow-up, will be recorded in a register and could be made available to Ministry of Health to ensure that long-term impact can be monitored.

9) Include a clear statement that participation in the study is voluntary and that patients who choose not to participate will not be disadvantaged in any way.

Intimate Contacts of xenotransplantation product recipients include persons who have engaged repeatedly in activities with a recipient that could result in intimate exchange of body fluids, including blood or saliva. Examples of intimate contacts include, but are not limited to, sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal, or other direct exposures. Mere sharing of housing or casual contact, such as hugging or kissing without the exchange of saliva, would not be interpreted as intimate contact.

New Scientific Information – Sponsors should commit to providing recipients with updated information as soon as possible in the event that new data on risks, benefits or the need for additional treatments relevant to their clinical course becomes available or necessary. Sponsors should be willing to make a long-term commitment to provide information to a recipient's family in the event that the recipient has died and new safety information of relevance to their potential exposures becomes known. If you are the sponsor, you should ensure that the investigators are also willing to commit to providing new information to recipients and their families**.**

9. Additional Documents

9.1. Curriculum vitae of the chief investigators highlighting the relevant training and experience of those who will be responsible for preparation of therapeutic products, preclinical studies, administration of gene products and assessment of outcomes.

9.2. Reprints of publications directly relating to the proposal.

9.3. Names and addresses of a maximum of 3 referees without conflicts of interest who could be approached by GTAC for an independent expert opinion on a particular application.

9.4. Names of referees considered to be unacceptable (with justification).