

**Process and Guidelines for Application for
Approval of Proposals
Involving Administration of Gene Products
to Human Subjects
in New Zealand**

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HRC Gene Technology Advisory Committee

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A. Process for Approval of Proposals Involving Gene Products

1. Introduction and GTAC Terms of Reference

In New Zealand, gene therapy and other protocols involving administration of nucleic acids are regulated under the Medicines Act (1981). The term 'medicine' means any substance or article that is manufactured, imported, sold or supplied wholly or principally - (a) for administering to one or more human beings for a therapeutic purpose (Section 3).

A therapeutic purpose means:-

- (a) treating or preventing disease; or
- (b) diagnosing disease or ascertaining the existence, degree, or extent of a physiological condition; or
- (c) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by reducing or postponing, or increasing or accelerating the operation of that function, or in any other way (Section 4).

If the "medicine" is to be used for the sole purpose of obtaining clinical and scientific information then the investigator is required to seek permission for its use under Section 30 "Exemption for clinical trial" of the Medicines Act (1981). Approval under Section 30 is given by the Director-General of Health on the recommendation of the Health Research Council of New Zealand (HRC).

For pharmaceuticals the recommendation to the Director-General of Health is made by the HRC's Standing Committee on Therapeutic Trials (SCOTT).

The Gene Technology Advisory Committee (GTAC), a Standing Committee of the HRC, acts in a similar capacity as SCOTT with respect to protocols which fall within GTAC's Terms of Reference.

GTAC's Terms of Reference are as follows:

GTAC is to review for the purposes of seeking an exemption under Section 30 of the Medicines Act (1981) or as required by an accredited ethics committee or the HRC or any of its committees:-

- (i) Proposals for clinical trials which include the introduction of nucleic acids (genetically manipulated or synthesised in the laboratory) or genetically manipulated microorganisms, viruses or cells into human subjects for the purpose of gene therapy or cell marking.

- (ii) Proposals for clinical trials in which the introduction of nucleic acids (genetically manipulated or synthesised in the laboratory), or genetically manipulated microorganisms, viruses or cells is designed to stimulate an immune response against the subject's own cells, as in the treatment of certain cancers.
- (iii) Proposals for clinical trials in which nucleic acids either from or within cells from animal species are transferred into humans for the purpose of disease treatment i.e. xenotransplantation.
- (iv) Proposals for clinical trials in which human nucleic acids have been introduced into the genome of an animal species, including genetically manipulated microorganisms, for the purpose of developing products to be used for either disease prevention or treatment in human subjects.
- (v) Proposals for clinical trials involving vaccines in which nucleic acids (genetically manipulated or synthesised in the laboratory) or genetically manipulated microorganisms, viruses or cells have been introduced to stimulate an immune response to antigenic determinants of an infectious agent.

Under Section 30 of the Medicines Act (1981) GTAC will be required to meet a 30 day timeline for its review of applications. Applications will be made to the Ministry of Health in the prescribed format (see Section B Guidelines for Preparation of Applications). The investigator seeking an approval under Section 30 of the Medicines Act will also be required to lodge a \$9,843 fee which in the case of public good research may be waived by the Ministry of Health on the recommendation of the Chief Executive of the HRC.

2. Process for GTAC Approval

- 2.1 Applications to the Ministry of Health for GTAC approval are to be made by letter using the Guidelines in Section B available from the HRC. Applications for clinical trials involving xenotransplantation should be made using separate GTAC guidelines.¹ The format used by GTAC is based on that used by the NH&MRC (Australia) and the Points to Consider used by the FDA (USA). The fee or a letter seeking an exemption from the fee should accompany the application.
- 2.2 The application will be reviewed by GTAC within 30 days. The investigator may be required to attend a meeting with the Committee to discuss the application.
- 2.3 GTAC will provide the Director-General of Health with their recommendation as to whether the trial be approved.

¹ *Guidelines for Preparation of Applications Involving Clinical Trials of Xenotransplantation in New Zealand*, available from the HRC website (www.hrc.govt.nz)

- 2.4 If a proposal involves materials which originate from the USA, the investigator will be required to meet the regulatory requirements of the FDA to obtain an export certificate. The Director-General of Health will not give approval for a Section 30 exemption until the appropriate documentation has been received and has been approved by the Ministry of Health.
- 2.5 Approval from an accredited ethics committee can not be sought until the Director-General of Health has received a recommendation from the HRC (GTAC) that the trial under review be approved.

When the Director-General of Health has received recommendations for approval from GTAC and an accredited ethics committee, written approval for an exemption under Section 30 of the Medicines Act (1981) may be given. Only then can the investigator proceed with the trial.

Xenotransplantation is listed as a “restricted procedure” in Part 7A of the Medicines Act, and can only be authorised by the Minister of Health. Applications for xenotransplantation that have been recommended by GTAC and an accredited ethics committee will be considered by the Minister of Health, who will make a final decision based on all of the assessments of the application and advice from the Ministry of Health.

- 2.6 Investigators should also ensure that they meet **all** the requirements of their host institutions with respect to making applications to gain approval from GTAC, relevant ethics committees, biosafety committees and ERMA (Environmental Risk Management Authority).

3. **Criteria for GTAC Approval**

GTAC will review applications to establish:-

- (i) Whether there is adequate scientific evidence from laboratory and experimental studies in animals to allow a trial in humans to proceed.
- (ii) Whether the proposed trial will provide a clinical benefit and scientifically useful information particularly in relation to safety and efficacy.
- (iii) Whether there is adequate information on the safety and toxicity of the materials to allow them to be used in a trial in humans.
- (iv) Whether the investigators have the qualifications, experience and track record to conduct the proposed trial.
- (v) Whether the investigators have conducted appropriate risk assessment of their proposed procedures.

GTAC will provide the Director-General of Health with a written report and a recommendation as to whether the proposed study should be approved, declined or deferred.

4. **Membership of GTAC**

Chair		
Professor Kathryn Crosier (Molecular Medicine)	MBChB PhD FRACP FRCPA	The University of Auckland

Members		
Professor Grant Gillett (Ethicist and Surgeon)	MBChB FRACS	University of Otago
Dr Martin Kennedy (Molecular Biology and Genetics)	PhD	University of Otago Christchurch
Emeritus Professor Colin Mantell (Obstetrics and Gynaecology, Maori and Pacific Health)	MBChB PhD FRCOG	The University of Auckland
Dr Ian Morison (Cancer Genetics)	MBChB PhD FRCPA	University of Otago
Dr Robin Olds	MBChB PhD FRCPA	Health Research Council of New Zealand
Professor Stephen Robertson (Clinical Geneticist)	MBChB DPhil FRACP	University of Otago
Associate Professor Richard Robson (Clinical Trials and Chair SCOTT)	MBChB PhD FRACP	Christchurch Clinical Studies Trust
Dr Bruce Scoggins (Health Research Policy)	PhD	Auckland
Dr Deborah Young (Molecular Medicine)	PhD	The University of Auckland

Ex officio	
Dr David Abbott	NHMRC, Australia
Dr Ian Alexander Chair of the NHMRC's Cellular Therapies Advisory Committee (CTAC)	The Children's Hospital at Westmead, New South Wales, Australia

5. **Preparation of Applications for GTAC Review**

The purpose of the guidelines which follow (Section B) is to assist clinicians and scientists in New Zealand in the design of protocols for the transfer of recombinant DNA-derived products or proteins from transgenic animals into the genome of human subjects. This document draws heavily on recommendations covering gene therapy and related procedures in the UK, USA and Australia as it is seen important that there is a compatibility between these countries. From time to time, this document will be updated in the light of more experience in regulating these forms of treatment. The HRC or Ministry of Health should be consulted to ensure that a current version of this document is used by potential applicants.

The HRC understands that the information required by GTAC will vary with different proposals. These guidelines include a list of headings under which the protocol can be presented but applicants may feel there are segments missing for a full consideration of the proposal. In such a case, the applicants should ensure that the application contains all pertinent information.

B. Guidelines for Preparation of Applications for GTAC Review

1. Objectives and Rationale

Introductory statement of the objectives and rationale of the proposed research and whether its intention is therapeutic (benefit to the patient) or non-therapeutic (to add to scientific/clinical knowledge)

1.1 Therapeutic

1.1.1 Details of the disease to be treated with particular reference to prevalence, aetiology, clinical features, staging (where relevant), phenotypic variability, range of cells/tissues affected, severity and natural history.

1.1.2 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? Have any of these treatment regimens been used on subjects to be recruited to this study?

1.1.3 Why is the proposed strategy appropriate for this disease?

1.1.4 Anticipated quality of life for patients following treatment.

1.1.5 Is the clinical course of the disease sufficiently well understood to allow outcomes of the treatment to be assessed? What measure of disease progression/severity are available?

1.1.6 What promise does the proposed strategy hold for reversing the disorder or bringing about a remission in both the short and long-term?

1.1.7 What are the possible side effects of the proposed treatment?

1.1.8 Define the group(s) of patients to be offered the proposed treatment.

1.1.9 If study is to be conducted in multiple centres within New Zealand or overseas, please describe and document the approvals obtained from all other relevant regulatory bodies.

1.2 Non-therapeutic

1.2.1 The reason for carrying out the study in this particular group of patients.

1.2.2 The perceived importance of the study.

1.2.3 Indicate how patients will be recruited, where no perceived direct benefit to them is likely.

2. Recruitment of Subjects to Study

Provide information relating to:-

- 2.1 Criteria for eligibility and exclusion. Indicate if a particular disease stage is being selected.
- 2.2 Numbers of subjects to be entered into study including statistical basis for selecting this number. Emphasise whether procedures and requirements for selection are fair and equitable.
- 2.3 How has consent been obtained from candidates for the proposed treatment? Where subject is a child, describe the mechanism for securing consent. It is essential that parents or guardians of a child are given the opportunity to receive information and advice from an independent paediatrician or relevant specialist before consent is sought. Will there be an independent person who patients could approach to express concerns, or to obtain information?
- 2.4 A plain language statement designed for patients and their families should be included with any application to GTAC. The plain language statement should be written in a non-technical way and should include the following information:
 - A brief review of the disease and the nature and impact of conventional treatment.
 - The rationale behind the study and the likelihood of providing benefit (in the case of a therapeutic study) or a clear statement indicating that there will be no direct benefit to the subject (in the case of a non-therapeutic study).
 - A full explanation of the procedure.
 - The potential benefits and risks to the subject in the short and long-term.
 - Potential risk to third parties.
 - Clear statement that participation in the study is voluntary and that patients who choose not to participate will not be disadvantaged in any way.
 - Subjects should be told that information relating to their therapy will be recorded in a register to ensure that long-term impact can be monitored.

- The need for life-long follow-up and the importance of autopsy.
- The means by which subjects will be informed of the outcome of the study and the name of an individual with whom they can discuss the study if they wish.

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

3. Design of the Study

3.1 Structure and characteristics of the system for gene or cell transfer. The following points should be addressed:

3.1.1 Nature of the DNA/RNA to be introduced? Is the nucleic acid modified? Provide detailed information including restriction maps, the steps used in deriving the construct and the stages involved in generating the recombinant molecule to be used in therapy. In the case of cell therapies indicate the full details of cell isolation and methods adopted to ensure desirable quality of product. Ensure that the structure of the material to be administered to the subject is detailed and summarise the steps that have been taken to detect and eliminate contaminants such as other viruses/micro-organisms, serum and substances that might have biological side effects.

3.1.2 By what means will nucleic acid or cells be administered to subjects? Where viral vectors are to be employed, provide full details of structure and principles governing expression and regulation. Has the viral vector or cellular material been used in any previous study? Where the system of delivery has not previously been employed, it is necessary to provide full details demonstrating the efficiency of transfer and expression and survival.

3.1.3 In what setting (hospital in-out patient or home) will the course of therapy be administered? Where subjects to receive therapy will be in-patients, will they be in a general ward or a room designated for this purpose? How long will subjects be in hospital? Provide details of the facilities and services that will be made available for the conduct of the trial. Detail the expertise of staff administering and monitoring therapy and indicate whether nursing staff have been well instructed about the nature, significance and conduct of the trial.

3.1.4 Indicate whether this study requires the approval of any other body especially if patients or collaborators reside normally in another country. If yes, attach the relevant documentation.

- 3.1.5 If relevant, indicate the containment facilities (including waste disposal) to be followed with respect to all products being administered.
- 3.1.6 Provide a simplified version of the protocol which will assist health professionals (eg. GPs or nurses) who may come into contact with treated patients to understand what is being done.
- 3.1.7 Does the study follow the Interim New Zealand Guidelines for Good Clinical Research Practice (1998)?

3.2 **Prior studies**

Describe the evidence relating to the possible efficacy of the gene delivery system and explain why the one chosen is the most appropriate. Where such data are not available GTAC will wish to have a full account of how assessments were made. With cell transfer systems proposed, explain why the current decisions have been made. Data presented should include the following:

- 3.2.1 Studies of delivery system.
- 3.2.2 Studies to demonstrate gene transfer, expression and target specificity of system.
- 3.2.3 Are there animal models of the disease in question? Has the proposed therapy been tried in this model and if so, with what success?
- 3.2.4 Have there been clinical trials using a similar strategy for the disorder in question, or for other disorders, using the proposed system of gene transfer?
- 3.2.5 If the gene transfer or cell transfer approaches for the disorder in question have been used in previous trials, provide full details of the results, including biochemical, physiological, pathological or clinical endpoints.

4. **Monitoring Treatment**

A detailed description of clinical and laboratory assessment during and following therapy should be included. The information to be supplied should include:-

- 4.1 Procedures for monitoring presence and/or expression of administered nucleic acids.
- 4.2 How will it be determined whether the new gene sequences are limited to the target cell population?

- 4.3 Details of biochemical, physiological, pathological or clinical endpoints of the study and how assessment will be made. Which of these will be of value during the monitoring process? Indicate the frequency of monitoring, the nature of statistical evaluation, and what safeguards and procedures will be set in place to ensure that monitoring continues and records are maintained. Indicate where will records relating to the study be kept, for how long and in what form?
- 4.4 Indicate how biopsy material, blood samples and cell samples, from both donor and recipients, if appropriate, will be stored and the proposed duration of such storage.
- 4.5 In the event of a subject's death, what special arrangements have been made for autopsy and what special studies will be requested? How will this information be used?
- 4.6 During the initial conduct of the study, six monthly progress reports will be required by GTAC. This should be noted in the protocol.
- 4.7 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 noted in the protocol.

5. Risk Assessment

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

- 5.1 Provide a detailed and comprehensive appraisal of aspects of safety relating to the gene delivery system to be adopted.
- 5.2 Where defective viral vectors are to be used, provide details of assays for helper viruses.
- 5.3 Where the same delivery system has been employed in other gene therapy studies in human subjects, provide details, including copies of relevant papers. Include details of precautions taken and the criteria used to assess safety.
- 5.4 Where the gene delivery system has not previously been used it is essential to provide a full account of the theoretical arguments indicating that the procedure is safe to both the patient as well as health professionals and the community. What possible risks are posed to the subject by the gene therapy strategy and what possible side effects might be anticipated?
- 5.5 Is there any likelihood of the therapeutic (or non-therapeutic) gene being incorporated into the germline?

- 5.6 Comment on the standard of the laboratory in which products to be administered are prepared with reference to compliance with Good Manufacturing Practices.

6. Additional Documents

To be included with any proposal for review by GTAC.

- 6.1 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.
- 6.2 Reprints of publications directly relating to the proposal.
- 6.3 Names and addresses of referees who could be approached by GTAC for an independent expert opinion on a particular application.

7. Further Reading

- 7.1 Interim New Zealand Guidelines for Good Clinical Research Practice, Ministry of Health, August 1998 (<http://www.medsafe.govt.nz>).