

Appendix 3

Australian Health Ethics Committee Information Sheets

REVOKED

Australian Health Ethics Committee
INFORMATION FOR HRECs: MARCH 1995
Regulations for the Clinical Trial Notification Scheme

The Clinical Trial Notification (CTN) Scheme

The introduction of the CTN Scheme in 1991 deregulated the conduct of clinical trials in Australia by reducing the involvement of the Therapeutic goods Administration (TGA). Under the CTN Scheme the TGA must be notified of clinical trials but it does not assess the science or safety of the trial. These responsibilities are devolved to the institution or organisation conducting the trial. The approval of an ethics committee is also required.

A review of the CTN Scheme in 1993 recommended some changes to the conditions which apply to trials conducted under the Scheme. As a result the Therapeutic Goods Regulations have been amended as shown below.

Therapeutic Goods Regulations

Schedule 5A (Therapeutic goods exempt from the operation of Part 3 of the Act subject to conditions), Item 3 as amended by Statutory Rules 1994, No 150, reads as follows:

“Therapeutic goods [ie drugs] used solely for experimental purposes in humans

- a. before starting to use the goods, the sponsor must notify the Secretary [of the Commonwealth Department of Human Services and Health]:
 - i. in a form approved by the Secretary; and
 - ii. in accordance with the requirements (if any) determined by the Secretary for the form of notification;

that the sponsor intends to sponsor a clinical trial using specified goods; and

- b. the notification must be accompanied by the relevant notification fee referred to in item 14 or 14A of Schedule 9; and
- c. the approval of the goods for this purpose must be given by the sponsor (if the sponsor is conducting the trial), or by the body or organisation conducting the trial for the sponsor, having regard to the advice of the ethics committee that has, or will assume, responsibility for monitoring the conduct of the trial; and
- d. the terms of the approval by the sponsor, body or organisation referred to in paragraph (c) must be no less restrictive than the terms advised by the ethics committee; and

- e. the Secretary must not, at any time:
 - i. have become aware that to conduct or continue the trial would be contrary to the public interest; and
 - ii. have directed that the trial not be conducted, or be stopped; and
- f. the sponsor (if the sponsor is conducting the trial), or the body or organisation conducting the trial for the sponsor, must not receive, or have received, advice from the ethics committee that is inconsistent with the continuation of the trial.”

Bodies or organisations able to conduct trials

The previous guidelines referred to trials being conducted in a “hospital or institution”. This was seen to limit the range of bodies which could conduct a trial. The revised regulations use the phrase “body or organisation”.

In addition, the wording makes it clear that “a sponsor” may conduct a trial without the involvement of any intermediary body. For example, if a health service body wishes to trial a drug for indications other than those for which it is marketed and the drug’s Australian supplier is not willing to be the sponsor, then the health service body can be both the sponsor and the body conducting the trial.

The “sponsor”, as defined by the Therapeutic Goods Act, 1989:

- a. exports, or arranges the export of, the goods from Australia; or
- b. imports, or arranges the importation of, the goods into Australia; or
- c. in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere);
but does not include a person who:
- d. exports, imports or manufactures goods; or
- e. arranges the exportation, importation or manufacture of the goods; on behalf of another person who at the time of the exportation, importation, manufacture or arrangements, is a resident of, or is carrying on business in, Australia.

Ethics approval

The regulations now specify that approval for the conduct of the trial must be given by the body or organisation which is conducting the trial, rather than by the Chairperson of the Institutional Ethics Committee (IEC). This wording makes it clear that legal responsibility for the trial lies with the body or organisation conducting the trial. Ethics committee approval is still required and the approving ethics committee must be constituted and operating in accordance with guidelines issued by the National Health and Medical Research Council (NHMRC).

Trials can be halted

The regulation clarify the situation with regard to cessation of trials by stating that the approving ethics committee is responsible for monitoring progress of the trial and may recommend cessation of the trial. The sponsor or the body or organisation conducting the trial is obliged to act on such advice.

The Australian Health Ethics Committee is a principal committee of the National Health and Medical Research Council.

For further information, please contact the Australian Health Ethics Committee Secretariat, NHMRC, MDP 100, GPO Box 9848, CANBERRA ACT 2601

Phone: (02) 6289 9807 **Fax:** (02) 6289 9898 **Email:** ahec.nhmrc@nhmrc.gov.au



Australian Government

National Health and Medical Research Council

Information Sheet 2B

INFORMATION FOR HRECs: FEBRUARY 2004

Role of the Gene and related Therapies Research Advisory Panel (GTRAP) and implications for HRECs: updated Information Sheet 2

The Research Committee, a principal committee of the National Health and Medical Research Council (NHMRC) established the Gene Therapy Committee (GTC) in June 1993. This committee was renamed the Gene Therapy Research Advisory Panel (GTRAP) in 1997, and was recently renamed the Gene and related Therapies Research Advisory Panel (GTRAP). This Information Sheet is an update of Information Sheet 2, which should be discarded.

Part of GTRAP's role is to assist HRECs to assess research protocols involving human somatic cell gene therapy and related issues, including xenotransplantation. HRECs give the final approval for research protocols and monitor gene therapy studies under their jurisdiction. The Australian Health Ethics Committee (AHEC) has advised HRECs not to approve studies involving gene and related therapy, including xenotransplantation, without GTRAP review.

At the date of this Information Sheet, the NHMRC was undertaking public consultation on whether or not xenotransplantation research should proceed in Australia and, if it does, what guidelines should be developed to direct such research. GTRAP will continue to advise HRECs on xenotransplantation research proposals until such time as these issues are resolved.

The Research Committee expanded the role of GTRAP for the 2003-2005 triennium to include an Expert Advisory Group to advise on human stem cell research within GTRAP's brief.

Terms of Reference for GTRAP

Through the NHMRC Research Committee, GTRAP:

- provides advice to Council on scientific, medical and technical issues related to gene and related therapies, xenotransplantation and human stem cell research;
- provides scientific, medical and technical advice to HRECs, scientists and other interested parties during the formulation and ethical review of research in gene and related therapies and xenotransplantation. In relation to human stem cell research this would be limited to those cells that fall within the scope of the proposed Class 3 risk category outlined by the Therapeutic Goods Administration (TGA) in their *Discussion Paper - The Regulation of Human Tissues and Emerging Biological Therapies**;

* GTRAP will only start to review stem cell work when the TGA adopts the above discussion paper as formal policy

- functions as a source of information on gene and related therapies, xenotransplantation and human stem cell research to the public and other interested parties; and
- maintains a register of research trials in which gene therapies or xenotransplantation have been used.

Membership of the Gene and Related Therapies Research Advisory Panel

To cover its broad brief, the composition of GTRAP includes:

- a core group of individuals with expertise in research, clinical medicine, the law and ethics; representatives from the TGA, the Gene Technology Technical Advisory Committee (GTTAC) and AHEC; and a lay person;
- a gene therapy specialty group;
- a xenotransplantation specialty group; and
- a human stem cell specialty group.

When dealing with gene therapy matters, the core and the gene therapy specialist group meet. A similar procedure is used in relation to xenotransplantation and human stem cell related issues.

Manner of carrying out its functions and committee procedures

GTRAP is established as a working committee of the Research Committee of the NHMRC, under Section 39 of the *National Health and Medical Research Council Act 1992*. As such, GTRAP is subject to the NHMRC's endorsed Committee Procedures, including those relating to conflict of interest. GTRAP examines protocols for gene therapy and related technologies, including xenotransplantation, as submitted to HRECs and makes recommendations to HRECs as to whether these protocols are appropriate in terms of their scientific and medical content.

GTRAP meets face-to-face and conducts teleconferences to discuss protocols and issues when required. Regular contact is maintained by electronic means.

Approval process

Proposals for somatic cell gene therapy research and xenotransplantation undergo a process of review which involves an HREC, GTRAP, the TGA, an Institutional Biosafety Committee (IBC) and, when relevant, the Gene Technology Regulator.

- All such proposals must be submitted to an HREC for initial ethical and scientific review. Researchers are advised to submit their proposals for human gene therapy in the form set out in the GTRAP document *Guidelines for the Writing of Human Gene Therapy Proposals*, a copy of which can be found at the GTRAP website. When it has completed its review, the HREC forwards the proposal to GTRAP, having identified any aspects of the proposal requiring specific comment.

- For xenotransplantation, pending the possible availability of Australian guidelines, GTRAP will continue to follow recommendations and guidelines from the USA's Food and Drug Administration (FDA). For example, the FDA's Centre for Biologics Evaluation and Research publication *PHS guideline on infectious disease issues in xenotransplantation*, which may be found at: <http://www.fda.gov/cber/gdlns/xenophs0101.pdf>.
- GTRAP assesses the proposal. As part of this process the investigator and sponsor may be asked to attend a GTRAP meeting, at which time the proposal is reviewed and specific issues raised. Following this meeting, a final or interim report is prepared by GTRAP and sent to the investigators and the relevant HREC. An interim report usually forms the basis for a teleconference between GTRAP, the investigators, the sponsor's representative and a member of the HREC. At this teleconference outstanding issues are discussed. Additional meetings or teleconferences can be arranged as required and, before giving its final recommendations to the HREC, GTRAP may consult with other bodies concerned with monitoring the safety of innovative genetic manipulation techniques (OGTR) or the standards for product manufacture (TGA). A final report is then issued by GTRAP.
- GTRAP has recommended that, in general, gene therapy and xenotransplantation proposals follow the TGA's Clinical Trial Exemption (CTX) scheme, unless GTRAP considers the Clinical Trials Notification (CTN) Scheme suitable. For example, CTN might be appropriate if the gene therapy vector has already been approved for a similar clinical use by a regulatory body such as the USA's FDA.
- Proposals that fall under the jurisdiction of the Gene Technology Regulator must also be submitted to an IBC for initial assessment. When it has completed its assessment, the IBC forwards the proposal to the OGTR, having identified any aspects of the proposal requiring specific comment.
- The OGTR assesses the proposal and, before giving its recommendations to the IBC, may consult with GTRAP, or other bodies concerned with the safety of innovative genetic manipulation techniques.
- In the final step of the regulatory process, the HREC ensures that the proposal has been approved by all relevant bodies and decides whether or not the research may proceed.
- Although GTRAP works predominantly with HRECs, GTRAP's expertise is always available to investigators, sponsors, and the public. In the case of investigators, it might be beneficial during the early pre-clinical phases for them to approach GTRAP to determine in advance what will be expected before the gene therapy product can be introduced into clinical trials.

Expedited Review & Expedited Risk Assessment by GTRAP

There are clinical studies which utilise genetic material and might not require a full formal review and approval by GTRAP since the risks of the procedure to patients and the community are no different from traditional drug-based therapies. For example, oligonucleotides that involve transient and non-integrating/altering genome events. See *Information Sheet 7, Feb 2003*, for more information on oligonucleotides and GTRAP review (<http://www.health.gov.au/nhmrc/issues/committeehumansupport.htm>). In these circumstances, GTRAP has developed a proforma for Expedited GTRAP Review. These requests will be considered out-of-session with a guaranteed response within 30 days.

In some cases, investigators, sponsors or HRECs may not be sure if their proposal requires GTRAP review, in which case GTRAP can provide informal advice (see contact details below). Alternatively, the lodging of the proforma for Expedited GTRAP Review will ensure that there is a written response from GTRAP within 30 days.

Following receipt of the proforma for Expedited GTRAP Review, GTRAP will determine if a full formal review is necessary, or the proposal is exempt from further review. Exemptions given will apply to all similar trials being conducted in Australia.

A Guide for the Writing of Gene Therapy Proposals

A document entitled *Guidelines for the Writing of Gene Therapy Proposals* is available from the NHMRC's website:

<http://www.nhmrc.gov.au/research/gtrap/gene.pdf>.

Current issues under discussion by GTRAP

Information about current issues under discussion by GTRAP can be found at the NHMRC website: <http://www.nhmrc.gov.au/research/gtrap.htm>.

Further information

For further information on GTRAP, or to request a copy of the above guide, please contact the GTRAP Secretariat:

Secretary, Gene and related Therapies Research Advisory Panel
NHMRC
MDP 109
GPO Box 9848
CANBERRA ACT 2601

Phone: (02) 6289 9860

Fax: (02) 6289 9836

**Australian Health Ethics Committee
INFORMATION FOR HRECs: APRIL 1998**

UNESCO *Universal declaration on the human genome and human rights*

Articles 22 and 23 of the UNESCO *Universal declaration on the human genome and human rights* read:

Article 22 States should make every effort to promote the principles set out in this Declaration and should, by means of all appropriate measures, promote their implementation.

Article 23 States should take appropriate measures to promote, through education, training and information dissemination, respect for the abovementioned principles and to foster their recognition and effective application. States should also encourage exchanges and networks among independent ethics committees, as they are established, to foster full collaboration.'

The *Declaration* was adopted, unanimously and by acclamation, at the 29th session of the General Conference of UNESCO on 11 November 1997. The Australian Government is strongly in agreement with the Declaration which is the result of more than four years work carried out by the UNESCO International Bioethics Committee – in particular within its Legal Commission – and is the final outcome of the meeting of the Committee of Governmental Experts held in July 1997.

Article 11 relates to the cloning of human beings. The Commonwealth Minister for Health and Family Services, the Hon Dr Michael Wooldridge, announced in January 1998 that the Australian Government would pursue ways of trying to ensure that the cloning of human beings does not take place in Australia. Dr Wooldridge has asked the Australian Health Ethics Committee to provide advice on the potential and need for further pronouncement or possible legislation regarding the cloning of human beings. This forms part of the current work program for this year and will be completed before the end of 1998.

The Australian Health Ethics Committee is a principal committee of the National Health and Medical Research Council.

For further information, please contact the Australian Health Ethics Committee Secretariat, NHMRC, MDP 100, GPO Box 9848, Canberra, ACT, 2601.

Phone: (02) 6289 9807 **Fax:** (02) 6289 9898 **Email:** ahec.nhmrc@nhmrc.gov.au

**Australian Health Ethics Committee
INFORMATION FOR HRECs: FEBRUARY 2000
Fees for Ethical Consideration of Research Proposals**

1. Background

Many institutions and organisations have adopted the practice of charging a fee to researchers or research sponsors for access to HREC review of research proposals. It appears, from submissions made to the AHEC, that these practices vary widely as to the amount of the fees, their conditions and their rationale. Some institutions regard the charging of such fees as inappropriate.

During public consultation for the *National Statement* on Ethical Conduct in Research Involving Humans, some submissions to the AHEC requested guidance on such policies.

In this response to requests, the AHEC recognises that the decision whether or not to adopt a policy of charging a fee for access to HREC review is, to an extent, an administrative decision. Some institutions and organisations regard fees as simply one means of defraying the costs of establishing and adequately resourcing an HREC, as required by the *National Statement*. A summary of what the *National Statement* requires appears in paragraph 4 below.

However, there are ethically relevant issues involved in a decision to adopt a policy of charging fees for access to HREC review. It is to these issues that this advice is directed.

2. Institutional Policies for Resourcing HRECs

Where an institution decides to rely on fees for access to consideration of research proposals by the institution's HREC, it should develop and publish a comprehensive policy. That policy should address the rate or rates of fees; an explanation of how those rates were determined, eg by reference to the costs involved in the HREC process of consideration of all or different types of research proposals; by whom and in relation to which research proposals the fees are payable; in relation to which research proposals, if any, fees are not payable; the administrative arrangements for the payment of the fees and the use or uses to which the institution devotes the fee income.

3. Ethical Considerations

In reaching a decision to adopt such a policy, an institution or organisation needs to be satisfied that:

- (a) the payment of any fee will not compromise the integrity of the process of ethical review of research proposals and the monitoring of approved research, for example, higher fees should not be charged for expedited review; and
- (b) the imposition and administration of fees for access to HREC consideration will not impair or seem to impair the independence and autonomy of the HREC, for example, the collection, administration and use of the fees should be separate from administration of HREC activities; and
- (c) implementation of a policy of charging fees for access to HREC consideration of research proposals will not have the effect of preventing the consideration of research proposals that would otherwise have been considered in the work of the HREC, for example, by charging high levels of fees for staff or student research.

Where an institution or organisation cannot be satisfied that all of these requirements will be met, the adoption of a policy to charge fees for access to HREC review of research proposals may result in that HREC ceasing to fulfil the requirements of the *National Statement*.

4. Establishing and Resourcing HRECs by Institutions and Organisations

Guideline 2.1 of the *National Statement* on Ethical Conduct in Research Involving Humans requires institutions and organisations in which research involving humans is undertaken to establish, adequately resource and maintain HRECs composed and functioning in accordance with the Statement.

The functions of HRECs set out in the *National Statement* include:

- protecting the welfare and rights of participants (2.5);
- being sufficiently informed about and addressing all relevant aspects of a research proposal (2.7, 2.8);
- preparing agendas, minutes, distributing papers to members, conducting meetings, promptly notifying decisions (2.13);
- recording details of decisions (2.30 – 2.32);
- monitoring all approved research (2.33 – 2.38);
- receiving and responding to complaints (2.39 – 2.43); and
- providing reports to NHMRC and the AHEC (2.46 – 2.48).

Guideline 2.2 of the *National Statement* requires institutions and organisations, when establishing an HREC, to 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, to members. Guideline 2.3 of the *National Statement* provides that institutions or organisations (individually or jointly) must accept legal responsibility for decisions and advice received from the HREC and indemnify its members.

For further information, please contact the Australian Health Ethics Committee Secretariat, NHMRC, MDP 100, GPO Box 9848, Canberra, ACT, 2601.

Phone: (02) 6289 9807 **Fax:** (02) 6289 9898 **Email:** ahec.nhmrc@nhmrc.gov.au

**Australian Health Ethics Committee
INFORMATION FOR HRECs: SEPTEMBER 2001
Stem Cell Research**

The Australian Health Ethics Committee has been approached by human research ethics committees (HRECs) seeking advice on how to review research protocols that involve stem cell research.

The following guidance is interim. Formal guidelines will be developed by AHEC in the context of its review of the 1996 NHMRC Ethical guidelines on assisted reproductive technology.

1. Research on stem cell lines derived from human embryos should be considered in the same way as any other research on human products (eg blood, tissue). All research proposals involving the use of stem cell lines derived from human embryos should be presented to an HREC for consideration.
2. The *Ethical guidelines on assisted reproductive technology* (1996) only permit destructive research on embryos under certain exceptional circumstances (section 6.4). If the stem cell lines have been derived through destructive research on embryos that meets the conditions laid down in these sections, then research on stem cell lines derived from human embryos is not explicitly prohibited.
3. In considering such research the HREC must consider whether the stem cell lines derived from human embryos have been derived in an appropriate manner (*Ethical guidelines on assisted reproductive technology* (1996) sections 6.4 and 11.1).
4. If derived in Australia, the research leading to the development of the stem cell lines must have occurred:
 - under the auspices of an HREC operating in accordance with the requirements of the *National Statement on ethical conduct in research involving humans* (1999) and the *Ethical guidelines on assisted reproductive technology* (1996); and
 - in compliance with prevailing Commonwealth and State or Territory legislation.
5. If the stem cell line derived from human embryos was imported to Australia, the HREC should endeavour to confirm that the cell line was developed in accordance with the:
 - *Ethical guidelines on assisted reproductive technology* (1996) (sections 6 and 11); and
 - *National Statement on ethical conduct in research involving humans* (1999) (paragraph 1.21).

Two necessary considerations are that the embryo from which the stem cell line was derived was excess to an IVF program and that the donors gave informed consent.

6. If there are doubts regarding the origin of a stem cell line, or the requirements of Australian standards can not be satisfied, then the HREC should not permit the research to proceed.

AHEC has commenced a review of the Ethical Guidelines on assisted reproductive technology and related publications. This review will include wide public consultation. Pending the outcome of that review, HRECs are to be guided by this Information Sheet.

Dr Kerry J. Breen
Chairperson
Australian Health Ethics Committee

For further information, please contact the Australian Health Ethics Committee Secretariat, NHMRC, MDP 100, GPO Box 9848, Canberra, ACT, 2601.

Phone: (02) 6289 9807 **Fax:** (02) 6289 9898 **Email:** ahec.nhmrc@nhmrc.gov.au

**Australian Health Ethics Committee
INFORMATION FOR HRECs: December 2005**

World Medical Association revision of the Declaration of Helsinki (2000)

The 2000 revision of the *Declaration of Helsinki* (the *Declaration*) generated controversy about Paragraphs 29 and 30, which pertain to clinical trials. In September 2001, the National Health and Medical Research Council (NHMRC) issued Information Sheet 6 for HRECs to resolve discrepancies between the 2000 revision of the *Declaration* and the *National Statement on Ethical Conduct in Research Involving Humans* (the *National Statement*).

Information Sheet 6B provides an update on this issue and replaces Information Sheet 6 as a source of guidance for HRECs.

The World Medical Association (WMA) responded to concerns expressed by several key bodies by further considering the *Declaration* at meetings between October 2001 and May 2004, and subsequently issued Notes of Clarification on both Paragraphs 29 and 30.

Paragraph 29

Paragraph 29 states:

“The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.”

After the revision, researchers and regulatory agencies, here and overseas, expressed concern that Paragraph 29 was very restrictive in prohibiting the use of a placebo *whenever* there exists current treatment. Paragraph 12.4 of the *National Statement* states that a placebo can sometimes be justified even where there exists current treatment.

In October 2002, the WMA General Assembly issued the following Note of Clarification on Paragraph 29 for inclusion in the *Declaration*:

“The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
 - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive a placebo will not be subject to any additional risk of serious or irreversible harm.
- All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.”

AHEC considers that the WMA’s Note of Clarification on Paragraph 29 removes the inconsistency between the *National Statement* and the *Declaration* and now aligns closely with Paragraph 12.4 of the *National Statement*.

Paragraph 30

Paragraph 30 states:

“At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.”

Researchers, regulatory agencies and pharmaceutical manufacturers expressed concern that Paragraph 30 made unrealistic assumptions about factors such as the availability of treatment and infrastructure in third world countries and may also constitute irresistible inducement in such countries.

On 17 May 2004, the WMA issued a Note of Clarification on Paragraph 30 stating that:

“The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.”

Noting that the *National Statement* itself does not contain post-trial treatment provisions, AHEC considers that the WMA’s Note of Clarification on Paragraph 30 is consistent with advice referred to in NHMRC’s *Human Research Ethics Handbook*. The *Handbook* advises (at E12, Protocol and Study Design), that HRECs should consider the mechanisms proposed for access to continued treatment where long term therapy would be appropriate following the completion of the trial.

AHEC advises that HRECs should continue to regard the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* as the definitive guideline for the ethical review and conduct of research in Australia.

For further information, please contact the Australian Health Ethics Committee Secretariat, NHMRC, MDP 24, GPO Box 9848, Canberra, ACT, 2601.
Phone: (02) 6289 9575 Fax: (02) 6289 9580 Email: ahec.nhmrc@nhmrc.gov.au

Australian Health Ethics Committee

INFORMATION FOR HRECs: FEBRUARY 2003
Oligonucleotides as gene therapy products

The role of the Gene Therapy Research Advisory Panel (GTRAP), established under the NHMRC's Research Committee, includes assisting HRECs to assess research proposals involving human somatic cell gene therapy and related issues, including xenotransplantation. Information on GTRAP's functions and membership can be found in Information Sheet 2.

It has recently been brought to the attention of GTRAP that a number of studies pertaining to the therapeutic use of oligonucleotides have been approved by HRECs without consulting GTRAP.

Oligonucleotides are short molecules of DNA (or, sometimes RNA) that are usually less than 100 bases in length. They can be used for a variety of techniques in molecular biology (for example, the Polymerase Chain Reaction – PCR), and they can also have therapeutic uses in medicine. As an example, oligonucleotides are currently being used in an international trial to target cancer cells by blocking gene activity. These studies are unlikely to be problematic since they involve short acting oligonucleotides, which are **not** gene therapy products according to the United States' Food and Drug Administration (FDA). However, the FDA **does** consider another class of oligonucleotides that are used to alter the DNA sequence to be gene therapy products. Oligonucleotides with an extended half life would also need to be reviewed more carefully.

Because of this potential confusion, GTRAP would prefer to sight each proposal for the therapeutic use of oligonucleotides which HRECs receive, to confirm that there is no safety concern.

To expedite the review of protocols which utilise oligonucleotides to block gene transcription, GTRAP will soon place on its web site, (<http://www.health.gov.au/nhmrc/research/gtrap.htm>), an abbreviated proforma which allows HRECs or investigators to provide sufficient information to GTRAP to enable a rapid risk assessment. In the case of oligonucleotides that have a very short half life, GTRAP will exempt these proposals from a full GTRAP submission, as detailed in the "Guidelines for the Writing of Human Gene Therapy Proposals".

The exemption by GTRAP will apply to all centres involved in multi-centred studies which use the identical product and protocol.

For further information, please contact the Australian Health Ethics Committee Secretariat, NHMRC, MDP 100, GPO Box 9848, Canberra, ACT, 2601.

Phone: (02) 6289 9807 **Fax:** (02) 6289 9898 **Email:** ahec.nhmrc@nhmrc.gov.au



Australian Government

National Health and
Medical Research Council

INFORMATION SHEET 8

INFORMATION FOR HRECs: NOVEMBER 2003

***Research Involving Human Embryos Act 2002:* Advice¹ from the Australian Health Ethics Committee and the Licensing Committee of the NHMRC on the legislative requirements for obtaining proper consent for research on excess ART embryos**

The *Research Involving Human Embryos Act 2002* (RIHE Act) requires each licence to be subject to the condition that, before an excess ART embryo is used as authorised by the licence, each responsible person in relation to the excess ART embryo must have given proper consent to that use (Section 24). This interim document is intended to make licence applicants and HREC members aware of what constitutes proper consent in regard to this legislation².

This advice is given to guide HRECs only in relation to consent to uses of embryos that have been declared, by the persons responsible, to be excess to their needs. The advice is not given for use in relation to consent to any other decisions about embryos or research in assisted reproductive technology.

Preamble

The RIHE Act (Section 8) defines proper consent, in relation to the use of an excess ART embryo, as consent obtained in accordance with the NHMRC *Ethical Guidelines on Assisted Reproductive Technology 1996* (herein the Guidelines). The RIHE Act (Section 21) also determines that the NHMRC Licensing Committee must not issue a licence unless satisfied that the activity or project proposed in the application has been assessed and approved by a HREC that is constituted in accordance with, and acting in compliance with the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* (1999) (herein the *National Statement*).

It is essential that applicants and HRECs have a thorough knowledge of these documents. It should be noted that provisions of the RIHE Act and any regulations made under it, take precedence over any guidelines issued by the NHMRC and its committees.

The decision to make their excess ART embryos available for research is a difficult one for many people. There are differences of opinion in our community regarding the moral status of the human embryo. It is important that licence applicants are sensitive in their approach to obtaining consent. It should also be noted that the relationship between people and embryos for which they are responsible can change over time.

The procedures outlined in this document must not be initiated until all persons responsible have agreed in writing that the embryos are excess. Consent for the specified research project must not be sought until embryos are declared to be excess.

¹This advice is based on the current NHMRC *Ethical guidelines on assisted reproductive technology 1996* and legislation as at September 2003.

²HRECs should follow this advice pending the completion of the revised reproductive technology guidelines.

Licence applicants report in writing that an HREC has assessed and approved the activity or project to which the licence relates so as to show compliance with the conditions specified in Section 24 of the RIHE Act. It is the responsibility of the HREC to ensure that the activity or project has been designed so that proper consent will have been obtained before an excess ART embryo is used. A HREC must also ensure that no member of the committee adjudicates on research in which that member has any conflict of interest (see *National Statement 2.20*).

In reviewing and approving the proposed process for obtaining proper consent, the following points should be taken into consideration.

Principles of ethical conduct

The *National Statement* clearly defines its primary purpose as the protection of the welfare and rights of participants in research. The values and principles that researchers are required to demonstrate and follow towards participants include integrity, respect for persons, beneficence and justice (see *National Statement 1.1-1.21*). The definition of participants in the National Statement includes those upon whom the research impacts. This translates into the need to obtain consent from persons responsible for the embryos, before any research activity is undertaken.

Proper consent means consent that is:

- informed;
- given by a person competent to do so;
- voluntary; and
- specific.

1. Informed

- 1.1 Persons responsible for the embryos should be provided with information, at their level of comprehension, about the purpose, methods and possible outcomes of research, including the likelihood and form of publication of research results (*National Statement 1.7*). This should be done as an oral explanation, supported by written information in plain language which is provided in sufficient time for it to be taken away, read and considered, prior to the giving of consent. This explanation should be given with sensitivity to the individual needs of the patient (*Guidelines 3.1.2*).
- 1.2 Where persons responsible are not fluent in English, it is recommended that an independent interpreter be used to convey information and answer questions. Written information must be translated into the language of the responsible persons (*National Statement 2.26; Guidelines 3.1.2*). Similarly, where persons responsible have other communication needs, appropriate facilities should be provided.
- 1.3 Informed decision-making is required for all persons responsible, including the spouses or partners of donors of gametes and embryos at the time of donation. (*Guidelines 3.2.5, 6.4*). Licence applicants should be aware that in some cases, more than two adults will need to give consent for the use of any given embryo. These parties should be contacted at the time at which the future of the embryos is being decided and given the relevant information as outlined in this document.
- 1.4 The researcher is required to disclose to the HREC any financial interest in the research and the HREC must consider the extent to which disclosure of relevant financial aspects of research should be made to the persons responsible (*National Statement 2.21*). As persons responsible must be given all information which may be of significance (*Guidelines 3.1*), HRECs would normally decide to disclose all financial aspects to participants. For example, where researchers plan to request altruistic donation of embryos with the intention of gaining commercial profit, this must be made clear to the donors before consent is obtained.

- 1.5 Persons responsible should be provided with the name or position and contact details of the person nominated by the relevant HREC to receive complaints along with procedures for raising concerns or obtaining additional information on the research (*National Statement 2.42*).
- 1.6 Persons responsible must be informed that records may be viewed by NHMRC inspectors to meet the requirements of the RIHE Act.

2. Competence to make a choice

- 2.1 Persons responsible from whom consent is obtained must be competent to make a choice. Where a person responsible does not have the capacity to make a choice, the choice may be made by a person with lawful authority to decide for that participant. (*National Statement 1.7*).
- 2.2 Persons responsible are free to refuse to give consent to the use of an embryo without giving any explanation or justification for the refusal (*National Statement 1.8*).
- 2.3 Subject to prevailing state/territory legislation, where disputes arise between responsible persons about the use of an embryo, the embryo should be kept and not allowed to succumb until the dispute has been resolved and a decision taken about the embryo (*Guidelines 3.2.8*).
- 2.4 Should a person with responsibility to make decisions about an embryo die, the surviving person(s) responsible should make the relevant decisions about the use of the embryo, taking into consideration any advance directive from the deceased and subject to prevailing state/territory legislation.
- 2.5 Subject to prevailing state/territory legislation, should all responsible persons die, any advance directive from the deceased responsible persons should be considered. If there is no advance directive, or if an advance directive exists but has not been endorsed, or the advance directive cannot be complied with, the embryo should be allowed to succumb. (*Guidelines 3.2.9*).

3. Voluntary

- 3.1 Consent of persons responsible must be voluntary and not subject to any coercion, inducement or influence, such as financial or other rewards, that could impair its voluntary character. (*National Statement 1.10*)
- 3.2 In particular it is important that researchers be aware of the possibility of even unwitting coercion, for example where a doctor-patient relationship exists and the doctor is also the researcher (*National Statement 7.1*). For this reason, it is recommended that the person who approaches the persons responsible for the embryos to be used, be independent of their clinical care.
- 3.3 Any concealment of the purposes of a study from the persons responsible is not considered ethical and prevents informed and voluntary consent (*National Statement 17.1*).

4. Specific

- 4.1 Persons responsible should be provided with information about the intended use of the embryo. The consent form must specify the purpose for which that embryo or embryos may be used (*Guidelines 3.2.5*). Consent must be given for a specific purpose, for example, for destructive research (detail type of research and the rationale for the research). In the case of destructive embryo research, it must be made clear to the persons responsible for the embryo that the fate of individual embryos may not be able to be reported. The specific scope of the research and the consent sought must be made clear. For example, if stem cells were to be harvested from a given embryo, the persons responsible would be consulted about that use of the embryo, but, for the purpose of giving the proper consent required under the RIHE Act, would not need to be consulted about the subsequent use of those stem cells.

5. Withdrawal of consent

- 5.1 A person responsible must be free at any time to withdraw consent to further involvement in the research (*National Statement* 1.12). In the case of destructive embryo research, persons responsible for the embryo need to be aware that withdrawal is not possible after the embryo has been destroyed. In view of this, it is recommended that the consent of persons responsible to a use which will damage or destroy an embryo must not be acted upon until a suitable fixed period of time for re-consideration has been allowed, normally at least two weeks after their consent to such research. This 'cooling-off' period before consent becomes effective must be explained to the persons responsible when consent is obtained.

6. Consent forms

- 6.1 Consent should be given in writing (*Guidelines* 3.2.2).
- 6.2 The entire consent process, including forms and protocols, should be reviewed and approved by an HREC.
- 6.3 For clarity, terminology on the consent form should match definitions in the RIHE Act.
- 6.4 All of the documentation to be used in obtaining consent should be included in the application to the HREC (*National Statement* 2.24) as well as in the application for a licence to the NHMRC Licensing Committee.

For further information, please contact:

Australian Health Ethics Committee Secretariat
NHMRC
MDP 100
GPO Box 9848
Canberra ACT 2601

Phone: (02) 689 9575

Fax: (02) 6289 9580

Email: ahec.nhmrc@nhmrc.gov.au