**LRC790**

Australian Government

National Health and Medical Research Council

# National Health and Medical Research Council

# Submission to the Legislation Review Committee

# September 2005

The Honourable Mr John Lockhart AO QC
Chair of the Legislation Review Committee
c/- Secretariat Australia Pty Ltd
PO Box 4226
Manuka ACT 2603

Dear Justice Lockhart

Thank you for the opportunity to present the National Health and Medical Research Council (NHMRC) submission the Reviews of the *Research Involving Human Embryos Act 2002* and the *Prohibition of Human Cloning Act 2002*.

The NHMRC discussed the Reviews at its most recent meeting on 8 and 9 September 2005. These discussions were informed by advice from three of its Principal Committees, the Research Committee, the Australian Health Ethics Committee, and the Licensing Committee.
I understand that your committee also met informally with the Licensing Committee on 1 September 2005.

The attached submission represents the views of the Council of the NHMRC, and also contains as appendices, further advice from Research Committee, the Australian Health Ethics Committee, and the Licensing Committee.

The NHMRC is aware that the LRC is holding hearings and fora in State and Territory capitals throughout Australia. Some of the people invited to participate in these consultations are also members of the NHMRC and its committees. The Council advises that these persons are not representing the NHMC, at these events.

Yours sincerely

Professor John Shine
Chair of Council
National Health and Medical Research Council

22 September 2005

# CONTENTS

## EXECUTIVE SUMMARY

The National Health and Medical Research Council (NHMRC) is Australia's peak body for the support of medical research, the maintenance of ethical standards for research involving humans and the development of authoritative health advice and guidelines. It is also responsible for administering national legislation for the regulation of research involving human embryos and the prohibition of human cloning.

The NHMRC consolidates within a single national organisation the often independent functions of research funding and development of advice. One of its strengths is that it brings together and draws upon the resources of all components of the health system, including governments, medical practitioners, nurses and allied health professionals, researchers, teaching and research institutions, public and private program managers, service administrators, community health organisations, social health researchers and consumers. The functions of the NHMRC come from the statutory obligations conferred by the *National Health and Medical Research Council Act 1992*.

The NHMRC through its Licensing Committee is responsible for establishing and maintaining the regulatory system required under the *Research Involving Human Embryos Act 2002* and the *Prohibition of Human Cloning Act 2002*.

This submission provides the NHMRC's response to the Terms of Reference for the Legislation Review Committee and the Issues paper released by that Committee. The submission contains the views of the NHMRC Council supported by input from its Principal Committees provided in four appendices. Comment has been provided about the scope of the legislation where applicable and with respect to all the terms of reference where it is appropriate for the NHMRC to express a view.

The NHMRC has received the views of three of its Principal Committees and in doing so, the Council:

- Encourages ongoing community debate on the cloning of human embryos for research purposes.
- Recommends further study into the costs and benefits of establishing a stem cell bank in Australia. An alternative strategy could involve establishing agreements and procedures for access to existing resources overseas.
- Notes that both stem cell research and human embryo research have potential to underpin medical advances that will greatly improve the health and quality of life of Australians and recommends that researchers continue to have access to excess ART embryos to continue research in these areas.
- Recommends a number of suggestions that should be taken into account if Government decides to amend the legislation.

## ABBREVIATIONS

| | |
|---|---|
| AHEC | Australian Health Ethics Committee (a Principal Committee of NHMRC) |
| ALRC | Australian Law Reform Commission |
| ART | Assisted Reproductive Technology |
| ART guidelines 1996 | *Ethical guidelines on Assisted Reproductive Technology (1996)* |
| ART guidelines 2004 | *Ethical guidelines on the use of Assisted Reproductive Technology in Clinical Practice and Research (2004)* |
| COAG | Council of Australian Governments |
| CREGART | Committee to Review the Ethical Guidelines on Assisted Reproductive Technology |
| GTRAP | Gene and related Therapies Research Advisory Panel |
| HAC | Health Advisory Committee (a Principal Committee of NHMRC) |
| HREC | Human Research Ethics Committee (of an institution) |
| IVF | In-vitro fertilisation |
| LC | Licensing Committee (a Principal Committee of NHMRC) |
| LRC | Legislation Review Committee |
| National Statement | *National Statement on Ethical Conduct in Research Involving Humans (1999)* |
| NHMRC | National Health and Medical Research Council |
| NHMRC Act | *National Health and Medical Research Council Act 1992* |
| PGD | Preimplantation Genetic Diagnosis |
| PHCA | *Prohibition of Human Cloning Act 2002* |
| RC | Research Committee (a Principal Committee of NHMRC) |
| RIHEA | *Research Involving Human Embryos Act 2002* |
| RTAC | Reproductive Technology Accreditation Committee |
| SCNT | Somatic Cell Nuclear Transfer |
| TGA | Therapeutic Goods Administration |

**NHMRC SUBMISSION TO THE LEGISLATION REVIEW – PROHIBITION OF HUMAN CLONING ACT 2002 AND RESEARCH INVOLVING HUMAN EMBRYOS ACT 2002**

## Background

The National Health and Medical Research Council (NHMRC) is Australia's peak body for the support of medical research, the maintenance of ethical standards for research involving humans and the development of authoritative health advice and guidelines. It is also responsible for administering national legislation for the regulation of research involving human embryos and the prohibition of human cloning.

The NHMRC consolidates within a single national organisation the often independent functions of research funding and development of advice. One of its strengths is that it brings together and draws upon the resources of all components of the health system, including governments, medical practitioners, nurses and allied health professionals, researchers, teaching and research institutions, public and private program managers, service administrators, community health organisations, social health researchers and consumers. The functions of the NHMRC come from the statutory obligations conferred by the *National Health and Medical Research Council Act 1992*.

In developing this submission, the NHMRC's considerations have been informed by the differing perspectives of its Principal Committees. The four Principal Committees of the NHMRC are the Research Committee (RC), the Australian Health Ethics Committee (AHEC), the Health Advisory Committee (HAC) and the Licensing Committee (LC).

On 5 April 2002, the Council of Australian Governments (COAG) agreed to introduce nationally consistent legislation to ban human cloning and other unacceptable practices and regulate research involving human embryos that had been created for ART treatment but were no longer required for treatment ("*excess ART embryos*"). COAG also decided that the NHMRC would be responsible for administering the new national regulatory framework.

The legislation currently under review was developed in consultation with State and Territory governments and a range of experts in all States and Territories. The Commonwealth *Research Involving Human Embryos Act 2002* (RIHEA) and *Prohibition of Human Cloning Act 2002* (PHCA) received Royal Assent on 19 December 2002. Subsequently, in accordance with the terms of the COAG agreement, all States and Territories (with the exception of the Northern Territory) have introduced corresponding legislation.

The RIHEA establishes the Embryo Research Licensing Committee as a new Principal Committee of the NHMRC (the NHMRC Licensing Committee). This Committee has responsibility for implementing and administering the provisions of the RIHEA and PHCA. Information about the functions and achievements of LC is provided in Appendix 3.

The RC is responsible for advising and making recommendations to the NHMRC Council (the Council) on the use and monitoring of funds distributed as research grants and advising the Council on matters relating to medical research and public health research, including the quality and scope of such research in Australia. RC awards grants on the basis of scientific quality as judged by peer-review across the entire spectrum of health, medical and public health research. It also provides research support through a variety of mechanisms, including support for individual research projects, broad programs of research, training awards and fellowships and special research units. RC input to this submission is provided in Appendix 1.

AHEC is responsible for advising the Council on ethical issues relating to health, developing and

giving the Council guidelines for the conduct of medical research involving humans and performing other functions as the Minister determines. AHEC promotes community debate on health ethics issues, monitors the work of Human Research Ethics Committees (HRECs), and monitors and advises on international developments in health ethics.

AHEC has had a long involvement with issues related to the RIHEA and PHCA. These include the development of the *Ethical guidelines on Assisted Reproductive Technology (1996)* (ART guidelines 1996) and its successor, the *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research (2004)* (ART guidelines 2004), the 1998 report to the Minister for Health on human cloning, and the *National statement on ethical conduct in research involving humans (1999)* (National Statement). More information is provided in Appendix 2.

HAC is the Council's overarching committee for its advisory program. It manages and coordinates the development of advice and guidelines on all health issues. HAC has not contributed directly to this submission.

The NHMRC supports a number of expert committees and advisory groups which provide specialist advice on a variety of important areas. One of these, the Gene and related Therapies Research Advisory Panel (GTRAP) provides advice on scientific, medical and technical issues related to gene and related therapies, xenotransplantation and human stem cell research. GTRAP is a subcommittee of RC, and its advice is included in Appendix 1.

## The Legislation Review

The Terms of Reference require the Legislation Review Committee (LRC) to consider the scope and operation of the RIHEA and PHCA and a number of additional issues. This submission addresses the terms of reference which have particular relevance to the various functions of the NHMRC.

Following the passage of the human cloning and embryo research legislation in December 2002, the NHMRC has implemented the strong regulatory framework expected by governments and the community, including the licensing of research involving excess assisted reproductive technology (ART) embryos and appropriate monitoring and compliance arrangements.

The NHMRC has benefited from having LC as a Principal Committee. The LC operates in accordance with the NHMRC Act, while discharging its duties under the RIHEA. In making its decisions, it utilises the advice and guidelines from AHEC, including the National Statement and the ART guidelines 2004. Information on funding of research projects is also useful in facilitating regulation of the research, while advice on the legislative arrangements is useful in informing the assessment of research applications.

In the three years since the RIHEA and PHCA were passed, the NHMRC (through the LC) has:

- established the regulatory framework governing research involving excess ART embryos and for ensuring that human cloning and other "*unacceptable*" activities do not occur in Australia;
- developed a number of guidance documents, policies and procedures in this new regulatory area (see Appendix 3 for more detail);
- established a strong and workable system for monitoring compliance with the Acts, which includes ensuring that, as far as its powers permit, human cloning and other "unacceptable" activities do not occur in Australia;
- developed and implemented an information exchange program to facilitate knowledge and

understanding of the legislation;

- collaborated with AHEC in finalising the ART guidelines 2004 with respect to protocols for obtaining proper consent;
- issued nine licences and administered the operation of these licences; and
- considered a number of requests for variations to licences already issued.

## The *Prohibition of Human Cloning Act 2002*

The scope of the PHCA was decided by COAG in April 2002 following wide consultation. It was passed by the Federal Parliament in December 2002, following extensive parliamentary debate and a Senate inquiry.

Since December 2002, there have been a number of significant developments in science and technology, including the cloning of human embryos using nuclear transfer technologies, progress towards developing embryonic stem cells of suitable quality to use in clinical treatments, and the identification of adult stem cells in an increasing number of tissues.

A key prohibition in the PHCA is the ban on the cloning of human embryos for any purpose. The cloning of human embryos for research purposes, also called "*somatic cell nuclear transfer*" (SCNT)[1], is legal in the UK (subject to strict regulation) and not regulated by government in a number of other countries including Korea and the United States. The NHMRC notes that there is still a wide diversity of opinion on this matter within the research and wider community, and this is reflected across the membership of Council and its Principal Committees.

For example:
RC (Appendix 1, page 20) states:

> *RC suggests that it is appropriate to open a full and wide-ranging debate amongst the relevant stakeholders in Australia to determine whether our legislation should be also changed.*

AHEC (Appendix 2, page 36) states:

> *In publishing the list at pages 10-11 in the ART guidelines 2004, both CREGART and AHEC intended to make clear that, regardless of other outcomes of the legislation review, all the practices listed were regarded as unethical*[2].

The list of prohibited practices in the PHCA was included in its entirety in Chapter 4 of the ART guidelines 2004, as endorsed by the Council. Thus the ART guidelines 2004 represent the Council's endorsed position on prohibited practices. However, Council considers that that there should be regular community and parliamentary debate on these matters.

## The *Research Involving Human Embryos Act 2002*

The RIHEA establishes a strong regulatory framework that permits research to be undertaken utilising excess ART embryos. It should be noted that prior to the RIHEA and corresponding State and Territory legislation there was no regulation of such research in the majority of States and Territories.

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[1] Cloning for research purposes or *somatic cell nuclear transfer* is sometimes referred to as "therapeutic cloning". The NHMRC does not use this terminology.
[2] The list referred to in this statement is the list of prohibited practices in Chapter 4 of the ART guidelines, which is the same as in the PHCA. CREGART was the Committee to Review the Ethical Guidelines on ART.

The NHMRC considers that the current RIHEA strikes an appropriate balance between enabling vital health and medical research to occur, while providing strict controls over the operation of such research.

Since it was established, the LC has spent considerable time interpreting the legislation and establishing appropriate procedures and advice. While the NHMRC has received feedback that the time taken for LC to issue licences has been slower than expected, this has been necessary given the need for transparent and appropriate decision making in this sensitive and new regulatory field. As stated by LC (Appendix 3, page 40):

> *The LC issued the first licences 12 months after the Committee was appointed, that is 18 months after the legislation was passed. However, during that time, the LC has been required to concurrently receive applications for licences, develop policy and procedures to underpin the legislation, develop its relationship within the NHMRC structures and engage a community with a heightened expectation of what the implications of regulating embryo research would be.*

The LC has issued nine licences since the legislation was passed (Appendix 3). Four licences permit the use of embryos to derive embryonic stem cell lines, four licences are for improvements in various aspects of ART and one licence is for training embryologists in the techniques of embryo biopsy.

## Definitions

### Definition of "human embryo"

The key definitions in the PHCA and the RIHEA were developed to provide legal clarity in prosecution of the offence provisions, given the high penalties involved. The definition of human embryo was prepared in consultation with governments and experts in all states and territories and was drafted so as to be independent of technological developments. LC (Appendix 3, page 41) states:

> *The LC has not experienced any difficulties with the legal definition of "human embryo" and notes that from a legal perspective it works well. However, LC developed guidance at an early stage to clarify "live", since this is a key element in determining whether embryos are covered by the provisions of the RIHEA and in carrying out the exempt activity of allowing excess ART embryos to succumb (s.10(2)(c)). The LC notes that the definition of "human embryo" is broad in the scientific sense and includes most entities which researchers may wish to study.*

The concerns of a number of members of AHEC regarding the definition of human embryo in the PHCA and the RIHEA were raised with the Council at its 154th session in September 2004. Council asked the LC to provide it with further advice on this matter. This advice is currently being finalised by a working party of the LC.

AHEC states (Appendix 2, page 28):

> *This definition contains, in its opening words, a degree of circularity that has ethical implications for the effectiveness of the Act and the potential developments in ART. To define a human embryo as "a live embryo that…" leaves the central concept of embryo undefined. If in the development of ART processes, innovative methods are devised to generate entities that resemble or can develop into human beings, but which can be argued*

*are not "embryos", then the legislation can be argued not to regulate their use.*

As the agency responsible for administering the legislation, the NHMRC considers that the definitions in the Acts provide legal clarity. However, the NHMRC also considers that the issue raised by AHEC requires further debate. It is also noted that with the increasingly rapid rate of scientific and technological developments in this area, the biological definitions and ethical frameworks will continue to evolve.

If governments and the community want to continue to prohibit and regulate activities in this field, then it will be important to ensure that definitions have the flexibility to accommodate technological developments, with a process of regular review in the light of such developments.

**Definition of "excess ART embryo"**

The RIHEA is concerned primarily with regulating the use of excess ART embryos. The definition of excess ART embryo in the RIHEA is based on the determination by the couple for whom the embryo was created that the embryo is excess to their needs.

When the legislation was passed, it contained the restriction that research that may damage or destroy excess ART embryos could only be undertaken on embryos that were in existence on 5 April 2002. Following operation of the sunset clause in the RIHEA on 5 April 2005, this restriction no longer applies. The legislation now applies to all excess ART embryos equally, irrespective of when they were created. The LC (Appendix 3, page 47) states:

> *With the sunset of the 5 April 2002 provisions, the LC has been considering how and under what circumstances embryos that have not been cryostored could be used for activities licensed under the RIHEA.*

While no applications have been received for the use of embryos declared to be excess following preimplantation genetic diagnosis (PGD), the LC has received a number of inquiries. Because such research raises a number of ethical issues with respect to obtaining proper consent and providing for acceptable cooling-off periods, LC and AHEC are considering the matter in more detail. It is essential that any issues affecting the consent process are considered carefully. The submission from AHEC explores the ethical considerations surrounding the consent process in more detail (see Appendix 2, page 28).

## Regulation of Assisted Reproductive Technology

Since 2002, AHEC has developed and the NHRMC endorsed the "*Ethical Guidelines on the use of ART in Clinical Practice and Research (2004)*". The NHMRC notes that these guidelines are now adopted nationally through the Reproductive Technology Accreditation Committee (RTAC) of the Fertility Society of Australia.

Australian Governments decided in April 2002 that RTAC accreditation would be the benchmark for consistent regulation of ART in Australia. This decision was implemented through section 11 of the RIHEA which makes it an offence to use an embryo which is not an excess ART embryo for any purpose other than a purpose related to the ART treatment of a woman in an RTAC-accredited ART centre. LC (Appendix 3, page 49) states:

> *The LC regulates the use of excess ART embryos which is a small aspect of the total activity relating to ART in Australia. It has no regulatory role in the clinical practice of ART and relies on the integrity of doctor/patient relationships and the voluntary regulatory system administered by the Reproductive Technology Accreditation Committee of Fertility Society*

*of Australia.*

AHEC (Appendix 2, page 27) states that:

> *The RIHEA requires ART centres to be accredited by RTAC in order to be eligible for a licence. The implication is that RTAC is an appropriate, and appropriately informed and effective accrediting agency. A review of RTAC's guidelines, accessible at http://www.fsa.au.com/rtac/ shows them to be comprehensive as to technical and operational aspects of the practice of ART.*

However, AHEC has raised concerns (Appendix 2, pages 27 and 33) in relation to the adequacy of ethical oversight of ART clinical practice, as outlined in the RTAC guidelines:

> *However, there is no specific reference in those guidelines to the NHMRC ART guidelines that are designed to guide ethical practice and research. There is only a generic reference to NHMRC guidelines and to ethics committees (without clearly distinguishing research ethics committee functions from those of clinical ethics committees). It appears that even if RTAC fulfils all the reasonable expectations of an effective accrediting agency, its guidelines give insufficient prominence to ensuring that the ethical obligations of ART practitioners and researchers are fulfilled. Further, as noted above, AHEC is aware that there is uncertainty as to the role that RTAC plays in the monitoring compliance of ART centres with the ART guidelines.*

Appendix 2, page 33:

> *AHEC is aware that doubts have emerged as to the manner in which such accreditation involves monitoring the compliance by those units with the ART guidelines 2004. This has been, to AHEC's awareness, a matter of some concern to sectors of the community and it appears that, as a matter of public accountability, more clarity is needed.*
>
> *Although the matter does not directly arise under the Act, it does affect the status and reputation of the ART units whose practices are likely to be the subject of licences under the Act.*

If governments consider changing the current regulatory arrangements, then one possible option is a national regulatory framework such as that implemented in the UK http://www.hfea.gov.uk/Home. However it should be noted that ART is regulated by state legislation in some states and any alterations to the regulatory system would be complex.

## Export of human embryos

The NHMRC notes the current arrangements in place through the Attorney General's Department and the Minister for Justice and Customs. Regulation 7 of the Customs (Prohibited Exports) Regulations 1958 allows the Minister for Justice and Customs to permit the export of human embryos from Australia for the purpose of continuing *in vitro* fertilisation (IVF) treatment. An application for permission to export human embryos may only be made by the prospective mother or, in the event that the prospective mother is dead, the spouse of the prospective mother at the time that the embryo was created or donated.

The Attorney General's Department administers the permit arrangements and receives approximately 20 applications per year.

During 2003, the NHMRC Secretariat supported the work of an interdepartmental committee that reported to Government on the arrangements for the regulation of the export of human ART embryos. Government adopted the recommendation that the requirement for and effectiveness of

the arrangements be further reviewed in July 2006, following consideration of the reports of the LRC.

If, following consideration of the reports of the LRC, Australian Governments decide to amend the legislative arrangements that regulate the creation and use of human ART embryos in Australia, then there may also be a need to make consequent changes to the arrangements for regulating the export of human ART embryos from Australia.

The LRC may wish to consider the implications of the following options:

- The removal of Regulation 7 of the Customs (Prohibited Exports) Regulations 1958 and reverting to the previous arrangements whereby no restrictions were in place;
- The removal of Regulation 7(16) (the sunset clause) of the Customs (Prohibited Exports) Regulations 1958 so that the current arrangements would continue indefinitely; or
- The removal of Regulation 7 of the Customs (Prohibited Exports) Regulations 1958 and replacing that restriction with an absolute prohibition on the export of human embryos except under certain circumstances in other relevant legislation. (For example, a similar regulatory provision could be included in the PHCA).

## Import of Viable Material from human embryo clones

While the PHCA bans the creation, import and export of human embryo clones, the legislation does not regulate the import of material derived from human embryo clones (or from any embryos). At the time the legislation was developed it was considered unacceptable that Australian scientists should be able to freely import embryonic stem cell lines derived from an embryo that was created via a process that would be banned in Australia (such as SCNT).

An absolute prohibition on the importation of viable material derived from human embryo clones is given effect by Regulation 3 as goods specified in Schedule 1 (Item 27) of the Customs (Prohibited Imports) Regulations 1956. This prohibition is administered by the Australian Customs Service.

While the creation and use of human embryo clones for research is only a recent development, it is likely to increase in the future, as demonstrated by rapid scientific advancements and different regulatory environments in countries such as the United Kingdom and South Korea.

The LRC may wish to consider the implications of potential future benefits, if any, from the use of embryonic stem cells derived from cloned human embryos in research, and the value of retaining the prohibition on the import of viable products derived from human embryo clones.

## Import and export of stem cells

There are currently no controls in place to regulate the import and export of stem cells, beyond what is in place through quarantine legislation applying to all human and animal cell lines.

If Australian Governments decide to change the scope of the legislation to increase the regulation of stem cell research, then the Government may also need to consider the need to regulate import and export.

Australia is not the only country supporting stem cell research and it is important that any changes to the Customs Regulations do not hinder Australia's participation in the international research effort.

## Regulation of Stem Cells

The NHMRC supports the need for wide debate on stem cell research in Australia. In April 2002, COAG agreed that research on existing stem cell lines should continue subject to compliance with NHMRC/AHEC requirements.

The NHMRC's current requirements for stem cell research are outlined in *Information on Stem Cell Research* (http://www.nhmrc.gov.au/ethics/human/issues/stemcell.htm), which was prepared by AHEC in collaboration with LC and GTRAP. This is provided at Appendix 4.

AHEC has commented that:

> *The research use of embryonic stem cells raises both nationally and internationally issues of intense interest to scientists and the public…*
>
> *That level of interest and divided opinion offers, in AHEC's view, justification for considering whether the statutory regulation of the uses of excess ART embryos should be extended to regulate the uses of stem cells derived from them.*
>
> *Regulation need not be obstructive or constrain research. It may be adequate for a national committee to review proposals for the use of embryonic stem cells and to seek appropriate advice on, or review of, the relevant ethical considerations. The membership of the present LC could, for instance, be extended to include relevant expertise in stem cell research and the centralised ethics review committee, suggested above to review licence applications under the present regime, could provide the ethical advice or review"* (Appendix 2, page 37).

If additional regulation were to be considered, the NHMRC recommends that the LRC carefully consider the impact that any additional regulation would have on Australian research. The rationale and scope would need to be developed carefully and significant consultation would need to be undertaken to determine the impact on all stakeholders. This includes the Commonwealth, State and Territory governments, researchers and research organisations, private companies involved in research or developing therapeutic goods and any flow-on effects to the Australian public as the result of limiting research in Australia and limiting access to potential therapeutic goods in the future.

Issues (including ethical considerations) relevant to research involving embryonic stem cell lines, as opposed to the derivation of such cells which is closely regulated through the RIHEA, are comparable to the use of all human cell lines in research.

If there are concerns unique to the use of embryonic stem cells in research, these would need to be clearly articulated and consideration given as to:

- how these concerns could be addressed;
- exactly which uses of the stem cells should be regulated (i.e. basic research or clinical research);
- how such regulation would interact with existing regulatory oversight (for example through the Therapeutic Goods Administration (TGA)); and
- the costs of an expanded regulatory framework and its impact on research;

## Stem Cell Bank

The NHMRC considers that it would be desirable for researchers to have access to a stem cell bank and that such a bank should be adequately resourced and properly run, have the capacity to evaluate all cell lines deposited with it and allow researchers ready access to the deposited cell lines. As

stated by RC (Appendix 1, page 20):

> *RC strongly supports the development of a national stem cell bank. Such a facility will allow researchers to access and share resources and so will promote individual research progress as well as exchange of information and collaborative projects. The bank will need adequate infrastructural support to ensure good documentation and processes. All stem cell lines produced in the course of publicly-funded research in Australia should be required to be submitted to the bank. Consideration should also be made to enforcing lodgement of stem cell lines made by commercial companies, particularly since in this case as in publicly-funded research, the stem cells will have been derived from donated embryos. Any stem cell bank established in Australia should be required to operate in accordance with the National Statement.*

Whether or not such a stem cell bank needs to be established in Australia requires significant investigation of the costs and benefits. One benefit would be that access to embryonic stem cell lines through a stem cell bank may reduce the use of excess ART embryos for the derivation of new stem cell lines. Another approach would be to establish arrangements to ensure access by Australian scientists to cell banks in other countries.

The UK Stem Cell bank has been established with a remit to work with and for the scientific and clinical community to assure the quality of human cell lines used in research and therapy. It is backed by the expertise of the National Institute of Biological Standards and Control (NIBSC) which has an established reputation in relation to quality assurance and research related to biological medicines (http://ukstemcellbank.org.uk). Two Australian-derived cell lines have already been accepted for deposit in the UK Stem Cell Bank.

In the United States, the National Institutes of Health (NIH) is expected to announce the successful contractor to establish a National Stem Cell Bank in mid-September (http://grants2.nih.gov/grants/guide/notice-files/NOT-RR-05-002.html).

## Ethical Review of Research

AHEC have raised general concerns about the capacity of HRECs to approve and monitor research and their increasing workloads (Appendix 2, page 35):

> *HRECs in Australian institutions have widely varying workloads but the clear trend is a steady increase. This has reached the stage in some universities and health care institutions that the workload can only be managed by the multiplication of committees and/or the extension of meetings to lengths at which their efficacy can be threatened.*
>
> *Accordingly, additions to that workload are not welcomed, especially where these are accompanied by new, detailed and legislated sets of requirements. Opportunities to reduce workloads are, on the other hand, encouraged by AHEC. One of these, in areas in which there is wasteful repetition of ethical review, is the reduction of the number of HRECS conducting that review, or the centralisation of review.*

In order to address these concerns, AHEC (Appendix 2, page 35) propose a centralised HREC to provide the ethical consideration required by the RIHEA and to give advice to the LC:

> *AHEC proposes that the LRC consider amending the legislation to permit the initial ethical review of licence applications to be conducted by a central ethics committee, constituted by people with suitable ethical and technical expertise and who together meet the National Statement requirements for an HREC. In proposing consideration of this alternative, AHEC does not intend that such a committee would have any greater role than that presently given*

*by the legislation to HRECs. Accordingly, there would be no change in the functions and authority of the LC to make the final determination on any licence application.*

The Council has noted AHEC's proposal that a centralised expert HREC be established to consider applications to use excess ART embryos. However the Council has reservations about the proposal because it raises questions about how such a committee would be established and supported, how it would interact with the LC and whose decisions would have precedence in cases of disagreement. Thus the Council concluded that such a proposal would need to be explored further by the NHMRC.

## Horizon Scanning

Because of the very fast rate that this field is developing, the NHMRC is considering establishing a group with the task and expertise to consider the clinical, scientific, regulatory and ethical implications of new discoveries and technologies in areas related to the RIHEA and PHCA.

## Communication with Stakeholders

The NHMRC considers it important to communicate effectively with all its stakeholders.

It is worth noting that the NHMRC (through the LC and the Secretariat) has sought to engage relevant consumer organisations on a number of occasions, with little success. The NHMRC will however, continue with its endeavours to engage with these stakeholders.

## Operational Matters relating to the RIHEA

The following operational matters are discussed in Appendix 3. If Government decides to amend the RIHEA, then the LC has recommended a number of changes as outlined below.

**Delegation of powers**

The LC proposes amending the RIHEA to allow the LC to delegate decision making to the Chair to allow rapid responses to compliance matters. The RIHEA gives LC the power to suspend or revoke a licence if it believes on reasonable grounds that a condition has been breached. Because the process of decision making takes time, even if it is taken out of session, delegation of powers to the Chair in exceptional circumstances would increase assurance that the LC is ensuring strict and prompt compliance with the Act.

In addition, NHMRC inspectors are appointed by and report to the Chair of LC. The Act does not contain allowances for the Chair to delegate this authority to another person (e.g. the Deputy Chair) when the Chair is overseas or otherwise unavailable.

**Suspension or revocation of licences**

The LC may only suspend or revoke a licence if there are reasonable grounds to believe that there has been a breach of a condition (s.26(1)). The LC does not appear to have the power to suspend or revoke a licence for any other reason. If the LC receives information regarding a licence which leads it to conclude that it should reconsider its decision to issue that licence, then it should be able to suspend or revoke that licence without requiring the licence holder to have breached the licence.

**Issue of licences to joint licence holders**

Because regulatory control relates to the use of the embryo (and not steps that occur after the

embryo has been used), the LC has had to put in place sometimes complex administrative arrangements to ensure appropriate oversight of work being undertaken across different organisations. This has been most evident with some of the licences involving the development of embryonic stem cell lines, where the use of the embryo and initial isolation of stem cells occurs in one organisation and development of the cell lines occurs in a second organisation. One avenue to address this is to provide for the capacity to have joint licence applicants and holders, to confer the obligations for the provision of information and reporting on all organisations involved.

**Outcomes of licensed projects**

The LC wishes to be able to evaluate the effectiveness of the projects it has licensed. However its capacity to do this is limited, particularly when the control of the outcome of the project passes from the licence holder to a third party. The LC recommends that the LRC consider to what extent the LC should be able to obtain information about the longer term outcomes of licensed activities, for example by requiring an additional report within 12 months of the expiry of the licence.

**Replacing Licensing Committee members**

The RIHEA prescribes the categories of expertise to be appointed to the LC, and this membership has delivered a balanced committee with appropriate expertise. However, the complex appointment arrangements required by the RIHEA have led to extensive delays in appointing new members when sitting members have resigned.

**Status of unused embryos**

Some licensed projects may achieve their goals without using all the embryos licensed to the project. Other projects may terminate early for other reasons. Therefore, the LC decided that it was necessary to develop a condition to cover the status of any unused excess ART embryos at the end of a licence or project. The LC developed a new standard condition (4201) to cover this situation. However this may not be the most desirable way to deal with the situation.

## Conclusions

The NHMRC has received the views of three of its Principal Committees and attaches them to this document for consideration by the Legislation Review Committee.

In doing so, the Council:

1) Encourages ongoing community debate on the cloning of human embryos for research purposes.
2) Recommends further study into the costs and benefits of establishing a stem cell bank in Australia. An alternative strategy could involve establishing agreements and procedures for access to existing resources overseas.
3) Notes that both stem cell research and human embryo research have potential to underpin medical advances that will greatly improve the health and quality of life of Australians and recommends that researchers continue to have access to excess ART embryos to continue research in these areas.
4) Recommends that if Government decides to amend the RIHEA then the following suggestions to improve the efficiency and effectiveness be taken into account:
    - The Chair should be able to make decisions on behalf of the entire Committee in situations where a rapid response is necessary;

- The Chair should be able to delegate functions or powers to a Deputy Chair under certain circumstances;
- The LC should be able to suspend or revoke a licence in circumstances other than a belief that a licence condition has been breached;
- Provision should be made to allow the LC to issue a licence to joint licence holders to facilitate monitoring of all work being undertaken. This would also be necessary should the scope of the legislation be broadened to incorporate cloning for research purposes;
- Consideration should be given to the extent to which the LC could obtain information about the longer term outcomes of licensed activities, for example by requiring an additional report within 12 months of the expiry of the licence;
- Consideration should be given to streamlining the processes for appointing replacements to the LC; and
- Consideration should be given as to whether the status of excess ART embryos unused at the end of a licence or project needs to be covered by the RIHEA rather than administrative processes such as a condition of licence.

## APPENDIX 1 - COMMENT FROM RESEARCH COMMITTEE

Members of RC were requested to provide comment to the LRC about particular aspects of interest in the terms of reference or the Issues paper. Comments were received from RC and GTRAP.

## Comments from Research Committee:

### Issues – International exchanges of embryos and stem cell lines

import and export of human embryonic stem cells

RC considers that the processes and restrictions (eg. Australian Quarantine Inspection Service (AQIS) permits etc) applicable to import and export of other cell lines are sufficient to regulate import and export of stem cell lines.

### Issues – prohibited embryos and practices

cloning for research purposes

Cloning for research purposes is the synthesis of cloned human embryos expressly and solely for the purpose of developing a stem cell line that is a specific match for a given individual. The process requires using adult cells from the individual injected into enucleated oocytes, to persuade 'reprogramming' of the adult cells into pluripotential embryonic stem cells. This is a necessary technology to progress the clinical application of stem cell science for human medicine. The process is banned under existing legislation in Australia, but the law has recently changed in the UK to permit cloning for research purposes. RC suggests that it is appropriate to open a full and wide-ranging debate amongst the relevant stakeholders in Australia to determine whether our legislation should be also changed. For more information see http://news.bbc.co.uk/1/hi/sci/tech/859672.stm.

### Issues – National Stem Cell Bank

the applicability of establishing a National Stem Cell Bank

RC strongly supports the development of a national stem cell bank. Such a facility will allow researchers to access and share resources and so will promote individual research progress as well as exchange of information and collaborative projects. The bank will need adequate infrastructural support to ensure good documentation and processes. All stem cell lines produced in the course of publicly-funded research in Australia should be required to be submitted to the bank. Consideration should also be made to enforcing lodgement of stem cell lines made by commercial companies, particularly since in this case as in publicly-funded research, the stem cells will have been derived from donated embryos. Any stem cell bank established in Australia should be required to operate in accordance with the National Statement.

### Issue – Research developments

developments in medical research in the context of these two acts

RC considers that both stem cell research and human embryo research have enormous potential to underpin medical advances that will greatly improve the health and quality of life of Australians.

The clinical applications for stem cells in a wide range of degenerative and genetic diseases are well documented.

Research using surplus human embryos has the potential to alleviate the anguish of infertility,

which now affects 15% of Australian couples. Existing clinical interventions (including IVF and other assisted reproductive technologies) are limited in their usefulness, proving successful in only about 50% of patients. Ongoing research seeks to improve the success of ART and the range of options available to infertile couples. Furthermore, conventional ART techniques are now recognised to provide a less than optimal environment for the developing embryo, which may have adverse consequences for the lifelong health of children born after ART. Improvements in existing ART techniques are thus required. Australia is at the forefront of research in this area. Our sustained progress depends on being able to use for research those human embryos which are excess to patient requirements.

Of course the use of human embryos and stem cells in research must be constrained and informed by the relevant complex ethical issues.

## Comments from GTRAP

The issues paper requests that submissions provide information about the research developments that have occurred in Australia since the legislation was passed. GTRAP suggests that it would be useful to the public if the LRC's report summarised those developments.

GTRAP requests the LRC to consider the perception that the present RIHEA regulates research with human embryonic stem cells. Presently, the LC gives a licence to use excess ART embryos to derive stem cells but until the embryonic stem cells are used in a clinical trial (and so come under the review of the TGA and GTRAP), there is no national system for review of embryonic stem cell research.

The current system has one NHMRC Principal Committee regulating the initial use of embryos for research etc, and then a second NHMRC Committee overseeing the clinical use of embryonic stem cells. In between, there is local oversight from HRECs and institutional committees. If the status quo is maintained, it could be appropriate that the LC has some role to play in monitoring or following up beyond the initial provision of a Licence. Alternatively, research projects using embryonic stem cells could be recorded in a national database so that it is apparent to all what is being done, and there is no unnecessary duplication. Irrespective of the regulatory model adopted it is necessary to ensure that the role of the LC is clearly identified.

On the other hand, if the LRC recommends that the LC is no longer needed, then the comments made above about a "**gap**" are not relevant and research with embryonic stem cells will only undergo one additional regulatory step (compared to other cell types) when this type of research reaches the clinical trial phase. A similar situation exists now for research into gene therapy.

GTRAP wishes to state strongly that it does not consider that it should be responsible for regulating and overseeing basic research using embryonic stem cells. While it has the expertise, it does not have the capacity or resources to regulate use of stem cells beyond its current remit to oversee the use of stem cells in clinical trials.

## Other Information

### NHMRC funding of research using excess ART embryos

NHMRC is funding one project grant which requires a licence to use excess ART embryos. The principal investigators are Associate Professor Christopher O'Neill from the University of Sydney and Dr Tomas Stojanov. The project commenced this year and is worth $408000 over 3 years.

**NHMRC funding of research using stem cells**

Attachment 1 explains the situation in 2005 with respect to NHMRC funding of research using adult and embryonic stem cells.

Attachment 1 – Current NHMRC funding for Research involving Stem Cells

In 2005, the NHMRC will fund more than $39 million[3] in research that may involve the use of stem cells.

About 73% ($28.8 million) of the funding involves the use of animal stem cells. Of the remainder, 13% ($5.2 million) involves the use of human stem cells and 14% ($5.7 million) involves research that uses both human and animal stem cells.

Of the research that involves the use of human stem cells (27% of total funding), 87% of the funding involves the use of human adult stem cells and 13% involves human embryonic stem cells.

This is outlined in the table below:

| Research Involving Stem Cells | Type of Stem Cells | Number of awards active in 2005 | Expenditure in 2005 |
|---|---|---|---|
| **Human Stem Cells only** | Adult stem cells only | 12 | $5,049,917 |
| | Embryonic stem cells only | 1 | $64,750 |
| | Adult and Embryonic stem cells | 1 | $87,250 |
| | **Total** | **14** | **$5,201,917** |
| **Animal Stem Cells only** | | **104** | **$28,860,442** |
| **Human and Animal Stem Cells** | Human Adult and Animal | 16 | $4,365,786 |
| | Human Embryonic and Animal | 7 | $1,340,555 |
| | **Total** | **23** | **$5,706,341** |
| **Grand Total** | | **141** | **$39,768,700** |

More information is available if required.

[3] The 2005 expenditure was determined by keyword search, email survey of New Program Grant holders and holders of grants from the five previously block funded Medical Research Institutes and an email survey of all researchers awarded new funding in 2005.

## APPENDIX 2 - SUBMISSION FROM THE AUSTRALIAN HEALTH ETHICS COMMITTEE

# INTRODUCTION

**Australian Health Ethics Committee's Role and Contributions**

One of the functions of the NHMRC given to it by the *National Health and Medical Research Council Act 1992* (NHMRC Act) is to inquire into, issue guidelines on and advise the community on matters relating to ethical issues relating to health.

The NHMRC Act establishes the Australian Health Ethics Committee (AHEC) as a principal committee of the NHMRC, specifies its terms of reference to be:

a) to advise the Council on ethical issues relating to health; and

b) to develop and give the Council guidelines for the conduct of medical research involving humans; and

c) such other functions as the minister from time to time determines.

The NHMRC first issued guidelines on ethical aspects of research related to assisted reproductive technology (ART) as Supplementary Note 4 (*In Vitro Fertilisation and Embryo Transfer*) to the then *Statement on Human Experimentation* (NHMRC 1992). These guidelines were not continued when the NHMRC Act came into force and AHEC developed a new edition of the guidelines during 1993–96, which were published in 1996 (*Ethical Guidelines on Assisted Reproductive Technology*, ART guidelines 1996).

The ART guidelines 1996 stated that all reproductive medicine units offering ART services must obtain accreditation by a recognised accreditation body and that such accreditation was to include consideration of compliance with NHMRC guidelines. The recognised accreditation body was then, and remains, the Reproductive Technology Accreditation Committee (RTAC), a committee established by the Fertility Society of Australia.

In the ART guidelines 1996, it was also noted that only three states (Victoria, South Australia and Western Australia) had enacted legislation to regulate ART. AHEC recommended strongly that legislation be enacted in the other states and territories. Many of the issues surrounding ART (including surrogacy, eligibility, consent for posthumous use, preimplantation genetic diagnosis and sex selection) were as much social and political issues as they were ethical issues. In addition, it was noted that, without uniform legislation, regulation of national data collection, maintenance of a centralised database and monitoring of research could not be achieved.

Since 1996, there have been scientific developments that are relevant to the existing guidelines and laws relating to ART, such as:

- the development of somatic cell nuclear transfer, which was first announced with the cloning of Dolly the sheep; and
- the development of methods of extracting and propagating embryonic stem cells from a 5-day-old embryo created *in vitro*.

In 1998, in response to widespread concern about the possible use of somatic cell nuclear transfer to clone humans, the then Australian Minister for Health and Ageing requested AHEC to prepare an urgent report on human cloning. That report was entitled the *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings*.

In 1999, the NHMRC issued the *National Statement on Ethical Conduct in Research Involving Humans* (National Statement) in the form developed by AHEC.

The AHEC report to the Minister for Health and Ageing was referred to the House of Representatives Standing Committee on Legal and Constitutional Affairs, which conducted a public inquiry and handed down its report in August 2001. This report was considered by the Council of Australian Governments (COAG) and contributed to the development of new Australian legislation banning human cloning and regulating the use of human embryos that are no longer required for ART treatment.

In 2002, the Australian Parliament passed legislation banning human cloning (PHCA) and regulating certain uses of embryos (RIHEA).

The RIHEA acknowledges the importance of the application of ethical principles to research involving human embryos in several ways, including:

- there must be a member in common between AHEC and the Licensing Committee (LC) established by the Act to grant licences for uses of embryos;
- before an excess ART embryo is used under licence, 'responsible persons', as defined by the legislation, must give proper consent to that use. Proper consent is defined as consent obtained in accordance with the NHMRC ethical guidelines on ART; and
- the LC must not issue a licence unless satisfied that the activity or project proposed in the application has been assessed and approved by a human research ethics committee (HREC) constituted in accordance with, and acting in compliance with, the National Statement.

In 2002, AHEC commenced a revision of the ART guidelines 1996 and, in September 2004, following extensive consultation with the public and the States and Territories, issued the *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research* (ART guidelines 2004).

**AHEC's Contribution to the NHMRC Submission**

AHEC's involvement in ethical matters relevant to this legislative review extends for more than ten years and has involved the development and issue of two sets of guidelines as well as the provision of detailed advice to the Minister.

AHEC addresses subjects that other parts of the NHMRC submission also address, especially those from the LC. In its contribution, AHEC has sought to present to the LRC the ethical considerations that, in AHEC's opinion, should inform and be balanced in their deliberations on the review of the Acts. AHEC has intended that its contribution of ethical considerations will complement other contributions that are more closely informed about the operational level of the legislation.

## THE TERMS OF REFERENCE

Of the terms of reference, AHEC considers that it has sufficient experience and knowledge to offer a response on paragraph (i) (b), (c) and (d).

**(i) (b) developments in medical research and scientific research and the potential therapeutic applications of such research**

Through its work in relation to the ethics of research involving humans, AHEC is deeply aware of how important, but often difficult, it is to foresee the ethical implications of scientific innovation and advance. AHEC is equally aware of how difficult it is to address, with the thoroughness that

they deserve, those ethical issues at a time when the implementation of the innovation is being advocated.

These considerations are applicable to likely developments in medical and scientific research in ART. However, those developments have two features that are likely to deepen the importance of ethical assessment. High levels of investment and public interest mean that developments are likely to happen quickly. Second, their implementation will affect practices in fertility and human reproduction, on which there remain deeply held (and deeply divided) opinions within the Australian community.

For these reasons, it is AHEC's view that the LRC, in responding to this term of reference, needs to give careful and thorough attention to ethical issues embedded in developments in medical and scientific research and their potential therapeutic applications.

**(i)(c) community standards**

The Issues Paper makes clear that:

> *It is not the purpose of the reviews to revisit the underpinning community debate and rationale for the two Acts. Rather, the purpose is to review the Acts in the light of any changes in scientific or community understanding or standards since 2002, and any indications that the provisions are no longer appropriate and/or practical in their application (page 3).*

In 1998, AHEC provided the Minister for Health with advice on the *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings* and also made submissions to the subsequent House of Representatives Committee Inquiry into that advice. Further, AHEC was responsible for the development and completion of the *Ethical Guidelines on the use of assisted reproductive technology on clinical practice and research* (NHMRC, 2004) (the ART guidelines 2004) that were developed over a two year period. These replaced the *Ethical Guidelines on assisted reproductive technology* (NHMRC, 1996) also developed by AHEC.

These activities, covering a period of more than ten years, have, through the public consultation processes regularly involved, provided AHEC with extensive and repeated input from the community.

In the ART guidelines 1996, it was noted that the community opinion on the status of and research on human embryos was significantly divided and that the differences could not then be resolved. (ART guidelines 1996, page 10).

In the course of its work in relation to ART, and especially to the use of human embryos, since 1996, AHEC has not seen evidence that the differences in and among community opinions on these matters have declined. Accordingly, AHEC considers that references in the Terms of Reference to "*community standards*" are premature and that it is more accurate to refer to the range of community opinions on what community standards should be.

The ART guidelines, issued in 2004, thus do not show a significant change in position on the uses of human embryos from the position in 1996 and, in AHEC's view, this accurately reflects the balance of community opinion.

**(i)(d) the applicability of establishing a National Stem Cell Bank**

In *Essentially Yours: The Protection of Human Genetic Information* (ALRC, NHMRC, 2003), at chapters 18-20, AHEC contributed to the discussion and development of proposals about genetic

research databases, comprised of both information in the form of family histories and of human tissue samples.

Many of the issues that are relevant to those databases, as outlined in those chapters and their recommendations, would be relevant to the establishment of a stem cell bank.

Of high priority in such an initiative would be the determination of the point at which such stem cells ceased to be regarded as "*human tissue for the purposes of research use*".

This response is also relevant to the question on page 22 of the Issues Paper: What would be the advantages of an Australian stem cell bank?

**(ii)(b) the role played by State and Territory statutory bodies that regulate assisted reproductive technology (ART) treatment as well as the role of national organisations including, but not limited to, the Fertility Society of Australia and its Reproductive Technology Accreditation Committee (RTAC)**

Historically, AHEC recognises that State and Territory agencies have, appropriately, given Australia's constitutional arrangements, played essential roles in the regulation of ART. They have however largely concentrated on defining the practices that can be conducted and by and for whom they may be offered. The monitoring of the continuing quality of the practices of ART clinics has, however, been a matter that has largely been left to those clinics and to the Fertility Society of Australia, through RTAC to perform.

Through its involvement in the development of guidelines during the last decade, AHEC has given extended consideration to the ethical considerations that arise in the practice of ART and is deeply aware of how strongly the community holds divergent views about those. It has thus been a matter of continuing importance for AHEC that those ethical matters are routinely drawn upon in ART practice and it was in part to this end that the guidelines, especially, the ART guidelines 2004 were devised and promulgated.

The RIHEA requires ART centres to be accredited by RTAC in order to be eligible for a licence. The implication is that RTAC is an appropriate, and appropriately informed and effective accrediting agency. A review of RTAC's guidelines, accessible at http://www.fsa.au.com/rtac/ shows them to be comprehensive as to technical and operational aspects of the practice of ART.

However, there is no specific reference in those guidelines to the NHMRC ART guidelines that are designed to guide ethical practice and research. There is only a generic reference to NHMRC guidelines and to ethics committees (without clearly distinguishing research ethics committee functions from those of clinical ethics committees). It appears that even if RTAC fulfils all the reasonable expectations of an effective accrediting agency, its guidelines give insufficient prominence to ensuring that the ethical obligations of ART practitioners and researchers are fulfilled. Further, as noted above, AHEC is aware that there is uncertainty as to the role that RTAC plays in monitoring compliance of ART centres with the ART guidelines.

## THE ISSUES PAPER

From the many issues identified in this paper, AHEC has identified several on which it considers it has knowledge and expertise to offer a response. Each of these is set out below, (with page references to the Issues Paper) with AHEC's response following.

## Have there been any problems in interpreting or applying the definitions and terminology used in the Acts? (p.11)

The definitions on which AHEC offers a response are those of "human embryo", "*excess ART embryo*" and "*proper consent*".

Human embryo

This definition contains, in its opening words, a degree of circularity that has ethical implications for the effectiveness of the Act and the potential developments in ART. To define a human embryo as "*a live embryo that…*" leaves the central concept of embryo undefined. If in the development of ART processes, innovative methods are devised to generate entities that resemble or can develop into human beings, but which can be argued are not "*embryos*", then the legislation can be argued not to regulate their use. This may mean that the strict legislative and ethical system is ineffective over the very areas of activity that it was designed to govern.

The matter has been raised with NHMRC by AHEC and taken up by an LC sub-committee, which is yet to complete its work.

AHEC recommends that the definition be re-considered so that the intent of the legislation, namely, to regulate the uses of human embryos beyond their use in and for ART, is comprehensively achieved.

Excess human embryo

The discussion of this definition is also relevant as a response to the following issue from the Issues Paper:

Have any issues arisen with respect to the operation of the legislation (such as with giving and obtaining consent for an embryo to be an 'excess ART embryo'; or giving and obtaining consent from responsible persons for the use of excess ART embryos in research)? (p.16)

This definition contemplates that an ART embryo, created for use in the ART treatment of a woman, becomes an excess ART embryo when it is "*excess to the needs of*" the woman for whom it was created and her spouse, if any, "*at a particular time*", if they have given written authority for its use and determined in writing that it is "*excess to their needs*". The difficulty that has arisen relates to whether "*excess to their needs*" includes both surplus embryos, being those that are more in number than are needed, and never–to-be-implanted embryos, being those that, for reasons other than the number available (eg deemed to be unsuitable for implantation), will not be implanted.

*The second reading speech*

In the Second reading speech that introduced the bill to the Australian parliament, it was said that:

> *The bill that I put before you today also establishes a comprehensive regulatory system to govern the use of excess IVF embryos. Researchers and scientists proposing to undertake work on excess IVF embryos that would otherwise have been destroyed will be required to follow specific procedures and meet strict criteria.*

and that:

> *Importantly, research will only be allowed on excess IVF embryos that were in existence at 5 April 2002.*

These passages suggest that, in most circumstances, embryos would become excess through

decisions about embryos that had been created some time previously and were in storage. These decisions would be made by women and their spouses because they had reached the end of their ART treatment, so that remaining embryos were no longer needed. (The ART guidelines 2004, at paragraph 17.12 introduce the expression "*no longer needed*", but it does not appear in the Act.) Such a construction would be consistent with the ordinary meaning of "*excess*": "*an amount or quantity beyond what is normal or sufficient; a surplus.*"

The final version of the legislation did not prevent post-5 April 2002 embryos being used but did prevent them being used in a way that would damage or destroy them. It was thus possible that post-5 April 2002 embryos could be used in non-damaging or non-destructive ways.

The confinement of damaging or destructive uses of embryos to those created before 5 April 2002 has now lapsed. Any embryos can be used (within the scope of the legislation), whether they will be damaged or destroyed or not.

*ART diagnostic practices*

Practices in ART can determine, by observation, whether ART embryos are developing within normal parameters or show slow or below normal levels of cell division. Through the use of pre-implantation genetic diagnosis (PGD), diagnoses can be made about the probability that although these embryos will, after implantation, develop to achieve pregnancy, the resulting child is likely to suffer from an identifiable genetic condition. This information can be available as to several ART embryos at a time before any have been implanted.

As a result, it may be that there are two categories of embryos that will not be implanted, whether or not the woman decides to continue ART treatment or not: Those that through observation and application of experience and expertise, have developed outside normal parameters and those as to which a diagnosis of a likely genetic condition can be made.

It could be said that both types are, at that time, no longer needed and will otherwise be destroyed. The difficulty presented by these practices for the present definition is that it is not clear whether, at such a stage, particularly before any embryos have been implanted in a woman and before she and her spouse (if any) have decided to stop ART treatment, they can determine that the embryos are "*excess to their needs*". The grounds for that determination would be that, although they were not yet "*excess*" (in the ordinary sense of surplus), the embryos would be destroyed because they were inferior to what the couple needed or likely to lead to an outcome unacceptable to them.

However, if "*excess to their needs*" was taken to mean surplus, and this was made explicit in the definition, embryos would only become excess if they were more than what the woman and her spouse needed. One might expect that this point would normally not be reached until they had decided that they had reached the end of their treatment. One consequence of this would be that those embryos that were not to be implanted would not be available until the end of the ART treatment.

Research interests would be likely to argue in favour of including any embryos that were not to be implanted within the meaning of excess embryos. It could be said, with some reason, that there was no justification for having to wait, because it had been decided that these embryos would be destroyed in any event. Further, in relation to the embryos as to which a diagnosis of an unacceptable genetic condition had been made, research interests could reasonably point to the advantages of using those very embryos for research into that genetic condition.

On the other hand, the ambiguity may permit a woman and her spouse to determine that an embryo is excess to their needs because PGD has revealed it to have a disease or a gender that is

unacceptable to them and so excess to their needs, the word "*needs*" being undefined.

*The ambiguity of the definition*

Thus, in summary, the present definition of excess ART embryos can include not only any embryos that a woman and her spouse **no longer need** (because they have completed ART treatment and the embryos are surplus) but any embryos **that they have, at any particular time, decided not to use** for ART treatment.

*AHEC's views*

AHEC's view is that careful thought needs to be given as to whether to amend the legislation to address this ambiguity. Any amendment would need to take into account the full range of relevant ethical considerations. These include those that relate to the use of the embryos involved for purposes other than ART and those that relate to the decision to declare the embryos to be excess, so that they can be used for those other purposes.

Among the considerations relevant to the treatment of embryos are the views that, as the ART guidelines 2004 require, respect is shown for all embryos and that they are used for purposes other than ART only when they would otherwise be destroyed.

Another consideration is whether to rest the determination of when embryos are excess on some intrinsic feature, such as slow cell division. Relevant to this is the fact that if specific characteristics are identified, such characteristics will depend on present knowledge that is likely to be shortly superseded. On the other hand, if general descriptions of embryos are used, physical characteristics will be given differential moral significance without any clear justification. A further consideration is whether to rest the determination of when embryos are excess on the diagnosis of a predictable genetic condition. One ethically relevant consideration here is that, in the context of the ethical and emotional demands of ART treatment, to make such a decision before the end of treatment may, in retrospect, have foreclosed a decision to accept the embryo that, later, the woman and her spouse may be willing to make (but were not before).

The ethical considerations relevant to the decision of a woman and her spouse to determine that an embryo is excess include the broader ethical responsibilities of parents to act for the benefit of their children. Paragraph 2.5 the ART guidelines 2004 provides that the welfare of people who may be born as a result of the use of ART is paramount. A decision that one of a number of embryos is excess involves making distinctions among and between embryos that needs to be justified in an ethically consistent way.

Lastly, it is clear to AHEC from the submissions received in the development of the ART guidelines that the decision to determine embryos to be excess is one of great personal significance.

Proper consent

Discussion of this definition is also relevant to AHEC's responses to the issues identified in the Issues Paper that relate to the operation of the licensing system. Those responses appear later in this submission.

The definition of proper consent in the RIHEA is by reference to the 1996 guidelines or to other guidelines issued for the purpose. AHEC understand that the ART guidelines 2004 are intended to be incorporated in the regulations under the Act in the near future.

In essence, paragraph 17.14 of those guidelines defines "*proper consent*" in the following way:

> *Under the terms of the National Statement*, proper consent for research must be informed, competent, voluntary, specific and, for this purpose, it must be in writing. Researchers must comply with the National Statement in respect of all these conditions, and must also follow the specific guidance provided in paragraphs 17.16 and 17.17 of these guidelines.* (*The NHMRC National Statement on Ethical Conduct in Research Involving Humans, 1999)

Whether the consent meets these requirements, and especially those of being "*informed*" and "*specific*" will depend first on the nature of the research and second on the way that information about the research is conveyed to the potential participants. It will be HRECs, constituted in accordance with and acting in compliance with the National Statement (as required by the RIHEA) that will assess both these matters.

On the former, they will be guided by the paragraph 1.13 of the National Statement that requires research to demonstrate that it is justifiable by its potential contribution to knowledge and by paragraph 17.11 of the ART guidelines 2004 that requires research involving embryos offers a significant advance in knowledge or improvement in technologies for treatment. However, where the proposed research using excess ART embryos aims to derive stem cells, it may be difficult, in the present state of knowledge, to sufficiently specify the research that will use them. Where this cannot be done with sufficient precision, an HREC may conclude that the proposal meets neither the requirement of the National Statement or of the ART guidelines 2004.

As a result, it will also be impossible to meet the disclosure requirements for proper consent, as set out in paragraph 17.16 of the ART guidelines 2004, which requires that disclosure to include "*a full explanation of why the research would represent a significant advance in knowledge or improvement in technologies for treatment*". For example, an HREC may be reluctant to regard a request for consent to the use of stem cells (derived from an excess embryo) for future therapeutic benefit or for future training of scientists as sufficiently specific and so not "*proper consent*". On the other hand, a request for consent to use excess embryos to test the toxicity of drugs may be sufficiently specific, (even if there are grounds for declining to consent).

The interdependence between the need for research involving excess ART embryos to show likelihood of significant advance in knowledge or improvement in technologies for treatment and "*proper consent*" is related also to the relation between HREC review and the decision to grant a licence. This is discussed below under the heading "Have there been any difficulties of interpretation or application of the criteria for granting a licence? (p.19)" and in relation to the scope of the RIHEA.

## Are the prohibited embryos and practices described in the Act still relevant in light of advances in biotechnology since 2002? Do they appropriately reflect community standards? (p.14)

In its submission to the House of Representatives inquiry, AHEC said:

> *After pointing out (in AHEC's original 1998 advice to the Minister) the fundamental ethical difference between proposals to clone whole human entities (embryos, foetuses, etc) and existing practices of cloning parts of human entities (cells, etc), AHEC concentrated on the acceptability of proposals to clone whole human entities.*
>
> *In making the distinction between cloning human entities and cloning human parts, AHEC placed a different emphasis on the ethical issues from that which is espoused by the Australian Academy of Science in the Position Statement on Human Cloning (published in February 1999).*

*In that document the Academy adopted a distinction between 'therapeutic cloning'[4] and 'reproductive cloning' which implied that the most important ethical issue concerns the objective for which cloning techniques might be employed. In the view of AHEC, whether or not a proposed research project will involve destructive experimentation on human embryos is an important ethical and legal issue which ought not be glossed over.*

Since that time, AHEC is aware that considerable public debate has been conducted on these types of cloning and although its views as to the relative importance of ethical considerations, as stated in the quotation has not changed, it may be helpful to the LRC to note the nature of the ethical elements of that debate.

Arguments in favour of what is referred to as "*therapeutic cloning*" rest on the value of the research that this practice will make possible through the derivation of embryonic stem cells from the cloned entities. The argument is characteristically referred to as utilitarian or consequentialist, in that the merit of the proposal lies in the worth of the outcomes and results. On the other hand, in stating that the destruction of human embryos remains an important ethical issue, AHEC relies on an argument of a deontological kind: one that rests its merit on conformity to accepted ethical principle or value. The opposition of such arguments is recurrent in ethics and especially in medical ethics, where the promise of future benefit can only be bought at the price of some present compromise of principle or value. The opposition of such arguments usually also mirrors divisions in community opinion, whether intuitive or deliberated. In such circumstances of community difference, of which this issue is a prime example, it has been AHEC's view that the preferred advice is that which reflects enduring ethical traditions of thought and belief and which has clear, if not overwhelming, community support.

For these reasons, AHEC continues to hold the view on this issue that is expressed in the above quotation.

## Has the prohibition of payment beyond reasonable expenses (valuable consideration) for gametes and embryos affected access to these items? (p.14)

Although AHEC is not aware of statistics on which an answer to this specific question could be based, the issues have important ethical dimensions that AHEC wishes to draw to the attention of the LRC.

Consent to treatment and research and to the donation of tissue for either purpose is a well established ethical requirement. That such consent be free and adequately informed is entailed in the requirement.

Consent that results from a desire to receive a payment or other benefit does not meet that entailed requirement. Where the consequences of such consent include long term responsibilities, such as the obligation to provide identifying details that can be followed well into the future by recipients of donated gametes, the ethical significance of the free and informed quality of that consent is higher.

AHEC accordingly considers that payments for the donation of gametes ought clearly to be confined to those that meet expenses and conveniences, and not include any component of reward.

[4] At a forum conducted by the Australian Academy of Science on 16 September 1999, Professor Martyn Evans, one of the first scientists to isolate embryonic stem cells, argued that instead of coining a term ('therapeutic cloning') to make cloning sound more acceptable, researchers ought to say: cloning ought to be permitted in some circumstances and the public should be educated to accept that.

## Are the arrangements for accreditation and ethical oversight of ART centres appropriate? (p.16)

The ART guidelines 2004, at paragraphs 1.3, 1.13 and 3.3 contemplate that units conducting ART in Australia would be continue to be accredited by the RTAC of the Fertility Society of Australia and that the ART guidelines 2004 would be a key element in that accreditation.

AHEC is aware that doubts have emerged as to the manner in which such accreditation involves monitoring the compliance by those units with the ART guidelines 2004. This has been, to AHEC's awareness, a matter of some concern to sectors of the community and it appears that, as a matter of public accountability, more clarity is needed.

Although the matter does not directly arise under the Act, it does affect the status and reputation of the ART units whose practices are likely to be the subject of licences under the Act.

AHEC understands that RTAC, rather than conducting a separate monitoring process, relies on ethics committees in ART units to monitor the use of and compliance with the ART guidelines 2004. It is not always clear whether these committees have been established to provide advice on ethical aspects of clinical practice or, as HRECs, to review research proposals. If their role is only the former, there are no external requirements as to their composition or functions. If their role is the latter, the National Statement does define their membership and functions and sets out the standards on which they ought to function. Although an ART unit can assign additional functions to an HREC, there is no certainty that even then the members will have the necessary expertise or independence to fulfil a reliable oversight function. However, such a practice is subject to the weaknesses that beset HRECs that are described below.

The monitoring of compliance with the ART guidelines 2004 on ART practice does involve matters that are normally beyond the expertise of an ethics committee constituted to review proposed research, even a centralised national committee of the kind suggested below. However, it could be argued that the relationship between the ethics of the practice of ART and of research involving human embryos, in the context of the Act, is such that one body is likely to have sufficient expertise to monitor the former and review the latter. This would however be a unique arrangement and one for which AHEC is unaware of a precedent, although the Canadian experience, (see http://www.cihr-irsc.gc.ca/e/19312.html) may be informative.

## Have there been any difficulties of interpretation or application of the criteria for granting a licence? (p.19)

The legislation requires an HREC to have approved the activity or project in a licence application before the LC can grant a licence. One issue on which the HREC must decide is the likelihood of significant advance in knowledge or improvement in technologies for treatment as a result of the proposed use of excess ART embryos.

The difficulty arises because both the HREC, (in compliance with the National Statement, with which it is required by the Act to function, and the ART guidelines 2004), and the LC, in compliance with the Act, must consider this question. Difficulties arise if an HREC decides not to approve a project because it does not promise sufficient advance in knowledge, so that a necessary condition for the grant of licence by the LC is not met. Indeed, the HREC rejection may prompt the applicant not to submit the licence application at all. This appears to subvert the apparent intention of the Act that this matter is one on which the LC ought to make the final determination. Further, to so locate the final responsibility is preferable because the independence, accountability and expertise of the LC are superior to that of an HREC.

Similar difficulties, as noted above, arise where differences emerge between the HREC's view of whether documentation that secures proper consent, as required by the Act in conformity with the ART guidelines 2004, differs from that of the LC.

AHEC understands that initial difficulties experienced in managing the processes between HRECs and the LC have been overcome through clarification of the LC's expectations.

AHEC suggests that consideration be given to amending the legislation to make clear that an HREC review is always needed for a licence application but that the scope of that review is confined to matters of ethics of the activity. If, for example, the legislation required the LC to have regard to the advice of the HREC in reaching its decision, rather than making HREC approval a condition precedent to the grant of a licence, recurrence of the kinds of difficulties initially experienced might be avoided.

AHEC considers that the ethical review of a proposal for use of embryos should be conducted by an independent HREC but recognises that the present institutional location of many HRECs frequently prevents this. In order to address this and other weaknesses of the present statutory scheme for the provision of ethical advice, AHEC develops in the following paragraphs, an alternative process to meeting the needs for ethical advice to the LC.

## Are the monitoring and compliance requirements of the Act appropriate? Are there any other issues relating to the operation of the licensing system? (p.19)

One of the functions of AHEC is the support and annual reporting on HRECs in Australia. As a result, AHEC has extensive knowledge of the functioning of these committees and is well informed as to their workload and capacity.

There are several features of the Australian HREC practice that merit noting in the context of these two issues, as well as the issues of the extent to which the legislation should deal with stem cells (at page 11 of the Issues paper). These features will be noted and observations drawn from them that support AHEC's view that the LRC be invited to consider a simpler, more independent, more informed and more accountable mechanism for reviewing the ethical aspects of the use of excess ART embryos, especially those that have the purpose of deriving stem cells for research.

Local and institutional

The Australian HREC process has grown from institutional initiatives in the 1970's and 1980's and been stimulated by the decision of the NHMRC and later the ARC to require all institutions seeking access to their research funding to require that any research involving humans be reviewed by an institutional HREC. From the mid-1980's, these policies gradually resulted in increases of HRECs to the present number of about 225.

Strength, and a weakness, of these developments is the institutional location of HRECs. Being close to the institutions, they frequently have local knowledge of the situations in which, and the researchers by whom, research will be conducted and can so make realistic determination as to how the ethical requirements for the conduct of research can be satisfied.

One specific aspect of such conduct is how the conduct of an approved research protocol is monitored. Local knowledge can assist in devising realistic monitoring measures, although AHEC is aware that these opportunities are not always followed.

At the same time, the very closeness can lead to HRECs being influenced by the institution's service and research culture or needs in ways that can limit the independence of their thinking and decisions. In situations in which external funding incentives, such as access to NHMRC funding is

not important, there are no external standards for the constitution and operation of ethics committees, so that membership can lack the degree of independence and expertise that the National Statement requires.

Workload

HRECs in Australian institutions have widely varying workloads but the clear trend is a steady increase. This has reached the stage in some universities and health care institutions that the workload can only be managed by the multiplication of committees and/or the extension of meetings to lengths at which their efficacy can be threatened.

Accordingly, additions to that workload are not welcomed, especially where these are accompanied by new, detailed and legislated sets of requirements. Opportunities to reduce workloads are, on the other hand, encouraged by AHEC. One of these, in areas in which there is wasteful repetition of ethical review, is the reduction of the number of HRECs conducting that review, or the centralisation of review.

Expertise

Australian HRECs, being located in institutions, develop expertise in the kinds of research that they are frequently asked to review. Accordingly specialist knowledge in new and emerging areas of research is frequently lacking. This is another reason that some jurisdictions have begun to centralise review of some kinds of research in which such specific expertise is needed.

Monitoring

It is an obligation of institutions in which research is conducted and of the HREC that reviews research to monitor the conduct of the research to see that it follows the approved protocol. AHEC is aware that this is usually conducted in a minimal way, one that would fall far short of the standard of monitoring that the Act requires of licensed conduct. Accordingly it seems to AHEC that it is wasteful and unnecessary for an HREC to also monitor research conduct that is the subject of a licence. However, unless some change is made in the present legislative system, responsible HRECs will seek to do so.

Conclusion

Although research involving the use of human embryos is small in quantity, in the light of the above features, as well as the demand for high levels of expertise in its review and the desirability of independence in ethical review of licence applications, AHEC proposes that the LRC consider amending the legislation to permit the initial ethical review of licence applications to be conducted by a central ethics committee, constituted by people with suitable ethical and technical expertise and who together meet the National Statement requirements for an HREC. In proposing consideration of this alternative, AHEC does not intend that such a committee would have any greater role than that presently given by the legislation to HRECs. Accordingly, there would be no change in the functions and authority of the LC to make the final determination on any licence application. The manner in which such a committee was formed could include a sub-committee of NHMRC, a committee established by an independent organisation, such as the Fertility Society of Australia or co-operation among ART clinics. In addition to such a committee offering the likelihood of ethical review of licence applications that was better informed and more independent than that offered by HRECs at applicant institutions, such a committee might also add to the public assurance provided by the reporting of the LC that the system fulfils their expectations.

**What are the next steps in the research? What are the potential benefits of the research and when might these occur? What are the potential risks? (p.23)**

The foresight of research practice often precedes the recognition of its ethical implications. This is not to fault researchers for their innovation or creativity, but to recognise that scientific exploration and expertise moves with greater speed than does the acquisition of sufficient expertise by non-scientists to inform them of the ethical implications.

In this field, there are significant incentives to move fast. If the suggestion of a centralised ethics committee to review proposals for licensed activities were adopted, that committee might develop the expertise to be closer in the wake of scientific advance than others and be in a better position than others to offer ethical advice on research activity that emerges on Australia's horizon.

## OTHER ISSUES

It has been suggested by the NHMRC that the submission from the NHMRC address the following issues:

- Is the scope of each of the Acts adequate and appropriate?
- Should the Prohibition of Human Cloning Act 2002 include more or fewer prohibited practices?

The submissions that AHEC received during the development of the ART guidelines 2004 showed a clear, even overwhelming, majority of opinion opposed to any increase in the number of prohibited practices. Further, CREGART was aware that a review of the legislation was scheduled and turned its mind particularly to prohibited practices. In publishing the list at pages 10-11 of the ART guidelines 2004, both CREGART and AHEC intended to make clear that, regardless of other outcomes of the legislation review, all the practices listed were regarded as unethical.

- Should the Research Involving Human Embryos Act 2002 regulate the derivation and use of (embryonic) stem cells in addition to regulating the use of excess ART embryos?
- Should research into and use of stem cells be regulated in Australia and if so, by which organisation?

The present legislative scheme that regulates the use of excess ART embryos but does not regulate the implementation of licensed uses that do not involve embryos, but involve the derivation and research with embryonic stem cells, constrains the effectiveness of the legislative scheme and confounds the processes of the ethical review of research with human tissue.

For reasons discussed above in this submission, the fact that the LC does not have statutory authority to regulate uses of embryonic stem cells may prevent it from inquiring in detail about research proposals that propose to derive stem cells from excess ART embryos. It may also preclude it from monitoring the compliance with a licence to conduct such research.

HRECs faced with the task of reviewing research proposals to use excess ART embryos to derive stem cells are less constrained than the LC in establishing to their satisfaction the details of the research proposal meet relevant standards of the National Statement and the ART guidelines 2004. However, they are likely to lack the expertise and resources to effectively monitor the use of those cells in the conduct of that approved research.

The research use of embryonic stem cells raises both nationally and internationally issues of intense interest to scientists and the public, illustrated well in the debates about the expression "*therapeutic cloning*" noted above. That level of interest and divided opinion offers, in AHEC's view,

justification for considering whether the statutory regulation of the uses of excess ART embryos should be extended to regulate the uses of stem cells derived from them.

Regulation need not be obstructive or constrain research. It may be adequate for a national committee to review proposals for the use of embryonic stem cells and to seek appropriate advice on, or review of, the relevant ethical considerations. The membership of the present LC could, for instance, be extended to include relevant expertise in stem cell research and the centralised ethics review committee, suggested above to review licence applications under the present regime, could provide the ethical advice or review. Experience in Canada, as noted above, may be informative on these suggestions.

## APPENDIX 3 - COMMENT FROM LICENSING COMMITTEE

## Introduction

The Embryo Research Licensing Committee of the NHMRC (LC) was appointed in May 2003 as a Principal Committee of the NHMRC in accordance with the RIHEA. The LC has met in person eleven times since its inception and has also held additional meetings by teleconference as required. Throughout its activities it has been conscious of the object of the RIHEA to protect ART embryos while simultaneously enabling research using excess ART embryos under a strict regulatory regime. All its decisions have been taken in the light of these dual aims.

The LC has been aware of the requirement for the review of the two Acts from the time of its inception. At its meeting in September 2003 it instructed the Committee Secretariat to commence and maintain a list of issues with respect to the legislation which would inform its contribution to the NHMRC submission to the Review.

LC will confine this submission to information on its ability to regulate the use of excess ART embryos as required by the legislation and comments on the regulatory implications of possible changes to policy or law. As the regulator it is not appropriate for LC to comment directly on the desirability or otherwise of implementing particular policies and proposals.

### Licensing Process

LC business has involved the assessment of applications for licences under the RIHEA, receipt of reports on the information exchange visits and inspections conducted by the inspectors appointed under the RIHEA, the development of procedures and policy including guidance documents, consideration of applications to vary licences, the establishment and maintenance of the public database and the preparation and tabling of reports to Parliament.

The LC has issued 9 licences to date. Four licences permit the use of embryos to derive embryonic stem cell lines; four licences are for improvements in various aspects of ART and one licence is for training embryologists in the techniques of embryo biopsy (see Attachment 1 for more detail). The licences authorise the use of 1735 embryos, 58% of which will be used for research into improvements in ART, 32% will be used to derive embryonic stem cells and 10% will be used to train embryologists.

All licences can be viewed on the public database (http://www.nhmrc.gov.au/embryos/monitor/database/index.htm) in accordance with s.29 of the RIHEA. As required by s.24, the LC has made conditions which regulate the use of the excess ART embryos authorised each of the licences. It has spent considerable time developing the licence conditions to ensure that they provide adequate regulatory control while still being workable for licence holders.

For ease of administration, each licence consists of three parts; the Licence, the Standard Conditions and the Special Conditions. The Licence contains details about the issue and duration of the licence, the name of the licence holder and the title and description of the project. The Standard Conditions contain the conditions which apply to all licences unless explicitly stated otherwise. The Standard Conditions are organised into the following sections:

- requirements for maintaining current contact details;
- reporting requirements with respect to the people who are authorised by the licence to use excess ART embryos;
- reporting requirements with respect to conduct of the project;

- monitoring of licences;
- conditions about the use of embryos including how many may be removed from storage, when they may be removed, the necessity for linking the embryo back to the consent documents, the requirement to record an outcome for each embryo used, and the status of embryos remaining when the licensed activity ceases; and
- the form in which the LC is to be notified that proper consent has been obtained prior to the use of the embryo.

The Special Conditions contain information specific to the individual licences and include:

- the number of embryos that may be used in accordance with s.21(4)(a);
- the specific people who may use the embryos;
- the sites where the embryos may be used;
- any special reporting conditions; and
- any other matters required by the LC.

**Issues to which the Licensing Committee must have regard**

The RIHEA requires that when making decisions whether to issue licences, the LC has regard to a number of issues. These include "*restricting the number of excess ART embryos to that likely to be necessary to achieve the goals of the activity or project proposed in the application*" (s.21(4)(a)) and "*the likelihood of significant advance in knowledge or the improvement in technologies for treatment as the result of the use of excess ART embryos proposed in the application, which could not reasonably be achieved by other means*" (s. 21(4)(b)).

From the beginning of its consideration of applications for licences, the LC has been aware of the tension between these two aspects. The licence must permit the use of sufficient embryos to give a reasonable chance of achieving the goals of the project. There is little value in permitting an experiment to be conducted but preventing the use of the necessary number to give statistical validity to the results. In that case, the requirement to restrict the number of embryos would mean that the LC should not permit the experiment at all. However there is also the requirement not to permit the use of any more than the absolute minimum number of embryos necessary for the project. The LC has always considered both parts of the Act in parallel in order to achieve the necessary balance between these two important requirements.

The words about significant advance in knowledge originated in the NHMRC's *Ethical Guidelines on Assisted Reproductive Technology 1996* (ART guidelines 1996) and were incorporated into the RIHEA unchanged. Where the phrase "significant advance" is used in LC's section of the submission it should be understood as a shorthand reference to the complete concept conveyed in s.21(4)(b). The LC spent considerable time deciding criteria by which it could determine that proposed uses of excess ART embryos would be likely to give a significant advance. These discussions resulted in the guidance document *Advice from the Licensing Committee: Restricting the Number of Excess ART embryos used and Likelihood of Significant Advance in Knowledge or the Improvement in Technologies for Treatment* which is intended to help applicants provide information about the significant advance and number of embryos required (http://www.nhmrc.gov.au/embryos/monitor/application/guide.htm).

The LC considers that the projects for which licences have been issued met its criteria for likelihood of significant advance and that number of embryos authorised were determined with regard to s.21(4)(a) of RIHEA. If the licensed projects are successful, the LC expects that worthwhile

scientific information will be obtained.

**Guidance Documents**

In addition to the advice referred to above, the LC also developed other guidance documents to assist applicants:

- *When is an embryo live or dead?*
- *Advice 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.*
- *Obtaining consent: Stages where declarations or consent forms are required.*

These documents will be discussed further in the context of answers to the questions posed in the LRC Issues paper (see below).

**Communication with Stakeholders**

The LC has always considered that it has a responsibility to communicate with all its stakeholders as much as possible. Information about LC and Secretariat activities in this area are included in Attachment 2.

The NHRMC as a whole and the LC in particular, view consumer participation in decision making and the provision of information as important activities. Both the Secretariat and the consumer representatives on the LC have offered to provide information exchange visits and other opportunities to meet with consumer stakeholders. However, to date, there has been variable success and the LC is committed to continuing its endeavours to engage with these stakeholders.

The LC recognises that many ART consumers find it difficult to make decisions about their excess stored embryos and that if ART consumers are not prepared to donate their excess stored embryos to research then that research could not occur. The therapeutic aim of stem cell research is to alleviate or eliminate many chronic diseases and so the LC regards those groups representing the interests of people with disabilities as vital contributors to its debates. For these reasons the LC considers that information about its processes should be readily available to these stakeholders.

**Other Matters**

The LC issued the first licences 12 months after the Committee was appointed, that is 18 months after the legislation was passed. However, during that time, the LC has been required to concurrently receive applications for licences, develop policy and procedures to underpin the legislation, develop its relationship within the NHMRC structures and engage a community with a heightened expectation of what the implications of regulating embryo research would be. This process has been guided by the broad range of experiences of its Chair and members and the expertise which the NHMRC staff have brought to the process. New legislation, regulating a sensitive and controversial area such as embryo research, inevitably leads to challenges and as well as achievements.

Because there is a strong ethical and human dimension to regulating research involving excess ART embryos, the LC has worked closely with the Australian Health Ethics Committee (AHEC) in developing appropriate policy to complement the legislation. The LC has also been required to administer legislation that on the one hand gives permission to use embryos for research which may result in the destruction of those embryos, and on the other hand that imposes restraints and limitations to the use of such embryos. This has been undertaken within the context being a new

regulatory responsibility of the NHMRC, a body with extensive experience in the area of health research and Australia's premier expert health research body.

Other challenges were as follows:

- The scope of the RIHEA is limited to the use of excess ART embryos which is challenging for two reasons. The first is the public perception that the legislation regulates research involving stem cells when it doesn't, and the second is that when embryos are used for deriving embryonic stem cells, the regulation does not extend to the use of those embryonic stem cell lines;
- The LC has sought to engage with a broad community of interests including the general public. This has been undertaken in a systematic manner with the identification of the research community as a priority. However, some target audiences have been difficult to reach, including consumers.

The LC's achievements demonstrate the way it has handled the challenges presented by the legislation. The LC has developed a thorough and considered process in the absence of established policy, protocols and procedures, which has not been flustered by the expectations of licence applicants. This results from LC's responsibility to ensure that the objectives of the legislation have been met, and may have resulted in perceived delays in the process of approving licences.

The LC's experiences in administering the legislation provide essential information for the LRC's review of the two Acts. It is important that the implications and consequences of any changes to the scope and operation of the legislation are carefully considered.

While nine licences have been issued to date it is too early to analyse the outcomes of the research. There is also uncertainty regarding how many applications may be received in the future.

The remainder of this Appendix provides responses to the questions in the Issues paper and includes specific recommendations where applicable.

## Questions raised in the LRC Issues Paper

### Issues — definitions and terminology (p. 12)

The Legislation Review Committee would therefore like to hear the views of the Australian community on any aspect of the definitions and terminology used in the Acts. In particular:

**Are the definitions of '*human embryo*' and '*human embryo clone*' clear and unambiguous? Do they appropriately reflect community standards? Do they cover all of the activities that should be regulated under the legislation?**

Human Embryo

The LC has not experienced any difficulties with the legal definition of "*human embryo*" and notes that from a legal perspective it works well. However, LC developed guidance at an early stage to clarify "*live*" (see page 42), since this is a key element in determining whether embryos are covered by the provisions of the RIHEA and in carrying out the exempt activity of allowing excess ART embryos to succumb (s10(2)(c)). The LC notes that the definition of "*human embryo*" is broad in the scientific sense and includes most entities which researchers may wish to study.

As, there is tension between the scientific and legal perspectives on the definition of human embryo and in order to inform discussion on this issue, the NHMRC Council requested the LC to prepare a paper on the *Biological Definition of the Human Embryo*. The purpose of the paper was to provide

scientific information about the processes of early human development and to consider whether particular experimental procedures produce entities which would be captured by the biological definition. A draft version of the paper will be made available to the LRC.

**Are other definitions and terminology used in the Acts helpful for understanding and interpreting the legislation? Do they appropriately reflect community standards?**

Refer to Appendix 2.

**Does the legislation need to define stem cells? Is the focus on the use of excess ART embryos sufficient?**

The LC has had limited success in countering the perception that the RIHEA and PHCA regulate stem cells. Given that perception it is ironic that the LC has so little regulatory control over the derivation of embryonic stem cells: The LC's role ceases when the excess ART embryo has been destroyed by the removal of the inner cell mass (see pages 51, 54).

LC considers that if the scope of the legislation changes to include regulation of the use of stem cells then the amended RIHEA would need appropriate definitions to permit their regulation. The exclusive focus on the use of excess ART embryos will no longer be appropriate if it is decided to allow the use of embryos formed by other means. If the current scope is maintained there is no need to define stem cells.

The Committee would also like to hear the views of researchers, ART providers and people who use ART services on the following questions:

**Have there been any problems in interpreting or applying any of the definitions or terminology in the Acts in research or ART practice?**

See above re "*human embryo*" and below for other examples.

**Do you foresee any such problems arising (for example, because of new scientific advances, changing scientific understanding of biological processes, or changes in ART practice)?**

No LC comment

The Legislation Review Committee would also like to hear the views of government on the following question:

**Have there been any problems in interpreting or applying the definitions and terminology used in the Acts?**

<u>Live Embryo</u>

The RIHEA defines a human embryo as a "*live embryo ...*" and the object of the RIHEA is concerned with "*... regulating activities that involve the use of certain human embryos created by assisted reproductive technology*" (s.7). An early issue that the LC had to resolve was when an embryo is considered to be live or dead. If it is a live excess ART embryo then it may only be subjected to activities which are exempt or licensed under the RIHEA. If the activities must be licensed then the LC has a regulatory responsibility towards it. However if the embryo is dead it is outside the scope of the RIHEA and thus outside the LC's regulatory control. The LC developed the following piece of procedural guidance to help applicants and others make this decision:

An embryo is considered to be a live embryo unless:

- When maintained in suitable culture conditions, the embryo has not undergone cell division between successive observations not less than 24 hours apart, or

- The embryo has been allowed to succumb by standing at room temperature for a period of not less than 24 hours (http://www.nhmrc.gov.au/embryos/monitor/application/guide.htm#1).

The Committee deliberately avoided using terms such as "*viable*" and "*non-viable*" or "*suitable for implantation*" and "*not suitable for implantation*" because it considered that there was an element of subjectivity in categorizing embryos according to these descriptions.

Exempt Uses - Transport

Section 10(2) of the RIHEA lists a number of exempt uses of excess ART embryos. Licence holders have asked the LC whether, when conducted in conjunction with a licensed activity, exempt uses such as storage, removal from storage and transport, should be considered as part of the licensed activity. The Explanatory Memorandum to the legislation makes it clear that removal from storage of an embryo that is about to be used for a licensed activity is part of that licensed activity. With respect to transport, LC has advised that transport of excess ART embryos is not part of the licensed use.

Exempt Uses - Thawing

The status of thawing an embryo raised an issue of interpretation. With the exception of storage or transport, all uses of an excess ART embryo, whether exempt or licensed, involve thawing the embryo before anything else can be done. It is unclear whether Parliament intended that thawing of excess ART embryos should be understood to be part of "*removal from storage*" and thus part of an exempt or licensed use depending on the reason for the thawing. This question was raised by several licence holders who were concerned to know if only persons authorised by the licence were permitted to remove and thaw excess ART embryos before their use in licensed activities.

**Recommendation:** The LC recommends that the LRC considers whether the clarity of s.10 of the RIHEA could be improved to remove the ambiguity noted above.

## Issues — prohibited embryos and practices (p. 15)

The Committee would like to hear the view of researchers, consumer groups representing recipients of potential therapies, and others, about these issues. In particular:

**How has the ban on all human cloning affected research in Australia?**

No LC comment

**How have the other prohibitions affected research in Australia?**

No LC comment

The Committee would also like to hear from governments, special interest and community groups (including religious groups), and others, about the overall scope of the prohibitions.

In particular:

**Are the prohibited embryos and practices described in the Act still relevant in light of advances in biotechnology since 2002? Do they appropriately reflect community standards?**

As the regulator, the LC will not express an opinion on whether human cloning should continue to be prohibited in Australia. However, the LC does consider that it would be appropriate to comment on some of the consequences of amending the PHCA.

If Parliament should decide to amend the PHCA to permit cloning for research purposes (or SCNT

or "*therapeutic cloning*") there will be implications for the regulatory system overseen by the LC. If Parliament were to decide to permit cloning for research purposes to develop embryonic stem cell lines (for example, cell lines from individuals with known genetic conditions to provide material for research into the origins and treatment of the conditions), it would introduce a new category of embryos that would need to be regulated in addition to the excess ART embryos already covered by the RIHEA. Such embryos would not be excess ART embryos, as currently defined, but their creation and use would need to be licensed and strictly monitored. Such embryos would need to be defined in the RIHEA and provisions to allow the LC to license and the inspectors to monitor such activities would need to be included in the Act. In addition the PHCA would require extensive amendment.

**Recommendations:** The LC notes that if cloning for research purposes is to be permitted in limited circumstances, a new definition of "*embryo created by cloning*" will be required for the legislation.

If cloning for research purposes is incorporated into the regulatory ambit of the legislation, then appropriate amendments would be required to ensure that the regulatory powers of the LC extend to this area. As outlined above, this should include review of monitoring powers.

**Has the prohibition of payment beyond reasonable expenses (valuable consideration) for gametes and embryos affected access to these items?**

The LC has encountered one example of a potential breach of this provision which may interest the LRC. In 2004, the inspectors investigated an allegation that Reproductive Medicine Albury was intending to conduct commercial trading in human sperm. The progress and outcome of this investigation was included in the Report to Parliament for 1 April 2004 to 30 September 2004.

## Issues — use of excess ART embryos (p. 17)

The Committee would like to hear about the scope and operation of these arrangements from ART providers, consumers of ART services, special interest and community groups (including religious groups), government regulatory personnel, and others. In particular:

**Are the provisions of the legislation with respect to the use of excess ART embryos clear and unambiguous? Do they appropriately reflect community standards?**

Restriction on the use of embryos created since 5 April 2002

On 5 April 2002, COAG agreed on a framework permitting research to be undertaken on excess ART embryos, as outlined below in the extract from the COAG Communiqué:

*Governments agree to put in place a strict regulatory regime under nationally-consistent legislation and administered by the National Health and Medical Research Council (NHMRC) as the national regulatory and licensing body. The NHMRC would issue a licence for a person to use an excess embryo from an ART programme for research or therapy that damages or destroys the embryo. A licence would only be issued where that project has the approval of an ethics committee established, composed and conducted in accordance with NHMRC guidelines, and that the approval is given on a case by case basis that:*

- *there is a likelihood of significant advance in knowledge or improvement in technologies for treatment as a result of the proposed procedure;*
- *the significant advance in knowledge or improvement in technologies could not reasonably be achieved by other means;*
- *the procedure involves a restricted number of embryos and a separate account of the use of each embryo is provided to the ethics committee and the national licensing body;*

- *all tissue and gamete providers involved and their spouses or domestic partners, if any, have consented to research for each embryo used, including by specifying restrictions, if they wish, on the research uses of such embryos; and*
- *the embryo had been created prior 5 April 2002.*

*These regulations will be reviewed within three years.*

*The regulation restricting the use of embryos created after 5 April 2002 will cease to have effect in three years, unless an earlier time is agreed by the Council.*

This framework was implemented through the RIHEA and included restriction on the use of excess ART embryos created on or after 5 April 2002. As agreed by COAG, this restriction ceased to have effect on 5 April 2005 when the sunset clause came into operation.

When the sunset clause came into operation, the LC initiated variations of all current licences to remove references to make them consistent with the RIHEA. The variations were implemented on 27 April 2005.

In April 2004, the LC issued a licence authorising the use of excess ART embryos created after 5 April 2002. This decision was made because the restriction in the RIHEA on the use of embryos created on or after 5 April 2002 relates to uses that damage or destroy the embryo. The LC was satisfied that the proposed use would not damage or destroy the excess ART embryos used, and put in place stringent licence conditions to ensure that the work was closely monitored.

The sunset of the restriction means that the distinction between embryos created before or after 5 April 2002 no longer applies. The section on the potential use of fresh embryos is also relevant to this issue (see below).

**Have any issues arisen with respect to the operation of the legislation (such as with giving and obtaining consent for an embryo to be an 'excess ART embryo'; or giving and obtaining consent from responsible persons for the use of excess ART embryos in research)?**

What activities are permitted by the RIHEA?

The LC had to satisfy itself that it had a correct understanding about which activities Parliament intended should be able to be licensed in accordance with s.21 of the RIHEA. The LC found it relatively simple to decide that projects applying for a licence to use excess ART embryos for "*research*" eg. to test improvements or innovations in ART culture medium, would have the potential to give a "*significant advance*" if carefully designed and carried out. The assessment of such licence applications could then focus on the detail of the proposal.

It was less straightforward to determine whether training or quality assurance activities could be considered to have the potential to provide a "*significant advance*". The LC's decisions with respect to training and quality assurance are discussed in some detail on page 50.

Proper Consent

Applicants experienced considerable difficulties in incorporating the RIHEA requirements for obtaining proper consent into the existing consent procedures used in ART clinics. When the RIHEA was first passed, proper consent had to be obtained in accordance with the ART Guidelines 1996. These guidelines did not provide sufficient information to enable applicants to develop consent processes which were acceptable to the LC. The LC and AHEC developed interim advice to provide guidance to applicants until the ART guidelines 2004 were finalised (see "*Advice 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*" and "*Obtaining consent: Stages where declarations or consent forms are required*"). The interim advice is available on the NHMRC website (http://www.nhmrc.gov.au/embryos/monitor/application/guide.htm). The information was subsequently incorporated into the ART guidelines 2004. Once the ART guidelines 2004 are prescribed by regulation, the interim advice will be rescinded.

The consent process required by the RIHEA is a two stage process: a declaration that embryos are excess to the reproductive needs of the couple concerned, followed by consent from all responsible persons to use of the embryos in a specific project. The inclusion of an explicit declaration that embryos were excess to the reproductive needs of couples was a new step in the consent process for many clinics. In practice it was accommodated by changing the existing decision making processes to include an option for requesting information about possible research or other uses for embryos which couples no longer required for their reproductive needs. However the implementation of a new option in this process was problematic for some clinics, especially in Victoria where consent documents have to be approved by the clinic, its Human Research Ethics Committee, the Infertility Treatment Authority and, in some cases, by legal counsel retained by the ART clinic. Any changes have to be similarly approved. Consequently the process of refining the understanding of the requirements for obtaining proper consent took a long time for both the LC and the applicants.

Responsible Persons

The LC notes the requirement in the RIHEA that, for ART embryos created using donor gametes, proper consent could be required from up to 6 persons (the couple for whom the embryo was created, and the gamete donors and **their** spouses at the time the embryo was created). The unavailability of any one of those responsible persons or their decision not to give consent means that the embryo cannot be used. Licence holders have reported to the LC that the requirement for consent from all responsible persons makes it too difficult to use embryos created with donor gametes or donated to other couples before being declared excess. All licence holders to date request consent only in situations where there are only two responsible persons involved. The consequences of this decision in relation to the number of excess ART embryos that are available for research is not known but the number of excess ART embryos with more than two responsible persons is likely to be small. However, the LC is aware that couples with stored embryos created from donor gametes may see the situation as discriminatory should they wish to donate embryos formed for their use in research.

The Committee and Secretariat have also received two reports about people who have wanted to donate excess ART embryos to research but were unable to do so because one or more of the responsible persons had died. In one case, a woman with embryos in storage died and her parents wished to donate her embryos to research because they felt that by doing so someone might benefit. However because they were not the responsible persons under the Act they did not have the legal right to give consent.

Power of Delegation

The RIHEA does not have any provision for the LC to delegate a decision to the Chair. For example, s.26 of RIHEA gives the Committee the power to suspend or revoke a licence if it believes on reasonable grounds that a condition has been breached. It is clear from the Explanatory Memorandum that Parliament intended this to allow the Committee to "*take immediate action in the event of apparent non-compliance. By suspending or revoking the licence the work can no longer continue*." However, the process of decision making required by the LC takes some time, even if the decision is taken out of session. If the Chair had the power to make a decision on behalf of the Committee in such circumstances and then reported back to the Committee, it would increase public

assurance that the Committee is ensuring strict and prompt compliance with the Act.

**Recommendation:** The LC recommends that the Chair should be able to make decisions on behalf of the entire Committee in situations where a rapid response is necessary.

In addition, the activities of the inspectors are under the direction of the Chair of the Committee. If the Act or regulations allowed for the designation of another Committee member as Deputy Chair and made provision to delegate the Chair's powers, the inspectors would be better able to conduct their activities in the absence of the Chair.

**Recommendation:** The LC recommends that the RIHEA should be amended to allow the Chair to delegate functions or powers to a Deputy Chair under certain circumstances.

Requirements for Submitting Applications

When the LC was considering early licence applications and simultaneously developing policy and procedures, its activities were slowed by misunderstandings about the information required in applications. The LC engaged in extensive consultation and repeated rounds of question and answer in order to obtain the information it required to make a decision. Members of the LC and Secretariat also visited applicants to discuss the applications more efficiently. These activities all contributed to the perception that the LC was slow to make decisions. However, it also demonstrated the LC's willingness to communicate with applicants to help them improve their applications and its determination to observe all the requirements of the RIHEA.

Potential Use of Fresh Embryos

When the RIHEA was first passed, all the embryos that could be used for licensed activities had been frozen because of the requirement that all excess ART embryos used for activities that could damage or destroy them must have been created before 5 April 2002. With the sunset of the 5 April 2002 provisions, the LC has been considering how and under what circumstances embryos that have not been cryostored could be used for activities licensed under the RIHEA.

The consent process developed by the LC and AHEC cannot be applied to the use of fresh embryos. The critical aspects of the consent process are the declaration that embryos are excess to the reproductive needs of the couple concerned and the separate provision of information about and consent to a specific research project. It is important that the information about the research project is provided by a person who is not involved in the clinical care of the couple and that the information is provided as an oral explanation supported by written information which can be taken away and considered before the consent form is signed[1] . The joint advice (see reference above in the Introduction to this Appendix) introduced a cooling-off period before the consent is acted on. This has been included in the ART guidelines 2004 which state that "the consent of the persons responsible to a use that will damage or destroy an embryo must not be acted upon until a suitable fixed period of time for reconsideration has been allowed, normally at least two weeks after their consent to such research."

Two possible examples of applications to the LC involving the use of fresh excess ART embryos are:

- use of PGD to determine which embryos do or don't carry a particular genetic condition. The couple concerned have considered which embryos (affected or unaffected, depending on

[1] In some situations the information may need to be provided in a different form, better suited to the needs of the couple concerned (refer to National Statement. Note that the National Statement is currently being revised.)

the test) will be implanted or cryopreserved[2]. Consequently these embryos could be considered to be excess to the reproductive needs of the couple.

- embryologists determine that, based on observation and experience, particular embryos are not suitable for implantation or cryopreservation. Such embryos would usually be allowed to succumb.

In relation to these scenarios, there may be difficulties in developing consent processes which provide a suitable cooling-off period within the 3-4 days between determining that the embryo is unsuitable for implantation and the proposed research.

Given the requirement for a normal cooling-off period of two weeks, AHEC and LC are considering this matter in more detail.

In relation to the possible use of fresh embryos, the 5 April 2002 provisions were included specifically to prevent the creation of embryos for research, pending implementation of the ban in the PHCA on the creation of embryos for any purpose other than achieving pregnancy.

Variations and new licence applications

Section 25 of the RIHEA contains the provisions for varying licences. The LC has developed procedures for dealing with requests from licence holders for variations of an administrative nature such as changes to authorised staff members or changes of address and minor changes to the activity authorised by the licence. The LC has also developed a process for implementing variations which it has initiated (eg. extension of the period of the licences and sunset of 5 April 2002 restrictions). In this situation the LC agrees on the required change and develops new licence conditions in consultation with NHRMC's legal advisors. The LC then informs licence holders affected by the variation of the proposed change and gives them an opportunity to comment. After consideration of any comments, the LC then proceeds to vary the licence and licence holders are officially advised of the variation. Whenever a variation leads to a change in the licence documents, the new versions are placed in the public database as required by s.29 of RIHEA.

The consideration of applications to vary licences has been a substantial component of the LC's work during the past year. Half of the variations have been administrative changes to staff, addresses or duration of licence. Other variations were made after the sunset of the 5 April 2002 restrictions. The remaining applications have requested changes to the approved project. In response to these applications, the LC is developing policy on what can reasonably be considered to be a variation to the nature of the licensed activity and what should be the subject of a new licence application. When it has reached a decision the criteria will be published on the website.

Suspension or Revocation of Licence

The LC may only suspend or revoke a licence if there are reasonable grounds to believe that there has been a breach of a condition (s.26(1)). The LC does not appear to have the power to suspend or revoke a licence for any other reason and it is requesting legal advice to confirm or refute this conclusion. However, it is conceivable that a situation may arise where the LC considers it necessary or desirable to reconsider its decision to issue a licence. For example, if the LC were to become aware that the licence was issued on the basis of inadequate, incorrect or fraudulent information provided by the applicant and that information was such that the LC would have made a different decision had the information been received before the licence had been issued then the LC would wish to reconsider the decision to issue the licence. Currently the LC has no powers to

[2] A sub-category of these embryos is those female embryos identified as being carriers of an X-linked disorder but only male offspring of the female embryos would have the condition. The female embryos themselves would not.

suspend or revoke the licence in such a situation because a licence condition has not been breached.

**Recommendation:** Consequently the LC recommends that s.26(1) be amended as follows:

> *The NHMRC Licensing Committee may, by notice in writing given to the licence holder, suspend or revoke a licence if the Committee believes on reasonable grounds that it is necessary or desirable to do so.*

#### Are the arrangements for accreditation and ethical oversight of ART centres appropriate?

The LC regulates the use of excess ART embryos which is a small aspect of the total activity relating to ART in Australia. It has no regulatory role in the clinical practice of ART and relies on the integrity of doctor/patient relationships and the voluntary regulatory system administered by the Reproductive Technology Accreditation Committee of the Fertility Society of Australia to prevent the creation of embryos for research. In addition, three states have legislation regulating the use of ART. The LC will not comment further on this.

It may be of interest to the LRC to know that the Human Embryology and Fertility Authority of the UK regulates both ART treatment and research using human embryos. Also, from April 2006, all ART procedures and clinics in the European Union (EU) will be required to comply with the EU Tissues and Cells Directive. IVF clinics in Australia will also be subject to increased regulation (including compliance with the code of Good Manufacturing Practice) through the TGA because ART will be included in the Biological Therapies proposal.

## Issues — licensing and statutory arrangements (p. 20)

The Committee would like hear about the operation of the licensing system from all those involved in licensing arrangements, including government regulatory personnel (Australian, State, Territory), the Licensing Committee, researchers who have applied for a licence, human research ethics committees, ART providers, users of ART services, and others.

As noted in the LRC Issues Paper, corresponding state legislation has been passed in all States and Territories except the Northern Territory. Thus with the exception of the Northern Territory, the intended system of national regulation is now in place. Although States and Territories have taken different approaches with their legislation there have not been any practical difficulties to date because each jurisdiction has agreed for inspectors appointed under the Commonwealth legislation to monitor compliance with State and Territory legislation as well. In some cases the LC is developing formal Memoranda of Understanding with State authorities, in others there is an informal agreement about the roles and responsibilities of each party.

In Victoria, the Infertility Treatment Authority was required to modify its consent procedures in relation to declaring embryos to be excess in response to the requirements of the RIHEA and LC.

#### Have researchers or ART providers experienced any uncertainty about when to apply for a licence?

The LC and its Secretariat have endeavoured to provide certainty and clarity to potential applicants by offering information exchange visits (see below), full documentation, guidance documents and have made a practice of providing verbal and written assistance to applicants as quickly as possible.

The LC has not received any new applications for licences since October 2003. The LC attributes this to a combination of factors:

- The perception that the Committee is slow to make decisions. However as already stated, the Committee was simultaneously developing all its policies and procedures in a new area of regulation and was determined to develop a consistent and workable system.

- Some groups may be waiting for the LRC to present its report to Parliament
- Availability of excess ART embryos. It is difficult to obtain accurate information about the number of embryos which will be donated to activities regulated by the RIHEA. The COAG communiqué of 5 April 2002 requested that the NHMRC report to COAG on the adequacy of supply and distribution of excess ART embryos for research. The report was provided to COAG as requested but COAG has not released the information publicly. The LC wishes to collaborate with the National Perinatal Statistics Unit of the Australian Institute of Health and Welfare and with the Fertility Society of Australia to increase the information made available in the NPSU reports on ART (*Assisted Reproductive Technology Series*). LC proposes that more data about the fate of frozen embryos are collected and published. These data could then inform debate about the rates of donation to research, other couples etc.

At this stage the LC does not know how many more licence applications to expect.

**Have there been any difficulties of interpretation or application of the criteria for granting a licence?**

Training and Quality Assurance

As noted in the introduction to this Appendix, LC has spent much time discussing what can be considered to be a "*significant advance*". LC has considered this matter in relation to an application for training of embryologists in the technique of embryo biopsy. It is apparent from the Explanatory Memorandum that Parliament considered training to be an acceptable use of excess ART embryos provided all the requirements of the RIHEA could be satisfied. Consequently, the Committee has issued a licence for training embryologists and expects that there may be a need for additional training licences in the future.

It was difficult for the LC to obtain objective information about the number of live excess ART embryos required to adequately train an embryologist in the technique of embryo biopsy. The LC consulted with experts both in Australia and overseas before issuing its policy in this area. It decided that training using live excess ART embryos would only be permitted under strict criteria which can be seen at http://www.nhmrc.gov.au/embryos/monitor/application/index.htm. Briefly, embryologists may be trained in embryo biopsy using embryos under a training licence only if they are explicitly approved by the LC to so, they have not previously used live embryos for training in embryo biopsy and they provide details of their qualifications and experience. The ART clinic is also required to explain why it needs to have additional staff trained in the technique. The LC has imposed a limit on the number of embryos that each trainee may use.

The situation is less clear with respect to the use of excess ART embryos for quality assurance activities. Although quality assurance is included in the Explanatory Memorandum as an activity which is permitted by the RIHEA, the LC has not fully resolved its views on it. The LC has not yet needed to make a decision but will do so if it considers applications for quality assurance activities. The LC treats all applications on their individual merits and so would carefully consider any quality assurance applications submitted to it. Any applications for licences for training or quality assurance activities are assessed according to the requirements of s.21 of the RIHEA.

Adequacy of HREC consideration of applications

HRECs appear to have experienced some difficulties in understanding and performing their role in the consideration and approval of applications for licences. In some cases it appeared that the HRECs had not considered all the aspects they were required to, or, if they had considered them, had not provided sufficient information to LC about their decision making. LC engaged in dialogue and correspondence with HRECs to address these difficulties and the inspectors have invited HREC members to be present at their monitoring activities in order to reduce confusion about HREC

members' roles (see the comments from AHEC in Appendix 2 also).

Issue of licences to joint licence holders

Although some applications were submitted by two collaborating organisations, the LC was only able to issue licences to a single organisation – the organisation on whose premises the embryo would be damaged or destroyed. For example, in two of the licences for stem cells, the licence has been issued to the ART clinic alone because that is where the inner cell masses are isolated from the embryos. However within a few days the resulting cultures of embryonic stem cells are taken to the premises of collaborators in the research project because researchers there have the expertise and/or equipment to maintain and propagate the cells until they are established cell lines.

This presents a difficulty when the LC is determining whether an activity will give a significant advance. It also presents a monitoring and compliance issue. Collaborations between two or more groups or organisations are a reality of scientific research but under the RIHEA, the inspectors' powers relate to licence holders only and various administrative arrangements may be required to ensure that inspectors are able to monitor the whole sphere of collaborative activity. As explained in more detail later (see Assessing effectiveness of licences for achieving stated goals) the LC had difficulty writing conditions that provide adequate regulation of the whole project.

Because regulatory control relates to the use of the embryo (and not to steps that occur after the embryo has been used), the LC has had to put in place sometimes complex administrative arrangements to ensure appropriate oversight of work being undertaken across different organisations. This has been most evident with some of the licences involving the development of embryonic stem cell lines, where the use of the embryo and initial isolation of stem cells occurs in one organisation and development of the cell lines occurs in a second organisation. One avenue to address this is to provide for the capacity to have joint licence applicants and holders, to confer the obligations for the provision of information and reporting on all organisations involved.

**Recommendations:** LC recommends that the RIHEA be amended to allow it to issue licences to joint licence holders and to monitor them appropriately.

Should the scope of the legislation be broadened to incorporate cloning for research purposes, the LC would also recommend a similar provision to address the inevitable issue of research partnerships across legal entities.

#### Are the monitoring and compliance requirements of the Act appropriate?

Monitoring Compliance with the RIHEA and the PHCA

The inspectors appointed in accordance with the RIHEA are required to monitor compliance with both Acts (s.33 and s.41, RIHEA) on behalf of the LC, although the majority of their activities concern licences issued under the RIHEA. The inspectors have developed a comprehensive set of procedures which have been provided to the LRC and an ongoing inspection plan. They also provide information and education to individuals and organisations affected by the legislation and encourage a culture of cooperative compliance.

Information exchange visits are provided to a variety of stakeholders including applicants, potential applicants, researchers in related fields (eg. animal cloning), HRECs, and consumer and community groups. The inspectors tailor the information they include to the particular needs and interests of the recipients. Information exchange visits may be arranged at any time. The goal of these visits is to provide information and advice. To date, there have been more than 30 visits to stakeholders in all States except the Northern Territory.

Records Audit Inspections are conducted by inspectors within four weeks of the issue of a licence. The inspectors assess the licence holder's ability to comply with the legislation and the licence conditions. Record Audit Inspections have been conducted on each licence issued to date.

Monitoring inspections occur at least annually during the period of the licence. The inspectors monitor compliance with all licence conditions and statutory requirements. They also trace the records of randomly selected excess ART embryos from patient records through to the records of the outcomes of the use of each embryo. It should be noted that licence holders are not informed in advance which embryos will be traced. To date, inspectors have performed at least one monitoring inspection of each current licence holder.

Final inspections will occur on or immediately prior to the expiry date of a licence. The inspectors will provide advice about the final report which must be submitted to the LC and ensure that licensed activities will not continue after the expiry of the licence. Inspectors will also ensure that licence holders have processes in place to meet their obligations with respect to any excess ART embryos remaining in storage where consent has been obtained for the licensed activity which has now ceased (see Standard Condition 4201 discussed below).

Inspectors may conduct additional inspections at any time if required. The licence holder may or may not be informed in advance depending on the circumstances. Such inspections occur at the direction of the Chair of the LC and may be in response to media releases from licence holders about particular achievements and successes in their licensed activities or in response to other information obtained by the LC or its Secretariat. If the LC or inspectors become aware of a possible non-compliance, an investigation is carried out under the direction of the Chair of the LC. The Chair may also direct the inspectors to conduct unannounced inspections of a licence holder.

The LC has agreed the following with respect to unannounced inspections:

- under the terms of the existing Act, inspectors have the power to undertake unannounced inspections;
- any unannounced inspections must be undertaken at a reasonable time, and inspections of the premises of a licence holder should not disrupt any clinical treatments in progress at the time of the inspection; and
- the current procedures used by inspectors during monitoring inspections would be used during unannounced inspections. Alternative compliance procedures would only be implemented where there were demonstrated reasons for doing so.

The LC views unannounced inspections as more serious than the other types of inspection and they will only be used if circumstances warrant it.

To date, with the exception of two non-compliances, all licence holders have been found to be acting in compliance with the requirements of the RIHEA and the PHCA and with the conditions of their licences. The LC also noted that all licence holders have cooperated fully with the inspectors in all inspections.

Currently, the LC has responsibility for monitoring compliance with the PHCA, but its powers are limited if the organisation is not a licence holder. That is, NHMRC inspectors have the power to enter and inspect the premises of licence holders, but if the organisation is not licensed then entry and inspection can only be undertaken with consent from the occupiers of the premises. Inspectors only have powers to enter licensed premises if the entry is at a reasonable time (RIHEA, s. 35).

**Recommendation:** The LC recommends that the LRC review the adequacies of inspectors' monitoring powers with respect to investigating breaches of the legislation by organisations that are

not licensed.

**Are there any other issues relating to the operation of the licensing system?**

Appointing Replacements to Licensing Committee

The LC considers that the statutory categories of expertise (s.16, RIHEA) have provided a balanced committee with the expertise to consider and prepare advice and decide on the applications. The work of the LC has been hampered by the time taken to appoint replacement members when sitting members have resigned during the NHMRC triennium. This is a result of the complex requirements of the RIHEA in relation to making appointments to the Committee.

**Recommendation:** The LC recommends that the LRC considers a more efficient way to appoint replacements to the LC.

Number of Embryos

Determining the number of embryos permitted to be used is an important decision made during the LC's assessment of a licence application. The Special Conditions of each licence specify the maximum number of excess ART embryos that may be used in that licence. In each case, the number has been determined by taking several factors into account. The balance between the number of embryos and the significant advance described in the introduction is critical but, in addition, not all embryos survive thawing and, even if they do survive, not all will necessarily be suitable for the licensed activity. The LC used the available literature, overseas studies and survival rate statistics from the clinics supplying embryos for particular licences when determining how many additional embryos were likely to be needed to provide sufficient suitable embryos for each project. Some licences specify that up to a total number may be thawed in order to obtain the number required for a statistically valid experiment. If the survival rates are higher than expected not all the embryos will be required and once the stated goals of the project have been achieved, no more embryos may be removed from storage. In other cases the applicants incorporated their knowledge of survival rates into their justification for requesting a particular number of embryos. In these cases licences only state a single number of embryos. The restriction that no more embryos may be removed from storage once the goals of the project have been reached still applies.

Status of Unused Embryos

As stated in the discussion on number of embryos, some projects may achieve their goals without using all the embryos licensed to the project. In addition, some projects may terminate early for reasons unconnected with the science of the project. Therefore, the LC decided that it was necessary to develop a condition to cover the status of any unused excess ART embryos at the end of a licence or project. The LC developed a new standard condition (4201) to cover this situation. This condition was implemented as a variation to all licences in April 2005.

Responsible persons give consent for their excess embryos to be used in a specific project. If the embryos are not used the consent becomes ineffective and the embryos cannot be used for another project without going back to the responsible persons to request consent for that new project. Thus the condition requires that the licence holder must transfer unused embryos back to the ART clinic they came from, or, if the licence holder is also the ART clinic, approach the responsible persons for new consent. Of course, the responsible persons are free to decide that they do not wish to give their consent for a new project. In this case, they may decide that the embryos will be allowed to succumb.

**Recommendation:** The LC recommends that the LRC consider whether the status of excess ART embryos unused at the end of a licence or project needs to be covered by the RIHEA rather than by

administrative processes such as a condition of licence.

Assessing Effectiveness of Licences for Achieving Stated Goals

It is important for the LC to be able to evaluate the effectiveness of the licences issued particularly with respect to the likelihood of significant advance and the minimum number of embryos. It is difficult for the LC to gather this information when its regulatory role is limited, particularly when control of the outcome passes from the licence holder to a third party. For example, the LC would like to know how many stem cell lines result from the number of embryos authorised for use in each of the stem cell licences. It has been difficult to include conditions in the licences that require licence holders to get the information from third parties and forward it to the LC. In one licence, the LC made supply of additional inner cell masses to the third party dependent on the licence holder receiving reports of the progress made with cells from embryos used earlier. In this way the licence holder can monitor progress towards the goals of the project and remain in compliance with the licence conditions.

At this stage when the first licenses issued have only been operating for 16 months, it is too early to gauge the effectiveness and success of the licensed activities.

**Recommendation:** In an attempt to gain more information about the success and effectiveness of the licences, the LC recommends that it have the power to require a mandatory report from the licence holder within 12 months of the licence's expiry because this would help them obtain more information about the achievements of each licensed use of excess ART embryos.

## Issues — international exchanges of embryos and stem cell lines (p. 22)

The Committee would like to hear from ART providers, users of ART services, government regulators, and others, about import and export of embryos and stem cell lines. In particular:

**How have the import and export prohibitions (including the amendments to the Customs Regulations) affected the operation of ART centres, the access to reproductive materials by users of ART, or donation of reproductive materials by donors?**

No LC comment

**How has the legislation (including the Customs Regulations) affected stem cell research activities?**

No LC comment

## Issues — national stem cell bank (p. 23)

The Committee would like to hear from researchers and others with an interest in stem cell issues, about the applicability of setting up a national stem cell bank in Australia. In particular:

**Who would use a national stem cell bank in Australia?**

No LC comment

**What would be the advantages of an Australian stem cell bank?**

No LC comment

**Do Australian researchers have appropriate access to stem cell banks in other countries (such as the UK Stem Cell Bank)?**

The recently established UK Stem Cell Bank has already accepted two embryonic stem cell lines derived in Australia (see http://www.biotechnology.vic.gov.au/news/article.asp?id=236). The UK

Stem Cell Bank will provide the stem cell lines to approved researchers under controlled conditions (http://www.ukstemcellbank.org.uk). Acceptance of the stem cell lines recognises that the regulatory regime implemented by the LC, under the RIHEA, meets international standards.

### Issues — research developments (p. 24)

The Committee would like to hear from ART researchers, users of ART services, and others, about developments in human embryology.

**Has the access to excess ART embryos for research allowed a significant advance in knowledge and technology in ART?**

It is too soon to comment on this because the first licences issued have only been operating for 16 months. In accordance with s.24(1)(b) of the RIHEA, licence holders have reported to the LC that they have obtained consent to use 223 embryos. The LC monitors actual use of embryos through the 6-monthly reports from licence holders which are due by 30 April and 31 October each year.

**What are the next steps in the research? What are the potential benefits of the research? What are the potential risks?**

No LC comment

The Committee would like to hear from stem cell science and cellular therapy researchers, consumer groups representing potential recipients of stem cell therapies, and others, about developments in these areas. In particular:

**Have the advances in stem cell research been greater or less than expectations in 2002?**

See general comment above with respect to advances in knowledge for ART.

**Has the access to excess ART embryos for research allowed a significant advance in knowledge in this area?**

Sydney IVF has reported that they have established one embryonic stem cell line and Melbourne IVF in collaboration with Stem Cell Sciences Pty Ltd have reported that they have established two cell lines since their licences were issued last year (see above).

**What are the next steps in the research? What are the potential benefits of the research and when might these occur? What are the potential risks?**

Researchers have asked whether the LC would issue licences to derive stem cell lines from embryos with known genetic conditions (eg conditions detected by PGD). This relates to the request for permission to use fresh embryos and is under consideration by the LC (see above).

## Other terms of reference

### Scope of the Legislation

The public perception is that the RIHEA and PHCA regulate stem cells but this is not correct. The LC is responsible for regulating the use of excess ART embryos in activities including research (eg improvements in ART clinical practice and derivation of stem cell lines), training and quality assurance (see Explanatory Memorandum for RIHEA). The regulatory role of LC ceases when the licensed activities are completed.

Basic research using embryonic stem cell lines is not regulated in Australia. Once the embryos have been destroyed to obtain the inner cell masses, the next stage where use of embryonic stem cells would be regulated is when researchers have developed a potential treatment they wish to test

in a clinical trial. At that point GTRAP and the TGA become involved. The TGA is responsible for regulating Australia's medicines, medical devices, blood, tissues and chemicals (see http://www.tga.gov.au). The TGA is developing a regulatory framework for cell and tissue therapies used for clinical treatment. The use of stem cells for treatment would fit into this regulatory framework (http://www.tga.gov.au/bt/prtisreg_sum.htm). One of TGA's tasks is ensuring that all medicines, medical devices, blood, tissues and chemicals are produced in a way that complies with the Code of Good Manufacturing Practice. The production of new embryonic stem cell lines under GMP conditions is a precondition of developing clinical treatments using stem cells. The production of GMP-quality stem cells is one of the goals of several of the stem cell projects currently licensed under the RIHEA.

**The implications of cost recovery**

Any consideration of cost recovery should take into account the principles outlined in the Productivity Commission report Cost Recovery by Government Agencies (http://www.pc.gov.au/inquiry/costrecovery/finalreport/index.html).

## Conclusions

**Achievements**

The LC considers that in the three years since the RIHEA and PHCA were passed, it has made significant achievements. It has established a framework for fulfilling its responsibilities under the two Acts. It has issued 9 licences and dealt with many variations to those licences. It has developed necessary policies and procedures in an entirely new regulatory area. It has developed guidance documents to provide advice to applicants. It has established a strong and workable system for monitoring compliance with the Acts. It has collaborated with AHEC to finalise the ART guidelines 2004 so that potential licence holders have necessary information about how to conduct their activities in accordance with the required ethical standards. It has promoted a positive and helpful information exchange process to prospective licence holders and stakeholders.

The LC has identified a number of issues and made a number of recommendations under the broad headings identified below.

**Scope of the legislation**

Currently, the LC has responsibility for monitoring compliance with the PHCA, but its powers of inspection are limited if the organisation is not a licence holder. That is, NHMRC inspectors have the power to enter and inspect the premises of licence holders, but if the organisation is not licensed then entry and inspection can only be undertaken with consent. The LC recommends that the LRC review the adequacy of inspectors' monitoring powers, with respect to investigating possible breaches of the legislation by organisations that are not licensed.

If cloning for research purposes is incorporated into the regulatory ambit of the legislation, then appropriate amendments would be required to ensure the regulatory powers of the LC extend to this area. This should include review of monitoring powers.

**Public perceptions and expectations**

The LC considers that it has been challenged by the public perception that the RIHEA regulates research involving stem cells. However, the LC's consideration of applications to use excess ART embryos to derive embryonic stem cell lines has by necessity included consideration of how research using the stem cells resulting from the licence will contribute to advances in knowledge.

Any revision to the legislation should be accompanied by a communication strategy which addresses the full scope of the legislation and its purpose and intent.

The LC considers that the reports to Parliament, the public database and its communication strategy have been important for providing transparency about the work of the LC and for educating stakeholders about the requirements of the Acts.

**Scientific and Clinical Expertise**

Section 21 of the RIHEA requires the LC to have regard to a number of matters in deciding whether to issue a licence. If the Act is broadened to incorporate the regulation of embryos formed through cloning for research purposes for the development of stem cell lines, then the expertise of the LC (as outlined in s.16 of the RIHEA) will need to be broadened to enable the LC to fulfil its responsibilities.

The sunset of the requirement that only excess ART embryos formed before 5 April 2002 could be used for activities which would damage or destroy them has resulted in discussion about how the requirements of s.21 and the provisions relating to proper consent can be applied to the use of fresh embryos. The LC and AHEC have commenced processes to consider the scientific, legal and ethical aspects of this issue.

Some scientific and clinical evidence suggest that ART embryos created since April 2002 have a much greater chance of survival following thawing and a much greater capacity to develop into embryonic stem cell lines. This suggests that the objectives of the Act in relation to minimizing the use of embryos for the purposes of research may be met more easily by utilization of such embryos. Additional scientific and clinical advice on this point is required.

The LC endorses the proposal in the NHMRC submission that groups are set up within the NHMRC with the task and expertise to consider the clinical, scientific, regulatory and ethical implications of new discoveries and technologies in areas related to the RIHEA and PHCA. The LC also intends to explore the possibility of developing links to similar groups in other countries.

**Administrative and Licensing Issues**

While acknowledging that the current legislation provides an adequate and workable framework for its activities, the LC makes the following recommendations for amendments which would improve clarity or regulatory control:

- Because regulatory control relates to the use of the embryo (and not to the steps that occur after the embryo has been used), the LC has had to put in place sometimes complex administrative arrangements to ensure appropriate oversight of work being undertaken across different organisations. This has been most evident with some of the licences involving the development of embryonic stem cell lines, where the use of the embryo and initial isolation of stem cells occurs in one organisation and development of the cell lines occurs in a second organisation. One avenue to address this is to provide for the capacity to have joint licence applicants and holders, to confer the obligations for the provision of information and reporting on all organisations involved.
- Should the scope of the legislation be broadened to incorporate cloning for research purposes, a similar provision would be recommended to address the inevitable issue of research partnerships across legal entities.
- The LC recommends that the LRC considers whether the clarity of s.10 of the RIHEA could be improved to remove the ambiguity with respect to removal from storage and thawing.

- The LC recommends that the Chair should be able to make decisions on behalf of the entire Committee in situations where a rapid response is necessary.
- The RIHEA should be amended to allow the Chair to delegate functions or powers to a Deputy Chair under certain circumstances.
- The LC recommends that s.26(1) be amended to permit the LC to suspend or revoke a licence in circumstances other than a belief that a licence condition has been breached.
- The LC recommends that the LRC considers a more efficient way to appoint replacements to the LC.
- The LC recommends that the LRC consider whether the status of excess ART embryos unused at the end of a licence or project needs to be covered by the RIHEA rather than administrative processes such as a condition of licence.
- The LC recommends that the LRC consider to what extent the LC should be able to obtain information about the longer term outcomes of licensed activities, for example by requiring an additional report within 12 months of the expiry of the licence.

## *ATTACHMENT 1– Licences Issued to 31 August 2005*

**Sydney IVF Limited**

On 16 April 2004 the LC issued Sydney IVF Limited with four licences to use excess ART embryos.

**309701 Improvement in Laboratory Conditions for Embryo Culture**

The licence authorises research directed at improving the success rates of ART procedures. Researchers at Sydney IVF will use up to 670 excess ART embryos to test the effects of a variety of culture conditions on embryo growth. These studies are observational. In order to minimise the total number of excess ART embryos used in research at Sydney IVF, embryos used in these observational studies will, if suitable, also be used in the research authorised by licences 309702B or 309703. The proposed experiments require 512 embryos to achieve a statistically valid outcome. Once 512 embryos have survived thawing and been included in the growth studies, Sydney IVF is not permitted to thaw any more embryos.

**309702A - Effect of an Additive on Embryo Culture: Analysis of Growth and Epigenetic Programming**

The licence authorises research directed at improving the success of ART procedures by using excess ART embryos to study the effects of a particular additive in the culture media. Persons authorised by the licence will observe the effects of the additive on embryo growth and then analyse the resulting changes in gene expression. Sydney IVF may use up to 170 embryos in this licence. The proposed experiments require 128 embryos to achieve a statistically valid outcome. Once 128 embryos have survived thawing and been included in the growth studies, Sydney IVF is not permitted to thaw any more embryos.

**309702B - Development of Methods for Preimplantation Genetic and Metabolic Evaluation of Human Embryos**

The licence authorises Sydney IVF to undertake research into developing and improving methods for determining the genetic characteristics of ART embryos. These methods include chromosomal analysis and detecting specific gene mutations and polymorphisms. Analysis of these characteristics will provide new information about embryo metabolism, the way parental DNA affects embryo development and how these processes affect the success of ART pregnancies. Some of the excess ART embryos used in this project will have been used in the research authorised by licence 309701 before being used in the research authorised by this licence. A total of 255 embryos may be used in this licence.

**309703 - Development of Human Embryonic Stem Cells**

The licence authorises Sydney IVF to attempt to isolate human embryonic stem cells from 50 existing excess ART embryos for use in research into the diagnosis and treatment of human diseases. Thirty-five of the excess ART embryos used for this project will have been used in the research authorised by licence 309701 before being used in the research authorised by this licence. The remaining 15 embryos may be thawed specifically for use in Licence 309703. Licences 309702A, 309702B and 309703 have subsequently been varied to permit Sydney IVF to transfer up to 20 inner cell masses from licence 309702A or 309702B into licence 309703 in order to attempt to derive additional embryonic stem cell lines.

**Melbourne IVF Pty Ltd**

On 16 April and 11 June 2004, the LC issued Melbourne IVF Pty Ltd with two licences, including one collaborative project with Stem Cell Sciences Pty Ltd.

**309704 - Development of testing procedures for unbalanced chromosome errors in human embryos (issued 16 April 2004)**

The licence authorises use of excess ART embryos to validate tests to detect unbalanced chromosome errors. With this type of testing, Melbourne IVF aims to improve the ART success rates for couples with specific types of infertility which would otherwise cause recurrent miscarriage. Melbourne IVF is authorised to use up to 120 excess ART embryos during the course of the licence.

**309709 - A collaborative project between Melbourne IVF Pty Ltd and Stem Cell Sciences Pty Ltd to derive Human Embryonic Stem Cell Lines (issued 11 June 2004)**

The licence authorises a collaborative research project between Melbourne IVF Pty Ltd and Stem Cell Sciences Pty Ltd. Melbourne IVF is authorised to isolate the inner cell mass from up to 200 excess ART embryos to enable Stem Cell Sciences to attempt to establish six embryonic stem cell lines under improved and defined culture conditions. Resulting cell lines will be studied to determine their genetic characteristics, the best conditions for their continued growth, and how to direct their differentiation into specific cell types.

**IVF Australia Limited - 309708 – Derivation of Embryonic Stem Cell Lines**

On 5 November 2004 the LC issued IVF Australia Limited with a licence to use excess ART embryos in a collaborative project with the Diabetes Transplant Unit, Prince of Wales Hospital. The licence authorises IVF Australia to isolate the inner cell mass from up to 100 excess human ART embryos in order to establish six embryonic stem cell lines for research into the treatment of diabetes. The Diabetes Transplant Unit is responsible for the growth and maintenance of putative cell lines once the inner cell masses have been isolated from the excess ART embryos.

**Monash University - 309707 - Derivation of Embryonic Stem Cell Lines From The Human Embryo**

On 21 December 2004 the LC issued Monash University with a licence to use excess ART embryos to derive 20 embryonic stem cell lines with improved properties relative to existing cell lines. This licence authorises the use of up to 200 embryos. These improved properties include enhanced stability, greater capacity to differentiate and freedom from contamination by animal products.

**Monash IVF Limited - 309700 - Training in The Techniques Of Embryo Biopsy**

On 11 March 2005 the LC issued Monash IVF with a licence to use up to 175 excess ART embryos to train personnel in the technique of embryo biopsy, which is used in preimplantation genetic diagnosis (PGD). Considerable training is required to ensure that PGD is undertaken safely and effectively. PGD is a complex technique and it is important to ensure that embryos are not damaged when PGD is used as part of the ART treatment of a woman. The licence limits the number of embryos that can be used to train each embryologist.

## *ATTACHMENT 2- Licensing Committee communication with stakeholders*

The LC has always considered that effective communication with stakeholders is an important part of its role as the regulator under the RIHEA and PHCA. It has repeatedly stressed the importance of building understanding of and confidence in the Committee's activities. The activities listed below demonstrate the Committee's commitment to presenting the work and views of the LC.

In addition to the Information Exchange Visits conducted by the inspectors (see above), the LC and its Secretariat have carried out the following activities during the Committee's period of operation:

- Developed a Communication Plan to guide activities with respect to stakeholders.
- The Chair of the LC has spoken on behalf of the LC at numerous meetings and conferences since the Committee's inception. Examples include - "Reprogenetics: Whose rules apply?", a symposium held in Melbourne in November 2004. (Professor Chalmers and Dr Szoke also spoke at this meeting.); the Stem Cell Symposium in February 2005; the GTRAP workshop "Emerging Issues in Stem Cell Research" (May 2005), visits to organisations such as the Diabetes Transplant Unit and the National Stem Cell Centre.
- Other members of the LC have been requested to speak to a variety of community and consumer groups.
- Members and Secretariat staff have visited most applicants during the assessment of their applications. These visits have greatly improved the effectiveness and efficiency of the assessment process by providing opportunities for discussion and faster resolution of problems with the applications.
- Published two Bulletins (hard copy and website) which provide information to community and consumer groups and interested members of the public about the Committee's activities (see http://www.nhmrc.gov.au/embryos/information/reports/index.htm#2).
- Professor Campbell and Secretariat staff ran a training workshop for HREC members interested in research using excess ART embryos as part of the NHMRC's "Ethics in Human Research Conference" in May 2005.
- Information booth at Fertility Society of Australia conferences. In 2004 and 2005, Secretariat has staffed a booth at this annual conference to provide information and make contact with clinical staff and scientists in ART.
- Secretariat has always been conscious of its responsibility to provide accurate and timely advice to the LC and to the Committee's stakeholders. It is aware that stakeholders may not think that it has achieved its goals in this area.

Guidance Documents Issued by the LC:

- "*When is an embryo live or dead*"
- *Advice on the requirements for obtaining proper consent*
- *Stages where declarations or consent forms are required*
- *Advice from the NHMRC Licensing Committee on: Restricting the number of excess ART embryos used; and Likelihood of significant advance in knowledge or improvement in technologies for treatment*.

The guidance documents are available from http://www.nhmrc.gov.au/embryos/monitor/application/guide.htm.

The "*Application to permit a trainee to use excess ART embryos*" (http://www.nhmrc.

gov.au/embryos/monitor/application/index.htm) lists the information that the LC requires before an embryologist can be approved to use excess ART embryos during training.

The Secretariat developed an information kit in early 2003 to assist potential applicants to apply for licences in accordance with the RIHEA and it has been available on the NHMRC website since then. The information kit has been updated to reflect experience gained since then. The new kit will be available on the NHMRC website soon.

## APPENDIX 4 - INFORMATION ON STEM CELL RESEARCH

The following advice from the NHMRC is for the preparation and review of research protocols relating to the use of embryonic and non-embryonic human stem cells. It is an update of Human Research Ethics Committee (HREC) Information Sheet 5 (September 2001), which should be discarded. If circumstances change, the NHMRC will issue further advice as required.

### Derivation of human embryonic stem cells in Australia

The following legislation and guidelines regulate the derivation of new human embryonic stem cells:

- The Research Involving Human Embryos Act 2002 (the RIHE Act)[5].
  - The RIHE Act (and corresponding state and territory legislation) establishes a strong regulatory framework for the use of excess Assisted Reproductive Technology (ART) embryos. The RIHE Act also establishes the NHMRC Licensing Committee.
  - The RIHE Act requires that all uses of excess ART embryos require a licence issued by the NHMRC Licensing Committee, except for those uses listed as exempt in Section 10(2) of the RIHE Act. A licence is required for the derivation of new embryonic stem cell lines from excess ART embryos.
    - Section 21(3)(c) of the RIHE Act states that the NHMRC Licensing Committee must not issue a licence unless it is 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 National Statement on Ethical Conduct in Research Involving Humans (NHMRC 1999).
    - Before issuing a licence, the Licensing Committee must be satisfied that a number of statutory requirements are fulfilled, such as processes for obtaining proper consent for the use of the excess ART embryos and HREC approval. In addition, the Licensing Committee must have regard to issues such as restricting the number of embryos used to achieve the goals of the project and the likelihood of a significant advance in knowledge. These requirements are detailed in section 21 of the RIHE Act.
- The *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research* (NHMRC 2004) (the ART guidelines).
  - Paragraphs 17.10 to 17.18 of the ART guidelines provide guidance for research involving excess ART embryos, including requirements for obtaining proper consent.
- The National Statement on Ethical Conduct in Research Involving Humans (NHMRC 1999 – the National Statement).[5]

It is essential that institutions and researchers wishing to derive new human embryonic stem cell lines have a thorough knowledge of, and comply with, the above legislation and guidelines. Similarly, HRECs must be familiar with, and follow, the responsibilities that the legislation and guidelines impose when considering research proposals that involve the use of human embryos.

### Research using human stem cells

There is no legislative framework regulating the research use of human stem cells (embryonic or non-embryonic) after they have been derived. However, the use of human stem cell lines in

[5] The *Research Involving Human Embryos Act 2002* and the *National Statement on Ethical Conduct in Research Involving Humans* (NHMRC 1999) are currently under review. Should any revisions to the *RIHE Act* or the *National Statement* impact on this advice, it will be updated accordingly.

research must comply with relevant NHMRC guidelines (in particular the National Statement) and must be approved by an HREC that is constituted in accordance with, and acting in compliance with, the National Statement.

Licences issued by the NHMRC Licensing Committee authorise the defined use of the excess ART embryos, not subsequent research using embryonic stem cells.

To enable HRECs to effectively review research proposals involving the use of existing human stem cell lines, institutions and researchers must provide information to HRECs on all the points below when submitting protocols (common elements span both columns):

<table>
<tr><td>Embryonic Stem Cells</td><td>Non-Embryonic Stem Cells</td></tr>
<tr><td colspan="2">1. Evidence that the research proposal complies with the requirements of the National Statement, other relevant guidelines issued by the NHMRC, and prevailing Commonwealth, State and Territory legislation.</td></tr>
<tr><td>2. If the human embryonic stem cells were derived in Australia, evidence that the use of embryos for derivation of the stem cells was (or will be) authorised by, and undertaken in accordance with, a licence issued by the NHMRC Licensing Committee.</td><td>2. Evidence that the research to derive the human non-embryonic stem cells complied with the National Statement, other relevant guidelines issued by the NHMRC and relevant Commonwealth and State or Territory legislation.</td></tr>
<tr><td>3. If the human embryonic stem cell lines were derived outside Australia and have been imported into Australia, evidence that these imported cell lines were derived using procedures involving embryos that would have complied with the laws in Australia and guidelines issued by the NHMRC.<br><br>These laws include the RIHE Act[6], the Prohibition of Human Cloning Act 2002[7] and corresponding State and Territory legislation, and the Commonwealth Customs (Prohibited Imports) Regulations[8].</td><td>3. If the proposal involves the use of stem cell lines that have been imported into Australia, evidence that the work to derive these cell lines was undertaken in compliance with comparable standards to those in place in Australia.</td></tr>
<tr><td colspan="2">4. If the proposed research involves the use of stem cell lines (or their products) in humans, evidence that the requirements of the Therapeutic Goods Administration (TGA) have been taken into account. While materials used in initial clinical research are exempt from requirements for Good Manufacturing Practice (GMP), the TGA requires GMP to be implemented for phase 2 and 3 clinical trials[9].</td></tr>
<tr><td colspan="2">5. As outlined in the National Statement (in particular paragraphs 1.13 to 1.15), evidence that assures the HREC that the research proposed will be undertaken by researchers with appropriate experience and using appropriate facilities.</td></tr>
</table>

The NHMRC's Gene and related Therapies Research Advisory Panel (GTRAP) is available to provide advice to HRECs for clinical research using human stem cell lines.

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[6] While imported embryonic stem cell lines could not have been derived via a licence obtained under the RIHE Act, the HREC can seek assurance from the researcher/institution that the work to derive the cell lines was approved and monitored by an appropriately constituted ethics committee; that the embryo donors gave voluntary informed consent; and that the embryos used were excess ART embryos. The HREC should also seek assurance that the work to derive the cell line would not have breached the *Prohibition of Human Cloning Act 2002* (see footnote 3).

[7] The *Prohibition of Human Cloning Act 2002* prohibits, amongst other things, the creation of human embryo clones and the creation of human embryos for purposes other than achieving pregnancy.

[8] The *Customs (Prohibited Imports) Regulations* prohibit absolutely the import of viable materials derived from human embryo clones. This includes stem cell lines derived from human embryo clones.

[9] *The TGA is developing a national regulatory framework for human tissues and emerging biological therapies. It is proposed that this regulatory system will apply to human cells, tissues and cellular and tissue-based products used therapeutically. Various levels of regulation will apply, based on the potential level of risk. A new Code of Good Manufacturing Practice (cGMP) may be developed that is specific to cell and tissue therapies. In due course, researchers will need to become familiar with the requirements of these regulations, as well as any new cGMP, and to demonstrate to the HREC that their proposal takes account of these requirements.*

In relation to clinical research involving human embryonic stem cells, HRECs are strongly advised to consult GTRAP before giving final approval for such research.

For clinical research involving non-embryonic stems cells, HRECs are strongly advised to consult GTRAP for research involving (1) stem cells that are being used in a target organ or tissue different from their origin (for example, cardiac stem cells being used in the brain); and (2) marrow or blood stem cells used for clinical purposes other than for bone marrow reconstitution (that is, non-homologous use of marrow or blood stem cells) before giving final approval for such research).

Where relevant, a copy of research proposals should be forwarded to the GTRAP Secretariat:

NHMRC
GPO Box 9848 ( MDP 109)
CANBERRA ACT 2601

GTRAP is currently developing guidelines for the writing of clinical proposals involving the use of stem cells.

This document is available on the NHMRC website -
http://www.nhmrc.gov.au/ethics/human/issues/stemcell.htm