

Authority Paper

Committee:	Authority Meeting
Meeting Date:	15 February 2006
Agenda Item:	7
Paper Number:	Paper HFEA (15/02/06) 294
Paper Title:	Procurement of Gametes and Embryos for Research
Author:	Chris O'Toole
For Information or Decision?	Decision
Resource Implications:	Cost of communicating policy to centres and issuing guidance.
Implementation	If permitted these policies will be implemented through the Research Licence Committee (import of embryos for research) and the inspection process.
Communication	Letter to be sent to the Centres that made the initial queries.
Organisational risk	High - Possibly adverse publicity.
Recommendation to the Committee:	Members are asked to agree that: <ul style="list-style-type: none"> • Gamete donation and egg sharing schemes may be extended to include the use of the donated gametes in research. • The HFEA maintains its policy that the use of foetal material to produce eggs for research purposes is permitted provided that fully informed consent is given.
Evaluation	If permitted these policies would be assessed through the Inspection process and Regulation Activity Report

Procurement of Gametes and Embryos for Research

Introduction

1. It has publicly been announced that two licensed research Centres wish to recruit women to donate eggs for research. One of these Centres has formally notified us of this and has sought and received approval from its local Research Ethics Committee. The aim of this paper is to look at the ethical issues in relation to the procurement of gametes and embryos for use in licensed research projects compared to use in treatment services.

The Legal Framework

2. The storage and use of gametes in research does not always require a licence from the HFEA. The Human Fertilisation and Embryology (Special Exemptions) Regulations 1991, at paragraph 3(1), provide that: "*Subject to the provisions of this regulation, a person may store gametes which are to be used only for the following purposes, but only in so far as such purposes do not consist of or include treatment services or any purpose falling within paragraph (2) below –*
(a) *research on gametes,*
(b) *the development or testing of pharmaceutical or contraceptive products, or*
(c) *teaching requiring the use of gametes.*

Para. 3 (2) states that: *A purpose falls within this paragraph if it consists of or includes any of the following –*

- (a) *the use of gametes in any mixing of live egg and live sperm whether human or not,*
- (b) *any use of gametes which could not be authorised by a licence,*
- (c) *the supply of gametes to any person to whom a licence applies for use in any activity authorised by that licence,*
- (d) *the supply of gametes to any person for money or other benefit unless the giving of the money or other benefit would be authorised by directions in the case of gametes supplied in pursuance of a licence, or*
- (e) *the export of gametes from the United Kingdom.*

Therefore, research centres that carry out research on eggs or sperm are not regulated by the Authority unless the gametes are used to create embryos *in vitro*. Consequently, centres carrying out unlicensed research do not have to adhere to the HFEA's guidelines relating to the use of donor gametes.

3. The creation and / or use of embryos in research are permitted under the HF&E Act subject to strict statutory controls. The Act requires that prior to donating gametes or embryos to licensed research projects patients must give their effective consent to the use of their gametes or any embryos

created using their gametes. Therefore it is imperative that embryos (or gametes donated to produce embryos) for research are freely given and that people donating them have made an informed choice.

4. Research on embryos is important for the continuing development of fertility treatments. Furthermore, understanding human development and genetic disease, gained from research on human embryos, will ultimately improve the success of fertility treatment and other medical disciplines. This was recognised by the Warnock Committee, in its inquiry into human fertilisation and embryology. The Warnock Committee agreed that embryos *“might legitimately, be used as a means to an end that was good for other humans”*. This view was taken as the Committee acknowledged that that the advances in fertility treatment could not have taken place without research using embryos and that such research was necessary if advances in treatment and medical knowledge were to continue. In passing the HF&E Act, Parliament decided that embryo research should be permitted for certain purposes, and subject to statutory controls. This view was subsequently upheld when, in 2001, both Houses of Parliament decided, by free votes, to extend the purposes for which embryos could be used in research.

Background

5. The majority of embryos used in research projects are obtained from women undergoing fertility treatment. These embryos are usually unsuitable for use in the treatment of the patient because the embryos fail to develop or do not meet the criteria for freezing embryos. However, occasionally, patients decide that they do not wish to cryopreserve any spare embryos and consequently donate these to be used in a research project. In addition patients, who have embryos cryopreserved for future use, sometimes decide that they no longer wish to use these embryos in treatment services and consent to the embryos being used in a project of research.
6. The majority of eggs used in research projects are also obtained from women undergoing fertility treatment. These eggs usually fail to fertilise and thus are unsuitable for use in treatment services. However, fertile women undergoing laparoscopic sterilisation sometimes give consent to undergo a mild stimulatory IVF cycle in order for eggs to be collected, at the time of the sterilisation, and be donated for use in research projects. The use of ovarian tissue or eggs in research is not regulated by the HFEA unless the eggs are to be used to create embryos. A number of research projects require the creation of embryos in order to determine whether the research has been successful. For example, in order to ascertain whether eggs can be matured in the laboratory, a process known as *in vitro* maturation, the eggs need to be fertilised to determine if this procedure has been effective. Also in order to derive embryonic stem cells from cloned embryos it has been reported that fresh, good quality, eggs are required.

Potential sources of eggs and embryos for use in research projects

7. The HFEA has identified 5 potential additional sources of eggs, sperm and embryos for use in research:
 - Import of embryos from outside the UK
 - Import of gametes from outside the UK
 - Gamete donation
 - Egg sharing
 - Use of fetal tissue to produce eggs for research

Import of embryos

8. The Authority discussed this issue at its meeting in July and agreed that applications should be considered by the Research Licence Committee on a case-by-case basis and be subject to certain criteria. A copy of the criteria is attached at Annex A to this paper. It was also agreed that these criteria should not be over restrictive and should be consistent with the HFEA's policy for importing embryos for use in treatment services. The import of embryos for research will be monitored by the Regulation Committee and the Authority through the monthly Regulatory Activity Report.

Import of gametes

9. Even though sperm could be imported from outside the UK for use in research, the import of eggs would be more unlikely as the technology for freezing eggs is still in its infancy. However, the criteria for importing embryos could be applied to application to import both sperm and eggs for use in licensed research projects.

Recommendation

10. **The Committee is asked to agree that the criteria for permitting the import of embryos for use in licensed research projects be applied to application to import gametes for use in licensed projects of research.**

Gamete Donation

11. The Persons Responsible at two research Centres have announced that they propose to ask women not undergoing fertility treatment to donate eggs for use in research. As stated above, a few Centres already obtain eggs from fertile women who are undergoing sterilisation. However, this new proposal would involve women undergoing a stimulatory IVF cycle but, instead of the eggs being used in treatment, they would be used to create embryos for use in research projects.

Egg Donation

12. Egg donation is a medically and surgically intrusive process which can be physically demanding, painful and stressful. Furthermore, undergoing an IVF cycle is not without actual and potential health risks e.g. ovarian

hyperstimulation syndrome. The ovarian hyperstimulation syndrome (OHSS) is a consequence of superovulation therapy for assisted conception procedures. In IVF the rate of OHSS varies from 1-10% with severe cases occurring in 0.25-2% of IVF cases. Women who are at particular risk of developing this potentially fatal condition include those who have polycystic ovaries and those who are young (under 30 years of age)¹. Consequently, there is a view that a woman should not have a procedure which has risks when there is no benefit at all for her. However, women are allowed to undergo an IVF cycle, as egg donors, to help other women have children. It could equally be reasonable for a woman to volunteer to become an egg donor and donate all her eggs to research. Is it ethically acceptable to undergo a potentially risky procedure in order to help another woman have a child but, not so, if the eggs are to be used to create an embryo as part of a research project?

Sperm Donation

13. The process of producing a sperm sample is not itself dangerous, invasive or unpleasant. Therefore, sperm donors are unlikely to suffer any ill effects from donating sperm to research. Sperm from altruistic donors which can no longer be used in treatment, usually because the donor has reached the limit of 10 live birth events, is currently used, with the consent of the donor, to create embryos in licensed research projects.

Egg Sharing

14. Recently, a Centre that holds treatment and research licences, received ethical and HFEA approval to ask women, undergoing IVF treatment, to donate 2 eggs to research if more than 12 eggs are collected. These women will not receive any benefits in kind for this donation. This Centre has also enquired of the HFEA whether it would approve egg sharing where, instead of donating the eggs to another woman, in return for a reduction in the price of her treatment cycle, some of the eggs would be used in research projects.
15. The HFEA currently permits clinics to offer benefits in kind, notably a reduction in the price of treatment, to a woman who donates a number of her eggs to someone else whilst undergoing fertility treatment. This practice, known as egg sharing, was recently reviewed as part of the SEED review and it was agreed that this practice should be allowed to continue for treatment services.
16. The response from the BMA to the SEED Review argued that egg sharing was an unsuitable practice because it felt it places unacceptable pressures on women who cannot afford IVF treatment to donate their eggs. Furthermore, the BMA considered that the offer of free or reduced price treatment was an inducement which could affect the validity of the woman's

¹ Ovarian hyperstimulation syndrome – A short report for the HFEA by Professor Adam Balen (February 2005)

consent. Furthermore, anecdotal comments received from nurses, counsellors and clinicians working in field of infertility have questioned the practice of egg sharing and the UK is the only country in Europe that permits this practice.

17. At present approximately 50% of egg donors are themselves undergoing fertility treatment. Therefore, the extension of egg sharing schemes, to permit women to donate some of their eggs in return for a reduction in the cost of her fertility treatment, could result a reduction in egg donation for treatment. Women may prefer to donate their eggs to research rather than donate them to another couple.
18. The HFEA already produces extensive guidelines for clinics offering egg sharing arrangements. Clinics that offer egg sharing must comply with the requirements of the HF&E Act 1990 and the Code of Practice. In particular, Centres must ensure that suitable practices are used and that the interests of the egg provider are protected at all times.

Use of Fetal Tissue to Produce Eggs for Research

19. In January 1994 the Human Fertilisation and Embryology Authority published a consultation document on the issues surrounding the use of donated ovarian tissue in embryo research or infertility treatment. The document discussed possible clinical, scientific, ethical and social implications of using ovarian tissue from three sources: live donors, women or girls who have died and aborted fetuses.
20. Following this consultation the HFEA concluded that, in the case of infertility treatment, it would be acceptable to use tissue from live donors only. The Authority did not consider the use of fetal ovarian tissue to be acceptable in the treatment of infertile women. Consequently, the Criminal Justice and Public Order Act 1994 amended the 1990 Human Fertilisation and Embryology Act to include a ban on the use of fetal ovarian tissue in fertility treatment.
21. In the case of embryo research, again balancing benefits against the risk of harm, the Authority considered that the use of ovarian tissue from live donors, from adult women who have died and from fetuses was acceptable, subject to existing controls. The availability of tissue from all three sources could enable embryo research to increase understanding of the causes of infertility and of birth abnormalities. Improvements in the treatment of infertility may be developed which could reduce the need for egg donation in the future.
22. In July 2003 the HFEA confirmed that the use of fetal ovarian tissue in fertility treatment is currently banned in the UK, but that the HFEA has not banned the use of fetal material to produce eggs for research purposes if

fully informed consent is given. To date, the HFEA has not granted any licences permitting the use of eggs obtained from fetuses in research.

Recommendation

23. **The Committee is asked to agree that the HFEA should maintain its current policy that the use of fetal material to produce eggs for research purposes is permitted provided that fully informed consent is given.**

Ethical Issues

24. It has been reported that patients seeking treatment with donated sperm or eggs have been finding it increasingly difficult to obtain treatment using appropriate donors. If permitted, would authorising the use of gametes from donors or egg sharers be decreasing the supply of gametes available for use in treatment services? Should the availability of gamete donors for treatment be the primary concern of the HFEA?
25. Following the recent report into Professor Woo Suk Hwang's Research there were allegations regarding the propriety of the procedures used in acquiring and using human eggs. In particular, concern was raised regarding the recruitment and subsequent use of eggs donated by technicians working in Professor Hwang's laboratory. The HFEA has also received a request to permit the use of gametes to create embryos as part of a licensed research project from a relative of an employee of the licensed Centre.
26. The issue of whether employees of licensed fertility / research centres, or their relatives or friends, should be permitted to donate gametes for use in licensed research projects raises a number of ethical questions, notably, whether these potential donors would feel coerced into donating their gametes. The same issue applies to the use of gametes from relatives or friends of patients with serious diseases, who may be pressurised into donating thinking that the stem cells derived from embryos created using their gametes may cure their sick relative or friend. However, this issue is not new. The same question also applies to relatives or friends donating gametes to be used in the fertility treatment of a relative or friend. The HFEA permits this practice but recommends that the potential donor receives independent counselling to ascertain whether the donation is completely voluntary. Furthermore, if the HFEA found that a Centre had exposed donors or egg sharers to unnecessary risks, pressurised or induced them to donate or undergo treatment or failed fully to explain to them the possible consequences of donation, the HFEA could take action against that centre for failing to employ suitable practices.

27. Alternatively, the Authority could state that in cases where employees of fertility / research centres wish to donate their gametes for use in a licensed research project then the gametes must not be used in any research project for which the centre holds a licence i.e. the gametes must be donated and used at another research centre.
28. The ethical issues surrounding gamete donation for research were also discussed at the HFEA Research Conference on 1 December 2005. In addition to the issues raised above, the age of potential donors was discussed. Another concern arising from the Hwang investigation was that of the relatively young age of the technicians who donated their eggs to Professor Hwang's research project. Therefore, it was suggested that donors should only be permitted to donate their gametes to research if they have completed their own families.
29. The HFEA guidance [part 4.25 of the Code of Practice (6th edition)] on the age of people considering donation provides that "*where gametes are used to create embryos specifically for donation, or embryos are donated following licensed fertility treatment, treatment Centres are expected to follow the age limits that exist for gametes donors – 35 for egg donors and 45 for sperm donors – unless there are exceptional reasons for doing so.*" Furthermore, "*it is expected that gametes for the treatment of others shall not be taken from anyone under the age of 18.*" Therefore, the HFEA already has safeguards in place that, if applied to the recruitment of gamete donors for research, would prevent the recruitment of donors under 18. The HFEA does not currently insist that potential donors for treatment services must have completed their own families before they can donate their gametes for use in the provision of treatment services for another person or couple.

Public opinion

30. Prior to issuing a research licence authorising the creation of embryos by cell nuclear replacement (CNR) the Authority received correspondence from 19 members of the public / organisations regarding the application. The issues raised are also relevant to this discussion as the primary reason for extending gamete donation for use in research is to increase the number of good quality eggs available for creating embryos, especially by CNR, to derive embryonic stem cell lines. The issues raised are summarised in Table 1.

Table 1: Summary of issues raised by members of the public regarding the licensing of CNR

Key issue	No. of responses (%)
Creation of embryos for research is unacceptable	14 (74%)
Exploitation of women	6 (32%)
Shortage of human eggs (for use in treatment)	2 (11%)
Commercialisation of gametes and embryos	7 (37%)
Proposed work to be undertaken in a fertility centre – conflict of interest	4 (21%)
Excess number of embryos would be used	3 (16%)
Unethical to embark on research which has little chance of success	8 (42%)
Cell lines derived from cloned embryos could be dangerous	3(16%)
Embryos would be 'killed'	1 (5%)

Potential Benefits and Risks of Gamete Donation for Research

31. The HFEA has identified 4 potential categories of gamete donors for research:

- Altruistic donors
- “Known” Donors e.g. employees of fertility / research centres, relatives or friends of employees of fertility / research centres and relatives or friends of patients with a serious disease which a licensed centre has a licence to investigate.
- Egg sharers
- Fetal tissue (see paragraphs 16 – 20)

32. The potential benefits and risks associated with each donor category, except fetal tissue, is summarised in Table 2.

Table 2: Summary of risk and benefits associated with donating gametes for research

Donor Category	Benefits	Risks	SEED Report
Altruistic Donors	Benefits to research e.g. Potential increase in the quality of research due to an increase in the quality of the raw materials. Donor feels that they have contributed to research into infertility / serious disease.	Medical – undergoing a medical procedure and therefore an unnecessary risk that they would not otherwise undertake. Emotional consequences – possible regret in later life e.g. if the donor remains childless or in case the procedure affects the donors own fertility. Decrease in number of donors for treatment services.	The HFEA supports a woman’s choice to donate eggs when she is not herself undergoing treatment.

Donor Category	Benefits	Risks	SEED Report
"Known" Donors	<p>Benefits to research e.g. Potential increase in the quality of research due to an increase in the quality of the raw materials.</p> <p>Donor feels that they have contributed to research into infertility / serious disease.</p>	<p>Medical – undergoing a medical procedure and therefore an unnecessary risk that they would not otherwise undertake.</p> <p>Emotional consequences – possible regret in later life e.g. if the donor remains childless or in case the procedure affects the donors own fertility.</p> <p>Coercion – the donor feels obligated to donate their gametes.</p>	
Egg sharers	<p>Benefits to research e.g. Potential increase in the quality of research due to an increase in the quality of the raw materials</p> <p>Donor feels that they have contributed to research into infertility / serious disease</p> <p>Increase in patients' freedom of choice</p> <p>Increase in availability of treatments for patients in less advantaged personal circumstances. Patients, who require subsidised treatment, may be more willing to enter an egg sharing arrangement if the eggs are to be used in research rather than be used to create a child for another woman.</p>	<p>Emotional consequences – possible regret in later life e.g. if the donor remains childless or in case the procedure affects the donors own fertility.</p> <p>The egg sharer may require more stimulated cycles than might be necessary for her to achieve her own reproductive ends.</p> <p>Coercion – the donor feels obligated to donate their gametes in order to receive treatment.</p> <p>Exploitation of patients in less advantaged personal circumstances. Patients may only be able to afford treatment if it is subsidised thus they donate their gametes to research in order to receive treatment.</p> <p>Decrease in number of egg donors for treatment services, as women may prefer to donate their eggs to research rather than donate them to help another woman have a child.</p>	<p>None of the arguments against the practice of egg sharing appears to be decisive, as long as egg sharing arrangements are carefully managed to protect the interests of participants.</p>

33. The Committee is asked to review the evidence ‘for’ and ‘against’ permitting each category of donor to donate gametes for research and decide whether each of the potential categories of gamete donors should be allowed as a source of gametes for use in licensed research projects.
34. In considering these issues the Committee is reminded that the Authority, as a public body, must act in accordance with the principles of public law and the ECHR. Decisions must therefore be reasonable and proportionate. Any determinations which impose restrictions on the rights / freedoms of others must be balanced against the legitimate aim pursued in imposing the restriction. Therefore, in reaching a decision, Members are asked to consider whether prohibiting, or attaching limitations on, all or some sources of gametes for research would be proportionate to the potential or actual risks of donating gametes, and give reasons for their decision.
35. If the Committee considers that it is ethical to use gametes in licensed research from any or all of these donors, then the Committee is asked to consider whether any additional guidelines need to be put in place in order to prevent any actual or perceived coercion or conflict of interest. A list of safeguards for each category of Donor is attached at Annex B to this paper.

Recommendation

36. In relation to the import of gametes for research, the Committee is asked to agree that the criteria for permitting the import of embryos for use in licensed research projects be applied to application to import gametes for use in licensed projects of research.
37. In relation to the other four proposed sources of gametes for use in research, the Committee is asked to agree that each type of donation, altruistic, known and egg sharing should be permitted subject to additional guidelines issued by the Authority; furthermore, that the HFEA maintains its policy that the use of fetal material to produce eggs for research purposes is permitted provided that fully informed consent is given.
38. In order to avoid an actual or perceived conflict of interest it is recommended that employees or family / friends of employees of research centres should not be allowed to donate their gametes for use in a project of research at the centre where they or their family / friends are employed. These “known” donors should donate at another licensed research centre consequently all the consenting, counselling and use would take place at another licensed centre.
39. The HFEA inspection procedures would also ensure that Centres involved in such schemes are adhering to HFEA guidelines and ensure that there are no potential or perceived conflicts of interest between donation, treatment and research.

HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY

IMPORT OF EMBRYOS FOR USE IN RESEARCH

Criteria for permitting the import of embryos for use in licensed research projects

- The importation of embryos for research should only be allowed on a case-by-case basis.
- The research purpose for which the embryo would be used should be lawful in the country of origin, and the Person Responsible for the research licence would be responsible for demonstrating this.
- The patients for whom the embryo(s) were created must have consented to the use of their embryo(s) in research, in line with the policy regarding consenting to research in the UK. In addition the patients must have consented to the export of the embryo(s).
- The importing centre must be able to demonstrate that the import of the particular embryos concerned is necessary for the research activity. It is not sufficient for them merely to point to a regional shortage.
- The embryos to be imported must be subject to the same screening as embryos to be imported for use in treatment, unless the importing centre can demonstrate that this is not necessary.
- The importing centre must be able to provide evidence that the donors have not been paid for the embryos.

HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY

ETHICS AND LAW COMMITTEE

PROCUREMENT OF GAMETES AND EMBRYOS FOR RESEARCH

Proposed Guidelines for Donation of Gametes to Research

Altruistic Donors

- Individuals involved in advising donors about the clinical aspects of donating eggs e.g. drug stimulation and egg collection, including any potential risks involved in the proposed treatment, must not be involved in the research project to which donors are considering donating their eggs.
- The person responsible for supervising the donor's medical treatment must not be involved in the project of research.
- A designated individual who is not directly involved in the clinical aspect of the donor's treatment must be available to discuss the research, in order to ensure that the implications of donation are understood.

Known Donors

- These donors (either egg or sperm donors) must receive independent counselling to ascertain whether the donation is completely voluntary.
- The person obtaining the consent of the potential donor (either egg or sperm donors) must not be employed by or have any financial interest in the fertility / research centre.
- The person responsible for supervising the donor's (egg donor) medical treatment must not be involved in the project of research.
- Individuals involved in advising donors about the clinical aspects of donating eggs e.g. drug stimulation and egg collection, including any potential risks involved in the proposed treatment, must not be involved in the research project to which donors are considering donating their eggs.
- A designated individual who is not directly involved in the clinical aspect of the egg donor's treatment must be available to discuss the research, in order to ensure that the implications of donation are understood.

Alternatively, the Authority could state that in cases where employees of fertility / research centres wish to donate their gametes for use in a licensed research project then the gametes must not be used in any research project for which the centre holds a licence i.e. the gametes must be donated and used at another research centre.

