# DONATION OF HUMAN EGGS FOR RESEARCH

## A CONSULTATION PAPER

BIOETHICS ADVISORY COMMITTEE

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# DONATION OF HUMAN EGGS FOR RESEARCH

## SUMMARY

1. Human eggs have for some time been needed and used for the treatment of infertility, but recently they have also been needed for research, such as embryonic stem cell research. Understanding the nature of stem cells is generally viewed to be the key to unlocking the vast potential of stem cell therapy for serious and currently untreatable diseases, such as diabetes, Alzheimer's disease and Parkinson's disease.

2. Eggs for research are in short supply. Indeed, scientists have indicated that the scarcity of human eggs is a key limiting factor in embryonic stem cell research. Women who themselves are undergoing fertility treatment may sometimes donate suitable eggs for research. Eggs from other sources such as cadavers or foetuses, or women undergoing surgery, for example, the removal of ovaries, are often immature and unsuitable, and are anyway insufficient.

3. The procedures which a woman has to undergo in order to obtain eggs for fertility treatment or for research are essentially the same. The process of obtaining eggs is not straightforward and carries some risk to the donor. It is important that she understands the procedures and risks involved. There is also the question of inducement. Thus ethical concerns arise. The main issues are as follows:

*(a) The question of inducement*

Women could be induced to provide eggs for research, by offers of money or benefits in kind. Women who are poor would be most susceptible to inducement.

*(b) Limiting payment to reimbursement*

This avoids inducement, since there is no net gain in income, and reflects the view that altruistic donation free of inducement is the proper basis for contributing to research.

*(c) Compensation*

The possibility of some additional payment to compensate for time, risk and inconvenience, or for lost earnings does not contradict the idea of altruistic donation, although it is often difficult to clearly demarcate compensation from inducement in every situation. Nevertheless, payment of a large sum of money tends to suggest inducement rather

than compensation. In addition, payment should not be based on the quantity or quality of the donor's eggs.

*(d) Foreign donors*

Biomedical research is increasingly global. There are differences in payment or compensation schemes in different countries. This means that women from a country that does not allow compensation for the donation of eggs for research may be induced to make the donation in another country that does not prohibit a large payout to be made. Furthermore, researchers from wealthy countries could attempt to obtain eggs from women in poor countries, where any compensation would be financially less burdensome for these researchers.

*(e) The freedom to choose to donate*

Should healthy women be free to decide whether or not to donate eggs for research? Under Singapore's Ministry of Health (MOH) regulations, healthy women may presently donate eggs for research. The risk being explained, people can freely decide to accept it and support the research. Egg donation is of no benefit to a healthy donor not undergoing fertility treatment, and it can be argued that it is up to them, given the information they need, to decide whether the risk is acceptable. This is what happens with research participants in other areas of clinical research. Nevertheless, some may wonder if a medical risk of donation can be justified when the donor receives no benefit from the process.

4. There is a need to ensure that consent to donate eggs for research is freely given when a woman is undergoing treatment. A woman undergoing fertility treatment should not be subjected to more risks than her treatment requires, and the number of eggs obtained should not be excessive. It follows that her consent to donate eggs for research should be taken by an independent person wherever possible. This is because she may feel under some obligation to the medical team which is providing the treatment.

5. In Singapore, using eggs from women, whether for infertility treatment or for research is regulated by the MOH, and the payment of reasonable expenses, which includes the cost of collecting, storing and transporting the egg, is permitted by law. It is not clear if additional payment to compensate for time, risk and inconvenience is permissible.

6. The number of eggs likely to be obtained from healthy donors will probably remain low. Scientists may have to continue with the current practice of using eggs contributed by women undergoing fertility treatment or look for alternative means to achieve their scientific goals, such as using animal eggs. In principle, where women are allowed to donate eggs for research, scientists and

Institutional Review Boards, which review the ethics of research proposals, should ensure that these women understand the procedures and risks involved before consenting to donate and that their interests and safety are adequately protected.

7. The views of researchers, professionals, religious bodies, interested organisations and the general public on these issues will help the BAC in the making of any recommendations.

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# DONATION OF HUMAN EGGS FOR RESEARCH

## CONSULTATION PAPER

### Introduction

1. The Bioethics Advisory Committee (BAC) in its 2002 report on human stem cell research, reproductive and therapeutic cloning (Stem Cell Report), noted that recent developments in stem cell research have raised hopes of discovering new cures for debilitating and fatal illnesses and of alleviating suffering.[1] It also recognised that important ethical concerns were entailed. Since the publication of the Stem Cell Report, legislative and regulatory frameworks have been established in Singapore to address some of these concerns. Singapore does not act alone in these endeavours, as many leading scientific nations have done likewise. However, several issues remain ethically challenging, and one that has drawn considerable attention in many countries relates to the donation of human eggs (or oocytes) for research, in particular embryonic stem cell research, which holds great promise of benefit for mankind.

2. Eggs are donated mostly for the treatment of infertility, although a number have been donated for research. Donating eggs for fertility treatment has been practiced for more than two decades and is now considered a well-established method for helping women who have problems conceiving. In contrast, the donation of eggs for research is more recent, and follows from advances especially in embryonic stem cell research. Such research is important in contributing to our understanding the nature and potential of stem cells, and this understanding is generally viewed as the key to unlocking the vast potential of stem cell therapy for serious and currently untreatable diseases, such as diabetes, Alzheimer's disease and Parkinson's disease.

3. Although there has been significant progress in stem cell science and technology since the publication of the Stem Cell Report, many more years of research are required before its therapeutic benefits may be realised. A more immediate obstacle to achieving these is the limited availability of human eggs, given the requirement of patients undergoing fertility treatment, the invasiveness of the medical procedures involved in obtaining the eggs, and broader concerns with protecting women from exploitation.

4. The process of obtaining eggs is not straightforward. It involves medical procedures and carries some risk to the donors. Thus safety and ethical concerns arise, the most important being the possibility that vulnerable women may be

1 Bioethics Advisory Committee. *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*. Singapore, 2002, page 1.

exploited, through various forms of inducement to provide eggs for research. At a practical level, the difficulty lies in determining whether any payment or compensation should be given to egg donors beyond the reimbursement of expenses actually incurred, and if so, the appropriate form or amount, and how to regulate it. It is also necessary to consider if researchers can be allowed to obtain eggs from women who are not undergoing fertility treatment. In any case, it is important to ensure that the safety and welfare of women are adequately safeguarded regardless of their status.

5. The main objective of this Consultation Paper is to consider the ethical, legal and social issues that relate to the donation of human eggs for research. The BAC seeks the views of researchers, professionals, religious bodies, interested organisations and the general public on:

(a) Whether healthy women not undergoing fertility treatment should be allowed to donate eggs for research, and if so under what conditions;

(b) Whether egg donors for research should be compensated for time, inconvenience and risk, and if so, what type of compensation or monetary amount would be acceptable, and not amount to an inducement;

(c) Whether there are circumstances in which the compensation for eggs could amount to a sale and if so whether such a sale should ever be contemplated;

(d) Any prohibitions, limits or regulatory mechanisms that should govern the supply and use of human eggs for research in Singapore; and

(e) Any other matters related to the donation of human eggs for research.

6. The feedback received will help the BAC review and build on the ethical and regulatory framework that has been established since the Stem Cell Report. As with our previous public consultations, recommendations will be made in a Report to the Steering Committee on Life Sciences.

## Human Eggs in Research

7. Human eggs are required for embryonic stem cell research and research into assisted reproductive technologies. The eggs can be studied without being fertilised, for example, studies into methods of egg maturation and preservation, or they can be used to create embryos or other entities (such as parthenotes, described in paragraph 15 below), from which stem cells can be derived for research.

8. Stem cells are unspecialised (or undifferentiated) cells that are able to replicate themselves and become specialised (or differentiated) cells.[2] There are primarily two types of stem cells that scientists work with – adult stem cells and embryonic stem cells. Adult stem cells are present in a tissue or organ and are able to become (or differentiate into) specialised cell types of that tissue or organ, and some other cell types. Embryonic stem cells are unique cells, which can be derived from early embryos. They are able to continuously replicate themselves and are pluripotent i.e. they have the capacity to become or differentiate into all cell types. There is currently little evidence that adult stem cells are pluripotent.

9. Scientists are learning how to control and direct stem cell differentiation in ways that would lead to the production of specialised cells for the treatment of various diseases. Understanding the nature of embryonic stem cells is a critical step towards realising the potential of these cells in regenerative medicine, where new approaches to repairing and replacing injured and diseased tissues and organs are being explored.

10. An embryo can be created from an egg and a sperm using *in vitro* fertilisation (IVF) or through somatic cell nuclear transfer (SCNT), also sometimes referred to as research cloning or therapeutic cloning. SCNT involves the transfer of the nucleus of a somatic cell[3] into an egg cell, whose nucleus has been removed. This is then followed by stimulation of the cell to start dividing. After five to six days, stem cells can be extracted from the resulting embryo and used for research.

11. SCNT may be used to study nuclear reprogramming, which is a process whereby a somatic cell is converted into one that has the capacity of an unspecialised cell to develop into a living organism (totipotence) or differentiate into all types of cells (pluripotence). Understanding this process may lead to the possibility of achieving direct reprogramming, which does not involve the use of eggs or the need to create embryos.

12. When the nucleus of a somatic cell from a patient is used in SCNT, patient-specific stem cells may be derived from the resulting embryo. These cells have the advantage of not causing an immune reaction or tissue rejection, when used for treatment. Figure 1 shows how SCNT may potentially be used to produce patient-specific stem cells.

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2 Specialised or differentiated cells are mature cells with specific functions, for example, skin cells and liver cells.

3 A somatic cell is any mature (or differentiated) cell in the body that is not an egg or a sperm.

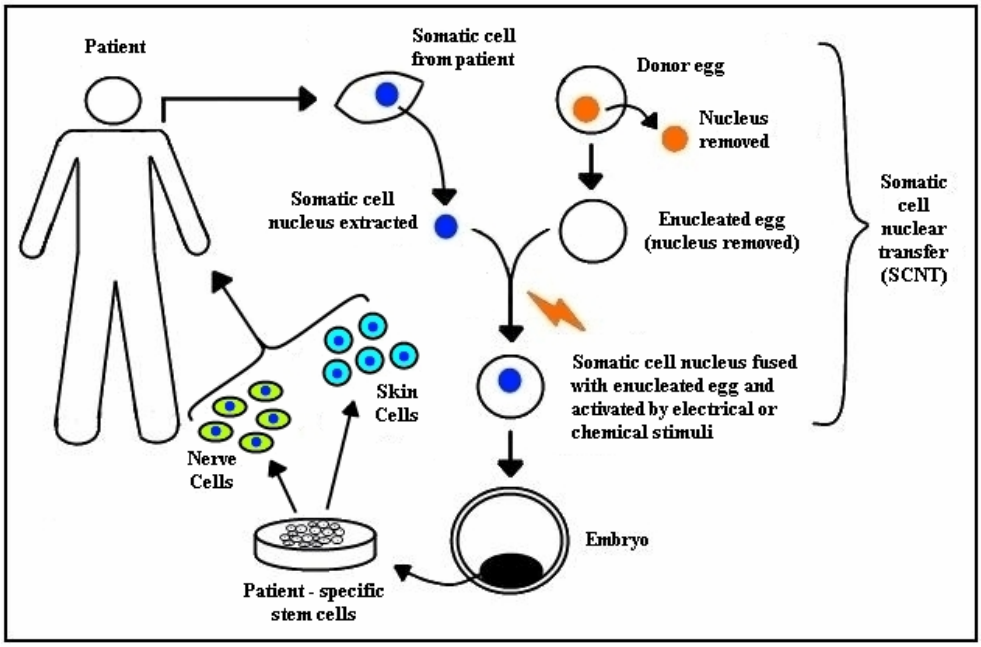


Figure 1. How SCNT may potentially be used to produce patient-specific stem cells

13. SCNT may also be used to study inherited diseases, when the somatic cells from patients with such conditions are used to generate disease-specific stem cells. These cells, which carry the genetic characteristics of the person suffering from the disease, could be used to study the development and progression of the disease in question. This may then lead to the discovery of better treatment or ways to reverse or prevent further progression of the condition.

14. Pluripotent stem cells can also be derived through parthenogenesis, which again requires eggs. Parthenogenesis, which means 'virgin birth' in Greek, occurs when the process of development of a new organism is initiated in an unfertilised egg.

15. Reproduction through parthenogenesis occurs naturally in certain insects and amphibians but not in mammals (including humans). However, the eggs of mammals can be stimulated by electrical or chemical stimuli to become embryo-like entities called 'parthenotes'. Mammalian parthenotes were thought to be unable to develop into offspring, but in 2004, a team of Japanese scientists reported the births of mice created via parthenogenesis.[4] In 2005, the Roslin Institute, which cloned Dolly the sheep, reported the creation of six human

4 Kono T et al. Birth of parthenogenetic mice that can develop to adulthood. *Nature*. 428 (2004): 860-864.

parthenotes with the intention of deriving stem cells for research.[5] These parthenotes were the first to be created in the UK. In June 2006, researchers at the University of Milan in Italy reported the creation of two stem cell lines from human parthenotes[6] and more recently a team of researchers claimed that they had succeeded in deriving pluripotent patient-specific stem cells from human parthenotes.[7] However much more research in this area is required before such cells can be used clinically.

**Sources of Human Eggs for Research**

16. While human eggs are very important for the advancement of embryonic stem cell research, they are not readily available. Currently, most eggs for research are obtained from women who have undergone fertility treatment. These could be surplus eggs which are not used for treatment, or they could be immature eggs that are either unsuitable for fertilisation or failed to fertilise following IVF. Other sources of eggs for research include cadavers, aborted foetuses and women undergoing medical procedures such as removal of ovaries. However, eggs from these latter sources may not be sufficiently effective for SCNT as they are usually immature, and access to these sources is nonetheless very limited for ethical and other reasons.

17. Theoretically, it might be possible to create eggs from human embryonic stem cells, and eggs created in this way could then be used in research. However, while it has been possible to create mouse eggs from mouse embryonic stem cells,[8] research on creating human eggs from human embryonic stem cells are in the preliminary stages. In 2005, researchers in the UK demonstrated that human embryonic stem cells displayed a capacity to generate immature gametes.[9]

18. In SCNT research, fresh eggs or surplus eggs from women undergoing fertility treatment are preferred to immature eggs or eggs that have failed to fertilise after IVF. Eggs that have failed to fertilise after IVF are less effective as they have been shown to have limited developmental potential.[10]

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5 Amos J. 'Virgin conception' first for UK. BBC News, 9 September 2005. http://news.bbc.co.uk/2/hi/science/nature/4228992.stm (accessed 1 November 2007).

6 Merchant J. Human eggs supply 'ethical' stem cells. *Nature*. 441 (2006):103.

7 Revazova ES et al. Patient-specific stem cell lines derived from human parthenogenetic blastocysts. *Cloning and Stem Cells*. 9 (2007):432-449.

8 Hubner K et al. Derivation of oocytes from mouse embryonic stem cells. *Science*. 300 (2003):1251-1256.

9 Aflatoonian B and Moore H. Germ cells from mouse and human embryo embryonic stem cells. *Reproduction*. 132 (2006):669-707.

10 Lavoir et al. Poor development of human nuclear transfer embryos using failed fertilized oocytes. *Reproductive Biomedicine Online*. 11 (2005):740-744.

19. Moreover, surplus eggs from fertility treatment are often retained for use by the woman herself or donated to other couples undergoing fertility treatment. For this reason, insufficient eggs are available for research. Indeed, scientists have indicated that the scarcity of human eggs is a key limiting factor in stem cell research. In many leading scientific nations, the possibility of obtaining eggs from women not undergoing any form of medical treatment (i.e. healthy women) is being considered. There are however significant ethical questions to be considered if this is done.

**Procedures and Risks Involved in Egg Donation**

20. The procedures which a woman has to undergo in order to obtain eggs for fertility treatment or for research are essentially the same. In both cases, it is important that she understands the procedures and risks involved.

21. Obtaining eggs is a time-consuming process, which has a certain degree of discomfort and possible health risks. A woman has to undergo stimulation of the ovaries through multiple hormone injections, followed by close monitoring of the development of her eggs in the ovaries through ultrasound scans and blood tests. Thereafter, the eggs are collected under mild anaesthesia via a special needle attached to an ultrasound vaginal probe. One can expect an average of between 20 to 40 injections under the usual regimes of ovarian stimulation.

22. The health risk entailed in egg donation is related to ovarian stimulation, where a condition called ovarian hyperstimulation syndrome (OHSS) may result. In addition, egg retrieval may cause excessive bleeding or infection. As the procedure of egg retrieval is done under mild anaesthesia, there are also risks associated with the type of anaesthesia administered. However, the risk in egg retrieval is relatively low. For example, in a review of 1000 cases of egg donors over a period of 13 years, it was found that there were two cases of severe adverse reactions to anaesthesia and two cases of bleeding. None of the patients who suffered these complications required hospitalisation and they recovered without any significant consequences.[11]

23. Mild OHSS is relatively common, usually occurring between five to nine days after egg retrieval and may affect up to 10% of women undergoing ovarian stimulation. The condition can be easily managed without hospitalisation and usually resolves spontaneously within several days. Severe OHSS is rare (occurring in less than 1% of egg donors)[12] and will require urgent medical

11 Sauer MV. Defining the incidence of serious complications experienced by oocyte donors: A review of 1000 cases. *American Journal of Obstetrics & Gynecology*. 184 (2001):277-278.

12 *Ibid*.

attention. It is of late-onset (occurring between ten days to three weeks after egg retrieval) and often associated with pregnancy. Women undergoing ovarian stimulation specifically for the purpose of donating eggs for research are unlikely to develop severe OHSS as pregnancy is not expected to follow the retrieval of eggs.

24. Women who are less than 30 years of age, with a low body weight, irregular menstrual cycles or polycystic ovaries are at increased risk of developing OHSS. OHSS can be prevented by careful selection of egg donors, judicious use of the drugs given for ovarian stimulation and close monitoring of the individual's response to the drugs.

25. There is some documented evidence that ovarian stimulation may lead to an increased risk of future cancers of the breast, ovary and uterus, although the risk appears low, particularly for ovarian cancer.[13] While the possibility of long term effects still needs further study, and current findings are not uniform or conclusive, it is not possible to rule out such effects, especially as ovarian stimulation exposes women to increased concentrations of hormones and such increases have been linked with cancers of the breast and uterus.

**Ethical Considerations and Regulatory Approaches to Egg Donation for Research**

26. Legislative and regulatory policies on egg donation vary from country to country. In some countries, egg donation is prohibited or limited to particular purposes. In Japan and Norway[14] for instance, egg donation for reproductive purposes is prohibited. This would prevent a couple undergoing fertility treatment from seeking 'egg donors' with certain preferred characteristics (such as physical appearance or academic accomplishment). In Denmark,[15] egg donation for reproductive purposes is restricted to women receiving treatment themselves, so that while 'egg sharing' among these women is permissible, a woman is not allowed to undergo ovarian stimulation in order to donate eggs for the infertility treatment of another woman.

27. Two issues that are most relevant for the purposes of this Consultation Paper are:

(a) Whether women should be allowed to donate eggs for research; and

(b) Whether any payment may be made to, or received by, the egg donor.

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13 Brinton L. Long-term effects of ovulation-stimulating drugs on cancer risk. *Reproductive Biomedicine Online*. 15 (2007):38-44.

14 *Act on the Medical Use of Biotechnology*. Norway, 2003, section 2-18.

15 *Order No 728 of 17 September 1997 on Artificial Fertilization*. Denmark, chapter 1, paragraph 9.

28. Table 1 provides a summary of the laws and regulatory guidelines of various countries on egg donation, which may be used as a general reference for the discussion on these issues.

***Should women be allowed to donate eggs for research?***

29. The permissibility of egg donation in a number of countries depends on the health status of a woman. Generally speaking, in countries where the practice of assisted reproductive technologies is allowed, women undergoing fertility treatment may donate eggs that are left over from their treatment for research. However, this may not be the case for healthy women who have to specially undergo ovarian stimulation to contribute eggs. The difference lies in the risks that these healthy women have to bear in order to donate their eggs.

*Obtaining eggs from women undergoing fertility treatment*

30. Before a woman undergoes ovarian stimulation for fertility treatment, she has to consider the possible options for the disposition of her excess eggs, should there be any. The options available are to store them for her own future use, to donate them to another couple, to make them available for quality assurance activities, to donate them for research, or to dispose of them. If she decides to donate her surplus eggs for the treatment of another woman's infertility, such a donation tends not to be ethically challenging since the donor is not subject to additional risk and her gift benefits the recipient directly.

31. However, if she is to be invited to consider donating her eggs for research, there are typically various safeguards to ensure her safety and that her contribution is informed and voluntary. For instance, a general requirement is that a woman should not be subjected to more risks than what her treatment requires and the number of eggs obtained should not be excessive. It follows that when a researcher is also the woman's attending physician, there may be an ethical expectation (as is generally the case in Singapore)[16] that requires her consent to be taken by an independent party wherever possible. This is because the prospective donor may feel under some obligation to the medical team which is providing the treatment.

*Obtaining eggs from healthy women*

32. When a research proposal seeks to involve healthy women as egg donors, the research tends to be subject to a higher level of ethical scrutiny. This follows from the general opinion that most women will not ordinarily subject

16 Bioethics Advisory Committee. *Human Tissue Research*. Singapore, 2002, paragraph 8.8; Bioethics Advisory Committee. *Personal Information in Biomedical Research*. Singapore, 2007, paragraph 5.9.

themselves to unnecessary discomfort, possible health risks and inconvenience in order to provide eggs for research. With an increasing need of eggs for research as biomedical science progresses, there is a real concern that the giving of eggs by healthy women may be unethically induced (by monetary or other benefits).

33. However, it may be argued that a woman should in principle be free to decide whether or not to donate her eggs for research regardless of her health status, provided that ethical and legal requirements are met. Even though egg donation for research is of no benefit to a healthy donor, whose donation is primarily altruistic in character, it can be argued that it is up to an informed donor to decide whether the risk is acceptable, in the same way as occurs with other research participants in other areas of clinical research. For example, when clinical trials are conducted, there is an element of risk, especially when the trial represents the first time a new drug is tried out in a human being. Yet, the risk being explained, people can freely decide to enter the trial and so voluntarily agree to accept the risk. It can be argued that a similar principle of participant autonomy can be invoked in the case of healthy egg donors.[17]

34. The case for allowing healthy women to donate their eggs for research rests heavily on such a libertarian principle – that people should not be prevented from volunteering for valuable research at some personal risk – and on the interest of society to advance the common good. This argument notwithstanding, the safety of the research participant or egg donor is paramount and the researcher is under obligation to provide all necessary assistance should any harm or complications arise in the course of the research or as a result of the egg donation.

35. In Singapore, the use of human eggs, whether for research or for treatment is regulated by the Ministry of Health (MOH).[18] Treatment and procedures involving human eggs must be carried out by qualified personnel in assisted reproduction centres licensed by the MOH. Under the current regulatory framework, a healthy woman may donate eggs for research. Research on human eggs require the explicit consent of the donor, the prior written approval of the MOH and the approval of the relevant ethics committee or institutional review board (IRB).[19] A prospective egg donor must be interviewed by a designated panel (which will take into consideration the public interest and community values) to ensure that the donor is of sound mind, has a clear understanding of the nature and consequences of the donation and has freely given consent.[20]

17 Capps has reviewed the ethics of human egg donation for research, and his background paper *Oocyte Procurement for Research* (2007) is available at: www.bioethics-singapore.org.

18 Ministry of Health. *Directives for Private Healthcare Institutions Providing Assisted Reproduction Services: Regulation 4 of the Private Hospitals and Medical Clinics Regulations (Cap 248, Reg 1).* Singapore, 2006.

19 *Ibid*, paragraphs 8.1 and 8.5.

20 *Ibid*, paragraph 8.6.

36. Similarly, egg donation for research or for treatment is allowed in the UK. In February 2007, the Human Fertilisation and Embryology Authority (HFEA) decided to allow the altruistic giving of eggs for research, provided there are strong safeguards in place to ensure that the donors have been properly informed of the risks and were not coerced.[21] It found that the medical risks for donating eggs for research are no higher than for fertility treatment and felt that a woman should be able to decide how she chooses to use her eggs, which includes donating them for research. Australia[22] and India[23] share this position in allowing healthy women to donate eggs for research.

***Should there be any payment for donating eggs for research?***

37. The recruitment of healthy women as egg donors and the amount of payment made to them are controversial as the procedures involved are risky and the payment may be seen to be an inducement or considered as commercialisation of human tissue, which is generally unacceptable. Consequently, there is at present no uniformity in the practices among countries on the amount of payment that a woman should receive for the donation of eggs, or indeed, if any compensation should be made at all.

38. Commercial trading in human eggs is explicitly prohibited by law in Singapore, and any contract or arrangement made in contravention of this will be void. However, any service (by receiving, storing, processing and subsequently implanting) undertaken for facilitating the donation and receipt of the egg is not regarded as commercial trading in human eggs.[24] Similar laws prohibiting the sale of human eggs have also been enacted in various countries including Australia, Canada and South Korea.

39. Commercial trading aside, there are three general approaches to financial compensation of women providing eggs for research:[25]

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21 Human Fertility and Embryology Authority. HFEA statement on donating eggs for research. UK, 21 February 2007. http://www.hfea.gov.uk/en/1491.html (accessed 1 November 2007).

22 National Health and Medical Research Council. *Ethical Guidelines on the Use of Assisted Reproductive Technology in Clinical Practice and Research*. Australia, 2004, revised June 2007, paragraph 17.21.3.

23 Indian Council of Medical Research. *National Guidelines for Stem Cell Research and Therapy*. 2006, paragraph 11.4.

24 *Human Cloning and other Prohibited Practices Act* (Cap 131B of Singapore, 2005 Rev Ed), section 13.

25 Isasi and Knoppers have proposed a broadly similar analytical framework comprising three categories (expense reimbursement, financial compensation and financial incentives), with an analysis of the advantages and disadvantages of each category; Isasi RM and Knoppers BM. Monetary payments for the procurement of oocytes for stem cell research: In search of ethical and political consistency. *Stem Cell Research.* (2007):doi:10.1016/j.scr.2007.09.003.

(a) No compensation but only reimbursement of expenses incurred. This implements a philosophy of altruistic donation that is relatively free of any risk of inducement;

(b) Reasonable compensation for time, risk and inconvenience, in addition to reimbursement of incurred expenses. This is not inconsistent with a philosophy of altruistic donation provided the quantum of reimbursement is not excessive and neither the quantity nor the quality of the donor's eggs affects the compensation; and

(c) Substantial compensation that amounts to outright payment of eggs as a commodity.

40. Only the first approach – reimbursement of expenses – is not affected by ethical concerns with inducement. Inducement to donate is generally regarded as unethical because it bears most strongly on the least economically empowered women, and thus is inequitable and could be socially divisive. As was earlier discussed, the concern with recruiting healthy women as egg donors is not the same as those raised by recruiting women who are undergoing fertility treatment, as there are no increased risks for the latter, who will be undergoing ovarian stimulation and retrieval of eggs anyway. It has also been noted earlier that the procedures for obtaining eggs are invasive with certain health risks entailed. These complicate the issue of compensation that may be provided in egg donation solely for research.

41. Some may consider that women who donate eggs for research should be compensated just as participants in some other research are compensated. However, it is difficult to determine a level of compensation that will not amount to undue influence or inducement as this would depend on a number of factors including the financial status of the woman concerned. This is made even more difficult as biomedical research assumes an increasingly global character. Owing to differences in payment or compensation schemes among countries, women from a country that does not allow compensation for the donation of eggs for research may be induced to make the donation in another country that allows a large payout to be made. Furthermore, there is concern that researchers from wealthy countries may attempt to obtain eggs from women in poor countries, where the compensation, if required would be financially less burdensome for these researchers in comparative terms. There is no simple response to this concern, but many countries are mindful that globalisation has a bearing on what might be considered as reasonable compensation for egg provision.

42. The European Parliament and the Council of the European Union indicated in a Directive the importance of ensuring that donations of tissues and cells (which include eggs) are voluntary and unpaid. However, donors are allowed "to receive compensation, which is strictly limited to making good the expenses and

inconveniences related to the donation. In that case, Member States define the conditions under which compensation may be granted." [26] In a specific resolution on human egg cells, the European Parliament expressed its desire to "see egg cell donation, like organ donation generally, strictly regulated in order to protect both donors and recipients and to avoid all forms of human exploitation".[27]

43. While payment beyond reimbursement of expenses incurred for the donation of eggs for research could be made in the US and the UK, there is a general recognition of the need to guard against such payment as inducement. For instance, both the International Society for Stem Cell Research (ISSCR)[28] and the California Institute for Regenerative Medicine (CIRM)[29] have issued a number of guidelines that include details on the informed consent process, information to be provided to prospective donors, monitoring of recruitment practices, rigorous review to ensure that reimbursements or financial considerations of any kind do not constitute undue inducement, and the requirement that egg procurement procedures be done by medically qualified and experienced physicians, using carefully controlled ovarian stimulation regimes to reduce the risk of OHSS. Should an egg donor require medical care as a result of providing eggs for research, there should be a provision to pay for the medical cost incurred. In addition, the ISSCR has recommended that "at no time should financial considerations of any kind be given for the number or quality of the eggs themselves that are to be provided for research."[30]

44. It may be considered that the compensation of time, risk and inconvenience is necessary in order to ensure that egg donors are not made worse off by their altruistic giving. A rationale for this has been provided by the European Society on Human Reproduction and Embryology (ESHRE) Task Force on Ethics and Law, which argued that the general principles of research ethics on the subject of compensation should apply to egg donation for research. Thus women who donate eggs for research should be treated similarly to research participants in clinical trials, so that they should receive reimbursement for all costs incurred, as well as compensation for time lost and inconvenience and discomfort suffered in the process.[31]

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26 *Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells*, article 12.

27 *European Parliament Resolution on the Trade in Human Egg Cells,* 10 March 2005, resolution 9.

28 International Society for Stem Cell Research. *Guidelines for the Conduct of Human Embryonic Stem Cell Research*. Northbrook, Illinois, US, 2006.

29 California Institute for Regenerative Medicine. *The CIRM Medical and Ethical Standards Regulations*. California, US, 2007, chapter 2.

30 International Society for Stem Cell Research. *Guidelines for the Conduct of Human Embryonic Stem Cell Research*. Northbrook, Illinois, US, 2006, paragraph 11.5b (ii).

31 European Society for Human Reproduction & Embryology, Task Force on Ethics and Law. Oocyte donation for non-reproductive purpose. *Human Reproduction*. 22 (2007):1210–1213.

45. In the UK, the HFEA allows donors to be compensated for loss of earnings (but not for other costs or inconveniences) up to a daily maximum of £55.19 (about S$168) and an overall limit of £250 (about S$760) for each cycle of egg donation.[32] In addition, the HFEA states that there is no restriction on the value of other benefits which may be given to a donor, but the only such benefits offered for this purpose may be treatment benefits provided in the course of the donation cycle unless medical considerations dictate otherwise.[33] This applies to donation for both clinical and research purposes.[34] Under the compensated 'egg sharing' arrangements with researchers by women undergoing fertility treatment, some cost of fertility treatment might be offset, as compensation, in return for the provision of eggs for research. The Medical Research Council has expressed support for this position by providing funds for subsidising the IVF treatment of women who choose to donate some of their eggs for a research project undertaken by the North East England Stem Cell Institute.[35] This scheme is the first of its kind in the world.[36]

46. The possibility of a compensated egg sharing scheme as an "ethically justifiable" way to obtain eggs for research has been earlier proposed in a paper by Heng, Tong and Stojkovic.[37] However, Isasi and Knoppers indicate that the presence of options of various schemes of monetary payment does not automatically rule out the possibility of exploitation, such as when participating in an egg-sharing programme with researchers is the only means to gain access to IVF treatment. Although there is no easy solution to this ethical dilemma, they emphasised the importance of making the ethical dimensions of the approach adopted (compensatory or otherwise) transparent.[38]

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32 Human Fertility and Embryology Authority. *Directions given under the Human Fertilisation and Embryology Act 1990: Giving and Receiving Money or Other Benefits in Respect of Any Supply of Gametes or Embryos*. UK, 2006, paragraph 4. http://www.hfea.gov.uk/docs/D2006_1_Directions_on_giving_and_receiving_money.pdf (accessed 1 November 2007).

33 *Ibid*, paragraph 5.

34 Human Fertility and Embryology Authority. HFEA statement on donating eggs for research. UK, 21 February 2007. http://www.hfea.gov.uk/en/1491.html (accessed 1 November 2007).

35 Medical Research Council. Women undergoing IVF to donate eggs for stem cell research in return for reduced treatment costs. UK, 13 September 2007. http://www.mrc.ac.uk/consumption/groups/public/documents/content/mrc003971.pdf (accessed 1 November 2007).

36 North East England Stem Cell Research Institute, News. Egg sharing: Women to get help with IVF treatment costs for donating eggs to research. UK, 13 September 2007. http://www.nesci.ac.uk/news/item/egg-sharing-women-to-get-help-with-ivf-treatment-costs-for-donating-eggs-to-research (last accessed 1 November 2007).

37 Heng BC et al. The egg-sharing model for human therapeutic cloning research: Managing donor selection criteria, the proportion of shared oocytes allocated to research, and amount of financial subsidy given to the donor. *Medical Hypotheses*. 66 (2006):1022-1024.

38 Isasi RM and Knoppers BM. Monetary payments for the procurement of oocytes for stem cell research: In search of ethical and political consistency. *Stem Cell Research.* (2007):doi:10.1016/j.scr.2007.09.003, pages 3-4.

47. There is no uniform practice in the US. The Bedford Stem Cell Research Foundation in Massachusetts, founded in 2000 and the first in the world to recruit women specifically for stem cell research, reimburses egg donors for travel, time and child care expenses. The National Research Council and the Institute of Medicine of the National Academies recommend that women who undergo ovarian stimulation specifically for research "should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an Institutional Review Board. No cash or in kind payments should be provided".[39] However, the Ethics Committee of the American Society for Reproductive Medicine is of the view that egg donors, whether for infertility treatment or for research should be compensated for their time, inconvenience and discomfort and decided that "at this time sums of $5,000 or more require justification and sums above $10,000 are not appropriate."[40]

48. In Singapore, the general ethical framework relating to the donation of tissue (which includes eggs) for research was established by the BAC in 2002. Such donation should be outright gifts and there should be no financial incentives, although reasonable reimbursement of expenses incurred should be allowed.[41] This ethical requirement in relation to the donation of gametes and embryos was taken up in legislation. Under Section 13 of the Human Cloning and Other Prohibited Practices Act (Cap 131B, 2005 Rev Ed), a person is prohibited from giving or receiving valuable consideration for the supply of human eggs, or to otherwise make an offer to that effect. Valuable consideration has been defined as including "any inducement, discount or priority in the provision of a service to the person, but does not include the payment of reasonable expenses incurred by the person in connection with the supply." Reasonable expenses include expenses relating to the collection, storage or transport of the eggs. However, the possibility of compensation for time, risk and inconvenience has not been addressed. Based on the general ethical principle of fairness, it appears that there could be circumstances where allowing reasonable compensation for time, risk and inconvenience is consistent with the existing ethical framework.

49. Some people might argue that compensation for participating in or contributing to research is justified when the research is done for profit by a commercial organisation, as when, for example, a pharmaceutical company compensates research participants in trials of a new drug. The rationale is that, because the venture is for profit, a participant should not be expected to donate time or take a risk altruistically, on a purely reimbursement basis. On this argument, eggs

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39 National Research Council and Institute of Medicine. *Guidelines for Human Embryonic Stem Cell Research*. Washington DC, The National Academies Press, 2007 rev, recommendation 16.

40 Ethics Committee of the American Society for Reproductive Medicine. Financial compensation of oocyte donors. *Fertility and Sterility*. 88 (2007):305-309.

41 Bioethics Advisory Committee. *Human Tissue Research*. Singapore, 2002, paragraphs 13.1.8 to 13.1.10.

could be sold for private sector research. However, there is also an argument that it is unacceptable to create a situation where there are two standards operating, one for the private sector and one for the public sector, and it seems inconsistent to suggest that risks become ethically acceptable in contexts where commercial profit is a motive but not otherwise. There is, in general, a tradition of altruism in research participation, in much the same way as there is for organ donation, and in previous reports, the BAC has taken this tradition for granted in considering the ethics of research with human subjects and the idea that research should be considered a public good.

**Conclusion**

50. Compensation for contributing eggs for research in an amount and manner that is fair and without inducement is likely to require the attention of ethicists, policy makers and regulators in the foreseeable future. As embryonic stem cell research gains a stronger foothold in Singapore, it is timely for this subject to be considered.

51. The availability of human eggs is a key limiting factor in embryonic stem cell research. Indeed, the number of eggs that is likely to be obtained from healthy donors will probably remain low. Scientists may have to continue with the current practice of using eggs contributed by women undergoing fertility treatment or look for alternative means to achieve their scientific goals, such as using animal eggs. In principle, where women are allowed to donate eggs for research, scientists and IRBs should ensure that these women understand the procedures and risks involved before consenting to donate and that their interests and safety are adequately protected.

## Table 1

## Regulatory Approaches of Selected Countries to Human Egg Donation[1]

| Country[2] | Egg Donation for Assisted Reproduction (AR) | Payment[3] (Egg donation for AR) | Egg Donation for research[4] | Payment[3] (Egg donation for research) |
|---|---|---|---|---|
| Austria | ✗ | na | ✗ | na |
| Australia (Commonwealth) | ✓ | R | ✓ | R |
| Belgium | ✓ | C | ✓ | NI |
| Brazil | ✓ | NI | ✓ | R |
| Canada | ✓ | R | ✓ | R |
| China | ✗ | na | ✓ | G |
| Czech Republic | ✓ | R | ✓ | R |
| Denmark | ✓ | C | ✓ | NI |
| Estonia | ✓ | R | ✓ | R |
| Finland | ✓ | R | ✓ | R |
| France | ✓ | R | ✓ | R |
| Germany | ✗ | na | NI | NI |
| Greece | ✓ | ✗ | ✓ | ✗ |
| Hong Kong | ✓ | C | ✓ | C |
| Hungary | ✓ | C | ✓ | C |
| India | ✓ | C | ✓ | R |
| Israel | ✓ | NI | NI | NI |
| Italy | ✗ | na | NI | NI |
| Japan | ✗ | na | ✓ | R |
| Korea (South) | ✓ | G | ✓ | G |
| Netherlands | ✓ | R | ✓ | R |
| New Zealand | ✓ | R | ✓ | R |
| Norway | ✗ | na | ✗ | na |
| Singapore | ✓ | R | ✓ | R |
| Slovenia | ✓ | R | NI | NI |
| South Africa | ✓ | R | ✓ | R |
| Spain | ✓ | C | ✓ | C |
| Sweden | ✓ | NI | ✓ | NI |
| Switzerland | ✗ | na | NI | NI |
| Taiwan | ✓ | C | NI | NI |
| Turkey | ✗ | na | NI | NI |
| United Kingdom | ✓ | C | ✓ | C |
| USA (Federal) | ✓ | C | ✓ | C |

**Legend:**

| | |
|---|---|
| ✕ | Prohibited |
| ✓ | Allowed |
| C | Compensation allowed |
| R | Reimbursement of expenses allowed |
| G | General prohibition against purchase and/or sale of eggs |
| na | Not applicable |
| NI | No information that directly addressed the issue was found or the position on the issue was unclear |

(1) The information set out in the table is indicative and need not necessarily be a complete representation of the regulatory approach of the specified country. In particular, the regulatory approach of the country presented has been interpreted in relation to that of Singapore and for the purposes of this Consultation Paper.

(2) Countries are selected based on several factors including availability of information (in the English language), availability of legislation and regulatory guidelines (both legally binding and non-binding) on the issues considered, and the extent that these issues have been deliberated on and debated in those countries.

(3) In this Consultation Paper, compensation is considered distinct from reimbursement. Reimbursement is defined as repayment for incurred expenses. In contrast, compensation is defined as recompense for presumptive loss of income and/or for risk and inconvenience. It is not intended to include any transaction for the purpose of monetary gain.

(4) Many countries have specific provisions for certain types of research involving eggs, such as the creation of an embryo, and therapeutic or research cloning. These specific types of research are not considered here. Rather, this column indicates whether eggs may be contributed for research in general. Countries with legislation or regulatory guidelines on egg donation for assisted reproduction may not have made similar (or explicit) provisions for egg donation for research. However, many of the countries that allow egg donation for assisted reproduction would generally allow a similar donation to research that is concerned with reproduction.

**GLOSSARY**

Adult stem cell – An unspecialised cell present in a tissue or organ, that is able to replicate itself and develop into specialised cell types of that tissue or organ, or some other cell types.

Alzheimer's disease – A common degenerative brain disorder, characterised by progressive deterioration of mental functions leading to impaired memory, thinking, judgment and ability to concentrate, emotional instability and increased reliance on others for daily activities.

Assisted reproductive technologies – The use of clinical and laboratory techniques to increase chances of conceiving a baby. An example is *in vitro* fertilization, or IVF.

Differentiation – The process whereby an unspecialised cell (eg stem cell) undergo changes to become a specialised cell.

Embryo – The earliest stage of development of an organism.

Embryonic stem cell – An unspecialised cell derived from an embryo, that is able to replicate itself and develop into various specialised cell types, for example, skin, nerve or heart cells.

Gamete – Sperm or egg cell.

Hormone – A chemical substance produced by an organ which can travel through the blood and exert functional effects on other organs.

Immune reaction – A response by the defence mechanism of the body that is able to recognise and attack foreign material (such as viruses or transplanted material) within the body.

Institutional review board (IRB) – A committee appointed by an institution to review the ethical standards of biomedical research proposals.

*In vitro* fertilisation (IVF) – A clinical and laboratory procedure whereby the eggs and sperm from a couple are extracted and fertilised outside their bodies. Such a procedure is a kind of assisted reproduction aimed at increasing the chances of a couple conceiving a baby.

Reprogramming – The process whereby a somatic cell (a specialised cell) is converted into one that has the capacity of an unspecialised cell to develop into a living embryo or into all types of cells or tissues in the body.

Nucleus – The part of a cell that carries most of the cell's genetic material.

Oocyte – An egg cell.

Ovarian stimulation – The administering of medication to stimulate egg development in the ovaries.

Ovarian hyperstimulation syndrome – A medical condition that may result from stimulation of the ovaries. Symptoms include nausea, vomiting, weight gain, pelvic pain, and difficulty breathing. In rare cases, the condition may be fatal.

Ovaries – The internal reproductive organs of a female that produce eggs.

Parkinson's disease – A disorder characterised by progressive degeneration of nerve cells in the brain, resulting in muscular tremors, rigid movement, stooped posture, and mask-like face.

Parthenogenesis – The process whereby the development of an organism starts in an egg that has not been fertilised. This is a form of non-sexual reproduction in some animals.

Patient-specific stem cells – Stem cells that are genetically matched to a specific patient and thus would not be rejected when transplanted into the patient's body.

Pluripotent – The capacity of unspecialised cells to develop into all types of specialised cells.

Polycystic ovaries – A hormonal disorder characterised by multiple cysts in the ovaries and irregular menstrual cycles. This is a common reason for infertility in women.

Reproductive cloning - The process of creating a genetically identical copy of a human being or animal.

Research cloning (also known as therapeutic cloning) – The use of cloning technology for research and therapeutic purposes that do not result in the creation of a complete animal or human being.

Somatic cell – Any mature (or differentiated) cell in the body that is not a sperm or an egg.

Somatic cell nuclear transfer – The process whereby the nucleus of a somatic cell is transferred into an egg cell, whose nucleus has been removed. This process may be used to create a cloned embryo so as to derive stem cells for research.

Stem cell – An unspecialised cell that is able to replicate itself and develop into specialised cell types (such as a skin, nerve, or heart cell).

Specialised (differentiated) cell – A mature cell with a specific function, for example, skin cells and liver cells.

Therapeutic Cloning – see Research Cloning

Tissue – An aggregation of similar cells that perform a particular function.

Totipotence – The capacity of an unspecialised cell to develop into any cell type, as well as developing into an organism.

Ultrasound scan – The use of high-frequency sound waves to create images of structures within the body.

Uterus – Also known as the womb, where a fertilised egg implants and a foetus develops.

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