and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute on Alcohol Abuse and Alcoholism. Special Emphasis Panel Alcohol Pharmacotherapy and the Treatment and Prevention of HIV/AIDS. (RFA AA 09 007/008) and Other AIDS Related Research.

Date: August 6, 2009.

Time: 8 a.m. to 11 a.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 5635 Fishers Lane, Bethesda, MD 20892. (Telephone Conference Call).

Contact Person: Katrina L Foster, PhD, Scientific Review Officer, National Inst on Alcohol Abuse & Alcoholism, National Institutes of Health, 5635 Fishers Lane, Rm. 2019, Rockville, MD 20852. 301–443–4032. *katrina@mail.nih.gov*.

(Catalogue of Federal Domestic Assistance Program Nos. 93.271, Alcohol Research Career Development Awards for Scientists and Clinicians; 93.272, Alcohol National Research Service Awards for Research Training; 93.273, Alcohol Research Programs; 93.891, Alcohol Research Center Grants; 93.701, ARRA Related Biomedical Research and Research Support Awards, National Institutes of Health, HHS)

Dated: June 29, 2009.

Jennifer Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. E9–15847 Filed 7–6–09; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of General Medical Sciences; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of General Medical Sciences. Special Emphasis Panel Minority Biomedical Research Support.

Date: July 19–20, 2009.

Time: 7 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: Hyatt Regency Bethesda, One Bethesda Metro Center, Bethesda, MD 20814.

Contact Person: Margaret J. Weidman, PhD, Scientific Review Officer, Office of Scientific Review, National Institute of General Medical Sciences, National Institutes of Health, 45 Center Drive, Room 3AN18B, Bethesda, MD 20892. 301–594–3663. *weidmanma@nigms.nih.gov.*

Name of Committee: National Institute of General Medical Sciences. Special Emphasis Panel MBRS Score.

Date: July 20–21, 2009.

Time: 8 a.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: Hyatt Regency Bethesda, One Bethesda Metro Center, Bethesda, MD 20814.

Contact Person: Lisa Dunbar, PhD, Scientific Review Officer, Office of Scientific Review, National Institute of General Medical Sciences, National Institutes of Health, 45 Center Drive, Room 3AN12, Bethesda, MD 20892. 301–594–2849. *dunbarl@mail.nih.gov.*

Name of Committee: National Institute of General Medical Sciences. Special Emphasis Panel New Innovator Awards.

Date: July 21, 2009.

Time: 1 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, Natcher Building, 45 Center Drive, Bethesda, MD 20892. (Telephone Conference Call).

Contact Person: Richard T. Okita, PhD, Program Director, Pharmacological and Physiological Sciences Branch, National Institute of General Medical Sciences, National Institutes of Health, Natcher Building, Room 2A5–49, Bethesda, MD 20892. 301–594–4469. *okitar@nigms.nih.gov*.

(Catalogue of Federal Domestic Assistance Program Nos. 93.375, Minority Biomedical Research Support; 93.821, Cell Biology and Biophysics Research; 93.859, Pharmacology, Physiology, and Biological Chemistry Research; 93.862, Genetics and Developmental Biology Research; 93.88, Minority Access to Research Careers; 93.96, Special Minority Initiatives, National Institutes of Health, HHS)

Dated: June 29, 2009.

Jennifer Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. E9–15846 Filed 7–6–09; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institutes of Health Guidelines for Human Stem Cell Research

SUMMARY: The National Institutes of Health (NIH) is hereby publishing final ''National Institutes of Health Guidelines for Human Stem Cell Research'' (Guidelines).

On March 9, 2009, President Barack H. Obama issued Executive Order 13505: *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells.* The Executive Order states that the Secretary of Health and Human Services, through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell (hESC) research, to the extent permitted by law.

These Guidelines implement Executive Order 13505, as it pertains to extramural NIH-funded stem cell research, establish policy and procedures under which the NIH will fund such research, and helps ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable law. Internal NIH policies and procedures, consistent with Executive Order 13505 and these Guidelines, will govern the conduct of intramural NIH stem cell research.

DATES: *Effective Date:* These Guidelines are effective on July 7, 2009.

Summary of Public Comments on Draft Guidelines: On April 23, 2009 the NIH published draft Guidelines for research involving hESCs in the **Federal Register** for public comment, 74 FR 18578 (April 23, 2009). The comment period ended on May 26, 2009.

The NIH received approximately 49,000 comments from patient advocacy groups, scientists and scientific societies, academic institutions, medical organizations, religious organizations, and private citizens. The NIH also received comments from members of Congress. This Notice presents the final Guidelines together with the NIH response to public comments that addressed provisions of the Guidelines.

Title of the Guidelines, Terminology, and Background

Respondents felt the title of the NIH draft guidelines was misleading, in that it is entitled ''National Institutes of Health Guidelines for Human Stem Cell Research,'' yet addresses only one type of human stem cell. The NIH notes that although the Guidelines pertain primarily to the donation of embryos for the derivation of hESCs, one Section also applies to certain uses of both hESCs and human induced pluripotent stem cells. Also, the Guidelines discuss applicable regulatory standards when research involving human adult stem cells or induced pluripotent stem cells constitutes human subject research.

Therefore, the title of the Guidelines was not changed.

Respondents also disagreed with the definition of human embryonic stem cells in the draft Guidelines, and asked that the NIH define them as originating from the inner cell mass of the blastocyst. The NIH modified the definition to say that human embryonic stem cells ''are cells that are derived from the inner cell mass of blastocyst stage human embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers.''

Financial Gain

Respondents expressed concern that derivers of stem cells might profit from the development of hESCs. Others noted that because the stem cells eligible for use in research using NIH funding under the draft Guidelines are those cells that are subject to existing patents, there will be insufficient competition in the licensing of such rights. These respondents suggested that this could inhibit research, as well as increase the cost of any future clinical benefits. The Guidelines do not address the distribution of stem cell research material. It is, however, the NIH's expectation that stem cell research materials developed with NIH funds, as well as associated intellectual property and data, will be distributed in accordance with the NIH's existing policies and guidance, including ''Sharing Biomedical Research Resources, Principles and Guidelines for Recipients of NIH Grants and Contracts'' and ''Best Practices for the Licensing of Genomic Inventions.'' *http://ott.od.nih.gov/policy/Reports.html* Even where such policies are not directly applicable, the NIH encourages others to refrain from imposing on the transfer of research tools, such as stem cells, any conditions that hinder further biomedical research. In addition, the Guidelines were revised to state that there should be documentation that ''no payments, cash or in kind, were offered for the donated embryos.''

Respondents were concerned that donor(s) be clearly ''apprised up front by any researchers that financial gain may come from the donation and that the donor(s) should know up front if he/she will share in the financial gain.'' The Guidelines address this concern by asking that donor(s) was/were informed during the consent process that the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefit from the use of the stem cells, such as who may be the recipients of cell transplants. The Guidelines also require that the donor(s) receive(s) information that the research was not intended to provide direct medical benefit to the donor(s); that the results of research using the hESCs may have commercial potential, and that the donor(s) would not receive financial or any other benefits from any such commercial development.

IRB Review Under the Common Rule

Respondents suggested that the current regulatory structure of IRB review under the Common Rule (45 CFR Part 46, Subpart A) addresses the core ethical principles needed for appropriate oversight of hESC derivation. They noted that IRB review includes a full review of the informed consent process, as well as a determination of whether individuals were coerced to participate in the research and whether any undue inducements were offered to secure their participation. These respondents urged the NIH to replace the specific standards to assure voluntary and informed consent in the draft Guidelines with a requirement that hESC research be reviewed and approved by an IRB, in conformance with 45 CFR Part 46, Subpart A, as a prerequisite to NIH funding. Respondents also requested that the NIH create a registry of eligible hESC lines to avoid burdensome and repetitive assurances from multiple funding applicants. The NIH agrees that the IRB system of review under the Common Rule provides a comprehensive framework for the review of the donation of identifiable human biological materials for research. However, in the last several years, guidelines on hESC research have been issued by a number of different organizations and governments, and different practices have arisen around the country and worldwide, resulting in a patchwork of standards. The NIH concluded that employing the IRB review system for the donation of embryos would not ameliorate stated concerns about variations in standards for hESC research and would preclude the establishment of an NIH registry of hESCs eligible for NIH funding, because there would be no NIH approval of particular hESCs. To this end and in response to comments, these Guidelines articulate policies and procedures that will allow the NIH to create a Registry. These Guidelines also provide scientists who apply for NIH funding with a specific set of standards reflecting currently recognized ethical principles and practices specific to embryo donation that took place on or after the issuance of the Guidelines, while also establishing procedures for the review of donations that took place before the effective date of the Guidelines.

Federal Funding Eligibility of Human Pluripotent Cells From Other Sources

Respondents suggested that the allowable sources of hESCs potentially available for Federal funding be expanded to include hESC lines from embryos created expressly for research purposes, and lines created, or pluripotent cells derived, following parthenogenesis or somatic cell nuclear transfer (SCNT). The Guidelines allow for funding of research using hESCs derived from embryos created using in vitro fertilization (IVF) for reproductive purposes and no longer needed for these purposes, assuming the research has scientific merit and the embryos were donated after proper informed consent was obtained from the donor(s). The Guidelines reflect the broad public support for Federal funding of research using hESCs created from such embryos based on wide and diverse debate on the topic in Congress and elsewhere. The use of additional sources of human pluripotent stem cells proposed by the respondents involve complex ethical and scientific issues on which a similar consensus has not emerged. For example, the embryo-like entities created by parthenogenesis and SCNT require women to donate oocytes, a procedure that has health and ethical implications, including the health risk to the donor from the course of hormonal treatments needed to induce oocyte production.

Respondents noted that many embryos undergo Pre-implantation Genetic Diagnosis (PGD). This may result in the identification of chromosomal abnormalities that would make the embryos medically unsuitable for clinical use. In addition, the IVF process may also produce embryos that are not transferred into the uterus of a woman because they are determined to be not appropriate for clinical use. Respondents suggested that hESCs derived from such embryos may be extremely valuable for scientific study, and should be considered embryos that were created for reproductive purposes and were no longer needed for this purpose. The NIH agrees with these comments. As in the draft, the final Guidelines allow for the donation of embryos that have undergone PGD.

Donation and Informed Consent

Respondents commented in numerous ways that the draft Guidelines are too procedurally proscriptive in articulating the elements of appropriate informed consent documentation. This over-

reliance on the specific details and format of the informed consent document, respondents argued, coupled with the retroactive application of the Guidelines to embryos already donated for research, would result in a framework that fails to appreciate the full range of factors contributing to the complexity of the informed consent process. For example, respondents pointed to several factors that were precluded from consideration by the proposed Guidelines, such as contextual evidence of the consent process, other established governmental frameworks (representing local and community influences), and the changing standards for informed consent in this area of research over time. Respondents argued that the Guidelines should be revised to allow for a fuller array of factors to be considered in determining whether the underlying ethical principle of voluntary informed consent had been met. In addition to these general issues, many respondents made the specific recommendation that all hESCs derived before the final Guidelines were issued be automatically eligible for Federal funding without further review, especially those eligible under prior Presidential policy, i.e., ''grandfathered.'' The final Guidelines seek to implement the Executive Order by issuing clear guidance to assist this field of science to advance and reach its full potential while ensuring adherence to strict ethical standards. To this end, the NIH is establishing a set of conditions that will maximize ethical oversight, while ensuring that the greatest number of ethically derived hESCs are eligible for Federal funding. Specifically, for embryos donated in the U.S. on or after the effective date of the Guidelines, the only way to establish eligibility will be to either use hESCs listed on the NIH Registry, or demonstrate compliance with the specific procedural requirements of the Guidelines by submitting an assurance with supporting information for administrative review by the NIH. Thus, for future embryo donations in the United States, the Guidelines articulate one set of procedural requirements. This responds to concerns regarding the patchwork of requirements and guidelines that currently exist.

However, the NIH is also cognizant that in the more than a decade between the discovery of hESCs and today, many lines were derived consistent with ethical standards and/or guidelines developed by various states, countries, and other entities such as the International Society for Stem Cell Research (ISSCR) and the National Academy of Sciences (NAS). These various policies have many common features, rely on a consistent ethical base, and require an informed consent process, but they differ in details of implementation. For example, some require specific wording in a written informed consent document, while others do not. It is important to recognize that the principles of ethical research, *e.g.*, voluntary informed consent to participation, have not varied in this time period, but the requirements for implementation and procedural safeguards employed to demonstrate compliance have evolved. In response to these concerns, the Guidelines state that applicant institutions wishing to use hESCs derived from embryos donated prior to the effective date of the Guidelines may either comply with Section II (A) of the Guidelines or undergo review by a Working Group of the Advisory Committee to the Director (ACD). The ACD, which is a chartered Federal Advisory Committee Act (FACA) committee, will advise NIH on whether the core ethical principles and procedures used in the process for obtaining informed consent for the donation of the embryo were such that the cell line should be eligible for NIH funding. This Working Group will not undertake a *de novo* evaluation of ethical standards, but will consider the materials submitted in light of the principles and points to consider in the Guidelines, as well as 45 CFR Part 46 Subpart A. Rather than ''grandfathering,'' ACD Working Group review will enable pre-existing hESCs derived in a responsible manner to be eligible for use in NIH funded research.

In addition, for embryos donated outside the United States prior to the effective date of these Guidelines, applicants may comply with either Section II (A) or (B). For embryos donated outside of the United States on or after the effective date of the Guidelines, applicants seeking to determine eligibility for NIH research funding may submit an assurance that the hESCs fully comply with Section II (A) or submit an assurance along with supporting information, that the alternative procedural standards of the foreign country where the embryo was donated provide protections at least equivalent to those provided by Section II (A) of these Guidelines. These materials will be reviewed by the NIH ACD Working Group, which will recommend to the ACD whether such equivalence exists. Final decisions will be made by the NIH Director. This special consideration for embryos donated outside the United States is needed because donation of embryos in foreign countries is governed by the laws and policies of the respective governments of those nations. Although such donations may be responsibly conducted, such governments may not or cannot change their national donation requirements to precisely comply with the NIH Guidelines. The NIH believes it is reasonable to provide a means for reviewing such hESCs because ethically derived foreign hESCs constitute an important scientific asset for the U.S.

Respondents expressed concern that it might be difficult in some cases to provide assurance that there was a ''clear separation'' between the prospective donor(s)' decision to create embryos for reproductive purposes and the donor(s)' decision to donate the embryos for research purposes. These respondents noted that policies vary at IVF clinics, especially with respect to the degree to which connections with researchers exist. Respondents noted that a particular clinic's role may be limited to the provision of contact information for researchers. A clinic that does not have any particular connection with research would not necessarily have in place a written policy articulating the separation contemplated by the Guidelines. Other respondents noted that embryos that are determined not to be suitable for medical purposes, either because of genetic defects or other concerns, may be donated prior to being frozen. In these cases, it is possible that the informed consent process for the donation might be concurrent with the consent process for IVF treatment. Respondents also noted that the initial consent for IVF may contain a general authorization for donating embryos in excess of clinical need, even though a more detailed consent is provided at the actual time of donation. The NIH notes that the Guidelines specifically state that consent should have been obtained at the time of donation, even if the potential donor(s) had given prior indication of a general intent to donate embryos in excess of clinical need for the purposes of research. Accordingly, a general authorization for research donation when consenting for reproductive treatment would comply with the Guidelines, so long as specific consent for the donation is obtained at the time of donation. In response to comments regarding documentation necessary to establish a separation between clinical and research decisions, the NIH has changed the language of the Guidelines to permit applicant institutions to submit consent forms,

written policies or other documentation to demonstrate compliance with the provisions of the Guidelines. This change should provide the flexibility to accommodate a range of practices, while adhering to the ethical principles intended.

Some respondents want to require that the IVF physician and the hESC researcher should be different individuals, to prevent conflict of interest. Others say they should be the same person, because people in both roles need to have detailed knowledge of both areas (IVF treatment and hESC research). There is also a concern that the IVF doctor will create extra embryos if he/she is also the researcher. As a general matter, the NIH believes that the doctor and the researcher seeking donation should be different individuals. However, this is not always possible, nor is it required, in the NIH's view, for ethical donation.

Some respondents want explicit language (in the Guidelines and/or in the consent) stating that the embryo will be destroyed when the inner cell mass is removed. In the process of developing guidelines, the NIH reviewed a variety of consent forms that have been used in responsible derivations. Several had extensive descriptions of the process and the research to be done, going well beyond the minimum expected, yet they did not use these exact words. Given the wide variety and diversity of forms, as well as the various policy, statutory and regulatory obligations individual institutions face, the NIH declines to provide exact wording for consent forms, and instead endorses a robust informed consent process where all necessary details are explained and understood in an ongoing, trusting relationship between the clinic and the donor(s).

Respondents asked for clarification regarding the people who must give informed consent for the donation of embryos for research. Some commenters suggested that NIH should require consent from the gamete donors, in cases where those individuals may be different than the individuals seeking reproductive treatment. The NIH requests consent from ''the individual(s) who sought reproductive treatment'' because this/these individual(s) is/are responsible for the creation of the embryo(s) and, therefore, its/their disposition. With regard to gamete donation, the risks are associated with privacy and, as such, are governed by requirements of the Common Rule, where applicable.

Respondents also requested clarification on the statement in the draft Guidelines noting that ''although human embryonic stem cells are derived from embryos, such stem cells are not themselves human embryos.'' For the purpose of NIH funding, an embryo is defined by Section 509, Omnibus Appropriations Act, 2009, Public Law 111–8, 3/11/09, otherwise known as the Dickey Amendment, as any organism not protected as a human subject under 45 CFR Part 46 that is derived by fertilization, parthenogenesis, cloning or any other means from one or more human gametes or human diploid cells. Since 1999, the Department of Health and Human Services (HHS) has consistently interpreted this provision as not applicable to research using hESCs, because hESCs are not embryos as defined by Section 509. This long-standing interpretation has been left unchanged by Congress, which has annually reenacted the Dickey Amendment with full knowledge that HHS has been funding hESC research since 2001. These guidelines therefore recognize the distinction, accepted by Congress, between the derivation of stem cells from an embryo that results in the embryo's destruction, for which Federal funding is prohibited, and research involving hESCs that does not involve an embryo nor result in an embryo's destruction, for which Federal funding is permitted.

Some respondents wanted to ensure that potential donor(s) are either required to put their ''extra'' embryos up for adoption before donating them for research, or are at least offered this option. The Guidelines require that all the options available in the health care facility where treatment was sought pertaining to the use of embryos no longer needed for reproductive purposes were explained to the potential donor(s). Since not all IVF clinics offer the same services, the healthcare facility is only required to explain the options available to the donor(s) at that particular facility.

Commenters asked that donor(s) be made aware of the point at which their donation decision becomes irrevocable. This is necessary because if the embryo is de-identified, it may be impossible to stop its use beyond a certain point. The NIH agrees with these comments and revised the Guidelines to require that donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable.

Medical Benefits of Donation

Regarding medical benefit, respondents were concerned that the language of the Guidelines should not somehow eliminate a donor's chances of benefitting from results of stem cell research. Respondents noted that although hESCs are not currently being used clinically, it is possible that in the future such cells might be used for the medical benefit of the person donating them. The Guidelines are meant to preclude individuals from donating embryos strictly for use in treating themselves only or from donating but identifying individuals or groups they do or do not want to potentially benefit from medical intervention using their donated cells. While treatment with hESCs is one of the goals of this research, in practice, years of experimental work must still be done before such treatment might become routinely available. The Guidelines are designed to make it clear that immediate medical benefit from a donation is highly unlikely at this time. Importantly, it is critical to note that the Guidelines in no way disqualify a donor from benefitting from the medical outcomes of stem cell research and treatments that may be developed in the future.

Monitoring and Enforcement Actions

Respondents have expressed concern about the monitoring of funded research and the invocation of possible penalties for researchers who do not follow the Guidelines. A grantee's failure to comply with the terms and conditions of award, including confirmed instances of research misconduct, may cause the NIH to take one or more enforcement actions, depending on the severity and duration of the non-compliance. For example, the following actions may be taken by the NIH when there is a failure to comply with the terms and conditions of any award: (1) Under 45 CFR 74.14, the NIH can impose special conditions on an award, including but not limited to increased oversight/monitoring/reporting requirements for an institution, project, or investigator; and (2) under 45 CFR 74.62 the NIH may impose enforcement actions, including but not limited to withholding funds pending correction of the problem, disallowing all or part of the costs of the activity that was not in compliance, withholding further awards for the project, or suspending or terminating all or part of the funding for the project. Individuals and institutions may be debarred from eligibility for all Federal financial assistance and contracts under 2 CFR part 376 and 48

CFR subpart 9.4, respectively. The NIH will undertake all enforcement actions in accordance with applicable statutes, regulations, and policies.

National Institutes of Health Guidelines for Research Using Human Stem Cells

I. Scope of the Guidelines

These Guidelines apply to the expenditure of National Institutes of Health (NIH) funds for research using human embryonic stem cells (hESCs) and certain uses of induced pluripotent stem cells (See Section IV). The Guidelines implement Executive Order 13505.

Long-standing HHS regulations for Protection of Human Subjects, 45 CFR part 46, subpart A establish safeguards for individuals who are the sources of many human tissues used in research, including non-embryonic human adult stem cells and human induced pluripotent stem cells. When research involving human adult stem cells or induced pluripotent stem cells constitutes human subject research, Institutional Review Board review may be required and informed consent may need to be obtained per the requirements detailed in 45 CFR part 46, subpart A. Applicants should consult *http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm*.

It is also important to note that the HHS regulation, *Protection of Human Subjects*, 45 CFR part 46, subpart A, may apply to certain research using hESCs. This regulation applies, among other things, to research involving individually identifiable private information about a living individual, 45 CFR 46.102(f). The HHS Office for Human Research Protections (OHRP) considers biological material, such as cells derived from human embryos, to be individually identifiable when they can be linked to specific living individuals by the investigators either directly or indirectly through coding systems. Thus, in certain circumstances, IRB review may be required, in addition to compliance with these Guidelines. Applicant institutions are urged to consult OHRP guidances at *http://www.hhs.gov/ohrp/policy/index.html#topics*.

To ensure that the greatest number of responsibly derived hESCs are eligible for research using NIH funding, these Guidelines are divided into several sections, which apply specifically to embryos donated in the U.S. and foreign countries, both before and on or after the effective date of these Guidelines. Section II (A) and (B) describe the conditions and review processes for determining hESC eligibility for NIH funds. Further information on these review processes may be found at *http://www.NIH.gov*. Sections IV and V describe research that is not eligible for NIH funding.

These guidelines are based on the following principles:

1. Responsible research with hESCs has the potential to improve our understanding of human health and illness and discover new ways to prevent and/or treat illness.

2. Individuals donating embryos for research purposes should do so freely, with voluntary and informed consent.

As directed by Executive Order 13505, the NIH shall review and update these Guidelines periodically, as appropriate.

II. Eligibility of Human Embryonic Stem Cells for Research With NIH Funding

For the purpose of these Guidelines, ''human embryonic stem cells (hESCs)'' are cells that are derived from the inner cell mass of blastocyst stage human embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. Although hESCs are derived from embryos, such stem cells are not themselves human embryos. All of the processes and procedures for review of the eligibility of hESCs will be centralized at the NIH as follows:

A. Applicant institutions proposing research using hESCs derived from embryos donated in the U.S. on or after the effective date of these Guidelines may use hESCs that are posted on the new NIH Registry or they may establish eligibility for NIH funding by submitting an assurance of compliance with Section II (A) of the Guidelines, along with supporting information demonstrating compliance for administrative review by the NIH. For the purposes of this Section II (A), hESCs should have been derived from human embryos:

1. That were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose;

2. That were donated by individuals who sought reproductive treatment (hereafter referred to as ''donor(s)'') and who gave voluntary written consent for the human embryos to be used for research purposes; and

3. For which all of the following can be assured and documentation provided, such as consent forms, written policies, or other documentation, provided:

a. All options available in the health care facility where treatment was sought pertaining to the embryos no longer needed for reproductive purposes were explained to the individual(s) who sought reproductive treatment.

b. No payments, cash or in kind, were offered for the donated embryos.

c. Policies and/or procedures were in place at the health care facility where the embryos were donated that neither consenting nor refusing to donate embryos for research would affect the quality of care provided to potential donor(s).

d. There was a clear separation between the prospective donor(s)'s decision to create human embryos for reproductive purposes and the prospective donor(s)'s decision to donate human embryos for research purposes. Specifically:

i. Decisions related to the creation of human embryos for reproductive purposes should have been made free from the influence of researchers proposing to derive or utilize hESCs in research. The attending physician responsible for reproductive clinical care and the researcher deriving and/or proposing to utilize hESCs should not have been the same person unless separation was not practicable.

ii. At the time of donation, consent for that donation should have been obtained from the individual(s) who had sought reproductive treatment. That is, even if potential donor(s) had given prior indication of their intent to donate to research any embryos that remained after reproductive treatment, consent for the donation for research purposes should have been given at the time of the donation.

iii. Donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable.

e. During the consent process, the donor(s) were informed of the following:

i. That the embryos would be used to derive hESCs for research;

ii. What would happen to the embryos in the derivation of hESCs for research;

iii. That hESCs derived from the embryos might be kept for many years;

iv. That the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefit from the use of the hESCs, such as who may be the recipients of cell transplants;

v. That the research was not intended to provide direct medical benefit to the donor(s);

vi. That the results of research using the hESCs may have commercial potential, and that the donor(s) would not receive financial or any other benefits from any such commercial development;

vii. Whether information that could identify the donor(s) would be available to researchers.

B. Applicant institutions proposing research using hESCs derived from embryos donated in the U.S. before the effective date of these Guidelines may use hESCs that are posted on the new NIH Registry or they may establish eligibility for NIH funding in one of two ways:

1. By complying with Section II (A) of the Guidelines; or

2. By submitting materials to a Working Group of the Advisory Committee to the Director (ACD), which will make recommendations regarding eligibility for NIH funding to its parent group, the ACD. The ACD will make recommendations to the NIH Director, who will make final decisions about eligibility for NIH funding.

The materials submitted must demonstrate that the hESCs were derived from human embryos: (1) That were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose; and (2) that were donated by donor(s) who gave voluntary written consent for the human embryos to be used for research purposes.

The Working Group will review submitted materials, *e.g.*, consent forms, written policies or other documentation, taking into account the principles articulated in Section II (A), 45 CFR part 46, subpart A, and the following additional points to consider. That is, during the informed consent process, including written or oral communications, whether the donor(s) were: (1) Informed of other available options pertaining to the use of the embryos; (2) offered any inducements for the donation of the embryos; and (3) informed about what would happen to the embryos after the donation for research.

C. For embryos donated outside the United States before the effective date of these Guidelines, applicants may comply with either Section II (A) or (B). For embryos donated outside of the United States on or after the effective date of the Guidelines, applicants seeking to determine eligibility for NIH research funding may submit an assurance that the hESCs fully comply with Section II (A) or submit an assurance along with supporting information, that the alternative procedural standards of the foreign country where the embryo was donated provide protections at least equivalent to those provided by Section II (A) of these Guidelines. These materials will be reviewed by the NIH ACD Working Group, which will recommend to the ACD whether such equivalence exists. Final decisions will be made by the NIH Director.

D. NIH will establish a new Registry listing hESCs eligible for use in NIH funded research. All hESCs that have been reviewed and deemed eligible by the NIH in accordance with these Guidelines will be posted on the new NIH Registry.

III. Use of NIH Funds

Prior to the use of NIH funds, funding recipients should provide assurances, when endorsing applications and progress reports submitted to NIH for projects using hESCs, that the hESCs are listed on the NIH registry.

IV. Research Using hESCs and/or Human Induced Pluripotent Stem Cells That, Although the Cells May Come From Eligible Sources, Is Nevertheless Ineligible for NIH Funding

This section governs research using hESCs and human induced pluripotent stem cells, *i.e.*, human cells that are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. Although the cells may come from eligible sources, the following uses of these cells are nevertheless ineligible for NIH funding, as follows:

A. Research in which hESCs (even if derived from embryos donated in accordance with these Guidelines) or human induced pluripotent stem cells are introduced into non-human primate blastocysts.

B. Research involving the breeding of animals where the introduction of hESCs (even if derived from embryos donated in accordance with these Guidelines) or human induced pluripotent stem cells may contribute to the germ line.

V. Other Research Not Eligible for NIH Funding

A. NIH funding of the derivation of stem cells from human embryos is prohibited by the annual appropriations ban on funding of human embryo research (Section 509, Omnibus Appropriations Act, 2009, Pub. L. 111–8, 3/11/09), otherwise known as the Dickey Amendment.

B. Research using hESCs derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not eligible for NIH funding.

Dated: June 30, 2009.

Raynard S. Kington,

Acting Director, NIH.

[FR Doc. E9–15954 Filed 7–6–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HOMELAND SECURITY

U.S. Customs and Border Protection

Agency Information Collection Activities: Importer's ID Input Record

AGENCY: U.S. Customs and Border Protection, Department of Homeland Security.

ACTION: 30-Day notice and request for comments; Extension of an existing information collection: 1651–0064.

SUMMARY: U.S. Customs and Border Protection (CBP) of the Department of Homeland Security has submitted the following information collection request to the Office of Management and Budget (OMB) for review and approval in accordance with the Paperwork Reduction Act: Importer's ID Input Record (Form 5106). This is a proposed extension of an information collection that was previously approved. CBP is proposing that this information collection be extended with no change to the burden hours. This document is published to obtain comments from the public and affected agencies. This proposed information collection was previously published in the **Federal Register** (74 FR 16226) on April 9, 2009, allowing for a 60-day comment period. This notice allows for an additional 30 days for public comments. This process is conducted in accordance with 5 CFR 1320.10.

DATES: Written comments should be received on or before August 6, 2009.

ADDRESSES: Interested persons are invited to submit written comments on the proposed information collection to the Office of Information and Regulatory Affairs, Office of Management and Budget. Comments should be addressed to the OMB Desk Officer for Customs and Border Protection, Department of Homeland Security, and sent via electronic mail to *oira_submission@omb.eop.gov* or faxed to (202) 395–5806.

SUPPLEMENTARY INFORMATION: U.S. Customs and Border Protection (CBP) encourages the general public and affected Federal agencies to submit written comments and suggestions on

Matthew Jennings, BSC Coordinator, CDC, Coordinating Office for Terrorism Preparedness and Emergency Response, 1600 Clifton Road, NE., Mailstop D–44, Atlanta, Georgia 30333, Telephone (404) 639–7357.

The Director, Management Analysis and Services Office, has been delegated the authority to sign **Federal Register** notices pertaining to announcements of meetings and other committee management activities for both CDC and the Agency for Toxic Substances and Disease Registry.

Dated: April 17, 2009.

Elaine L. Baker,

Director, Management Analysis and Service Office, Centers for Disease Control and Prevention.

[FR Doc. E9–9331 Filed 4–22–09; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Draft National Institutes of Health Guidelines for Human Stem Cell Research Notice

SUMMARY: The National Institutes of Health (NIH) is requesting public comment on draft guidelines entitled ''National Institutes of Health Guidelines for Human Stem Cell Research'' (Guidelines).

The purpose of these draft Guidelines is to implement Executive Order 13505, issued on March 9, 2009, as it pertains to extramural NIH-funded research, to establish policy and procedures under which NIH will fund research in this area, and to help ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable law. Internal NIH procedures, consistent with Executive Order 13505 and these Guidelines, will govern the conduct of intramural NIH research involving human stem cells.

These draft Guidelines would allow funding for research using human embryonic stem cells that were derived from embryos created by *in vitro* fertilization (IVF) for reproductive purposes and were no longer needed for that purpose. Funding will continue to be allowed for human stem cell research using adult stem cells and induced pluripotent stem cells. Specifically, these Guidelines describe the conditions and informed consent procedures that would have been required during the derivation of human embryonic stem cells for research using these cells to be funded by the NIH. NIH funding for research using human embryonic stem cells derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not allowed under these Guidelines.

NIH funding of the derivation of stem cells from human embryos is prohibited by the annual appropriations ban on funding of human embryo research (Consolidated Appropriations Act, 2009, Pub. L. 110–161, 3/11/09), otherwise known as the Dickey-Wicker Amendment.

According to these Guidelines, there are some uses of human embryonic stem cells and human induced pluripotent stem cells that, although those cells may come from allowable sources, are nevertheless ineligible for NIH funding.

For questions regarding ongoing NIH-funded research involving human embryonic stem cells, as well as pending applications and those submitted prior to the issuance of Final Guidelines, see the NIH Guide *http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-085.html.*

DATES: Written comments must be received by NIH on or before May 26, 2009.

ADDRESSES: The NIH welcomes public comment on the draft Guidelines set forth below. Comments may be entered at: *http://nihoerextra.nih.gov/stem_cells/add.htm.* Comments may also be mailed to: NIH Stem Cell Guidelines, MSC 7997, 9000 Rockville Pike, Bethesda, Maryland 20892–7997. Comments will be made publicly available, including any personally identifiable or confidential business information they contain.

SUPPLEMENTARY INFORMATION: On March 9, 2009, President Barack H. Obama issued Executive Order 13505: *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells.* The Executive Order states that the Secretary of Health and Human Services, through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.

The purpose of these draft Guidelines is to implement Executive Order 13505, issued on March 9, 2009, as it pertains to extramural NIH-funded research, to establish policy and procedures under which NIH will fund research in this area, and to help ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable law. Internal NIH procedures, consistent with Executive Order 13505 and these Guidelines, will govern the conduct of intramural NIH research involving human stem cells.

Long-standing Department of Health and Human Services regulations for Protection of Human Subjects, 45 CFR part 46, establish safeguards for individuals who are the sources of many human tissues used in research, including non-embryonic human adult stem cells and human induced pluripotent stem cells. When research involving human adult stem cells or induced pluripotent stem cells constitutes human subject research, Institutional Review Board review may be required and informed consent may need to be obtained per the requirements detailed in 45 CFR part 46. Applicants should consult *http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.*

As described in these draft Guidelines, human embryonic stem cells are cells that are derived from human embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. Although human embryonic stem cells are derived from embryos, such stem cells are not themselves human embryos.

Studies of human embryonic stem cells may yield information about the complex events that occur during human development. Some of the most serious medical conditions, such as cancer and birth defects, are due to abnormal cell division and differentiation. A better understanding of the genetic and molecular controls of these processes could provide information about how such diseases arise and suggest new strategies for therapy. Human embryonic stem cells may also be used to test new drugs. For example, new medications could be tested for safety on differentiated somatic cells generated from human embryonic stem cells.

Perhaps the most important potential use of human embryonic stem cells is the generation of cells and tissues that could be used for cell-based therapies. Today, donated tissues and organs are often used to replace ailing or destroyed tissue, but the need for transplantable tissues and organs far outweighs the available supply. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases and conditions, including Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, burns, heart disease, diabetes, and arthritis.

NIH currently funds ongoing research involving human embryonic stem cells as detailed under prior Presidential policy. Under that policy, Federal funds have been used for research on human embryonic stem cells where the derivation process was initiated prior to 9 p.m. EDT August 9, 2001, the embryo was created for reproductive purposes, the embryo was no longer needed for these purposes, informed consent was obtained for the donation of the embryo, and no financial inducements were provided for donation of the embryo.

These draft Guidelines would allow funding for research using only those human embryonic stem cells that were derived from embryos created by *in vitro* fertilization (IVF) for reproductive purposes and were no longer needed for that purpose. Funding will continue to be allowed for human stem cell research using adult stem cells and induced pluripotent stem cells. Specifically, these Guidelines describe the conditions and informed consent procedures that would have been required during the derivation of human embryonic stem cells for research using these cells to be funded by the NIH. NIH funding for research using human embryonic stem cells derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not allowed under these Guidelines.

Please note that, for NIH funded research using the permitted human embryonic stem cells, the requirements of the Department's protection of human subjects regulations, 45 CFR part 46, may or may not apply, depending on the nature of the research. For further information, see *Human Embryonic Stem Cells, Germ Cells and Cell Derived Test Articles:* OHRP Guidance for Investigators and Institutional Review Boards.

NIH funding of the derivation of stem cells from human embryos is prohibited by the annual appropriations ban on funding of human embryo research (Consolidated Appropriations Act, 2009, Pub. L. 110–161, 3/11/09), otherwise known as the Dickey-Wicker Amendment.

According to these Guidelines, there are some uses of human embryonic stem cells that, although those cells may come from allowable sources, are nevertheless ineligible for NIH funding.

In developing these draft Guidelines, the NIH consulted its Guidelines issued in 2000, as well as the thoughtful guidelines developed by other national and international committees of scientists, bioethicists, patient advocates, physicians and other stakeholders, including the U.S. National Academies, the International Society for Stem Cell Research, and others.

As directed by Executive Order 13505, the NIH shall review and update these Guidelines periodically, as appropriate.

The Draft Guidelines Follow:

National Institutes of Health Guidelines for Human Stem Cell Research

I. Scope of Guidelines

These Guidelines describe the circumstances under which human embryonic stem cells are eligible for use in extramural NIH-funded research, and they also include a section on uses of human embryonic stem cells or human induced pluripotent stem cells that are ineligible for NIH funding.

For the purpose of these Guidelines, ''human embryonic stem cells'' are cells that are derived from human embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. Although human embryonic stem cells are derived from embryos, such stem cells are not themselves human embryos.

II. Guidelines for Eligibility of Human Embryonic Stem Cells for Use in Research

A. The Executive Order: Executive Order 13505, *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells,* states that the Secretary of the Department of Health and Human Services (DHHS), through the Director of the NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.

B. Eligibility of Human Embryonic Stem Cells Derived from Human Embryos: Human embryonic stem cells may be used in research using NIH funds, if the cells were derived from human embryos that were created for reproductive purposes, were no longer needed for this purpose, were donated for research purposes, and for which documentation for all of the following can be assured:

1. All options pertaining to use of embryos no longer needed for reproductive purposes were explained to the potential donor(s).

2. No inducements were offered for the donation.

3. A policy was in place at the health care facility where the embryos were donated that neither consenting nor refusing to donate embryos for research would affect the quality of care provided to potential donor(s).

4. There was a clear separation between the prospective donor(s)'s decision to create human embryos for reproductive purposes and the prospective donor(s)'s decision to donate human embryos for research purposes.

5. At the time of donation, consent for that donation was obtained from the individual(s) who had sought reproductive services. That is, even if potential donor(s) had given prior indication of their intent to donate to research any embryos that remained after reproductive treatment, consent for the donation should have been given at the time of the donation. Donor(s) were informed that they retained the right to withdraw consent until the embryos were actually used for research.

6. Decisions related to the creation of human embryos for reproductive purposes were made free from the influence of researchers proposing to derive or utilize human embryonic stem cells in research. Whenever it was practicable, the attending physician responsible for reproductive clinical care and the researcher deriving and/or proposing to utilize human embryonic stem cells should not have been the same person.

7. Written informed consent was obtained from individual(s) who sought reproductive services and who elected to donate human embryos for research purposes. The following information, which is pertinent to making the decision of whether or not to donate human embryos for research purposes, was in the written consent form for donation and discussed with potential donor(s) in the informed consent process:

a. A statement that donation of the embryos for research was voluntary;

b. A statement that donor(s) understood alternative options pertaining to use of the embryos;

c. A statement that the embryos would be used to derive human embryonic stem cells for research;

d. Information about what would happen to the embryos in the derivation of human embryonic stem cells for research;

e. A statement that human embryonic stem cells derived from the embryos might be maintained for many years;

f. A statement that the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefit from the use of the stem cells;

g. A statement that the research was not intended to provide direct medical benefit to the donor(s);

h. A statement as to whether or not information that could identify the donor(s) would be retained prior to the derivation or the use of the human embryonic stem cells (relevant guidance from the DHHS Office for Human Research Protections (OHRP) should be followed, as applicable; see OHRP's *Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells, and Stem Cell-Derived Test Articles* and *Guidance on Research Involving Coded Private Information or Biological Specimens,* or successor guidances); and

i. A statement that the results of research using the human embryonic stem cells may have commercial potential, and a statement that the donor(s) would not receive financial or any other benefits from any such commercial development.

C. Prior to the use of NIH funds: Funding recipients must ensure that: (1) The human embryonic stem cells were derived consistent with sections II.A and B of these Guidelines; and (2) the grantee institution maintains appropriate documentation demonstrating such consistency in accordance with 45 CFR 74.53, which also details rights of access by NIH. The responsible grantee institutional official must provide assurances with respect to (1) and (2) when endorsing applications and progress reports submitted to NIH for projects that utilize these cells.

III. Research Using Human Embryonic Stem Cells and/or Human Induced Pluripotent Stem Cells That, Although the Cells May Come From Allowable Sources, Is Nevertheless Ineligible for NIH Funding

This section governs research using human embryonic stem cells and human induced pluripotent stem cells, *i.e.,* human cells that are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. There are some uses of these cells that, although they may come from allowable sources, are nevertheless ineligible for NIH funding, as follows:

A. Research in which human embryonic stem cells (even if derived according to these Guidelines) or human induced pluripotent stem cells are introduced into non-human primate blastocysts.

B. Research involving the breeding of animals where the introduction of human embryonic stem cells (even if derived according to these Guidelines) or human induced pluripotent stem cells may have contributed to the germ line.

IV. Other Non-Allowable Research

A. NIH funding of the derivation of stem cells from human embryos is prohibited by the annual appropriations ban on funding of human embryo research (Consolidated Appropriations Act, 2009, Pub. L. 110–161, 3/11/09), otherwise known as the Dickey-Wicker Amendment.

B. NIH funding for research using human embryonic stem cells derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not allowed under these Guidelines.

Dated: April 17, 2009.

Raynard S. Kington,

Acting Director, NIH.

[FR Doc. E9–9313 Filed 4–22–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of Federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7057; fax: 301/402–0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

On-Demand In Vitro Assembly of Protein Microarrays

Description of Technology: Protein microarrays are becoming an indispensable biomedical tool to facilitate rapid high-throughput detection of protein-protein, protein-drug and protein-DNA interactions for large groups of proteins. The novel Protein Microarray of this invention is essentially a DNA microarray that becomes a protein microarray on demand and provides an efficient systematic approach to the study of protein interactions and drug target identification and validation, thereby speeding up the discovery process. The technology allows a large number of proteins to be synthesized and immobilized at their individual site of expression on an ordered array without the need for protein purification. As a result, proteins are ready for subsequent use in binding studies and other analysis.

The Protein Microarray is based on high affinity and high specificity of the protein-nucleic acid interaction of the Tus protein and the Ter site of E. coli. The DNA templates are arrayed on the microarray to perform dual function: (1) Synthesizing the protein in situ (cell-free protein synthesis) in the array and (2) at the same time capturing the protein it synthesizes by DNA-protein interaction. This method utilizes an expression vector containing a DNA sequence which serves a dual purpose: (a) Encoding proteins of interest fused to the Tus protein for in vitro synthesis of the protein and (b) encoding the Ter sequence, which captures the fusion protein through the high affinity interaction with the Tus protein.

Applications:

- Simultaneous analysis of interactions of many proteins with other proteins, antibodies, nucleic acids, lipids, drugs, etc, in a single experiment.
- Efficient discovery of novel drugs and drug targets.

Development Status: The technology is in early stages of development.

Inventors: Deb K. Chatterjee, Kalavathy Sitaraman, James L. Hartley, David J. Munroe, Cassio Baptista (NCI).

Patent Status:

U.S. Patent Application No. 11/252,735 filed 19 Oct 2005 (HHS Reference No. E–244–2005/0–US–01).

U.S. Patent Application No. 12/105,636 filed 18 Apr 2008 (HHS Reference No. E–244–2005/1–US–02).

Licensing Status: Available for licensing.

Licensing Contact: Jeffrey A. James, Ph.D.; 301–435–5474; *jeffreyja@mail.nih.gov.*

Collaborative Research Opportunity: The National Cancer Institute Protein Expression Laboratory is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or

Federal Register

Wednesday,
March 11, 2009

Part IV

The President

Executive Order 13505—Removing Barriers to Responsible Scientific Research Involving Human Stem Cells

Memorandum of March 9, 2009—Presidential Signing Statements

Memorandum of March 9, 2009—Scientific Integrity

Federal Register
Vol. 74, No. 46
Wednesday, March 11, 2009

Presidential Documents

Title 3—

The President

Executive Order 13505 of March 9, 2009

Removing Barriers to Responsible Scientific Research Involving Human Stem Cells

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. *Policy.* Research involving human embryonic stem cells and human non-embryonic stem cells has the potential to lead to better understanding and treatment of many disabling diseases and conditions. Advances over the past decade in this promising scientific field have been encouraging, leading to broad agreement in the scientific community that the research should be supported by Federal funds.

For the past 8 years, the authority of the Department of Health and Human Services, including the National Institutes of Health (NIH), to fund and conduct human embryonic stem cell research has been limited by Presidential actions. The purpose of this order is to remove these limitations on scientific inquiry, to expand NIH support for the exploration of human stem cell research, and in so doing to enhance the contribution of America's scientists to important new discoveries and new therapies for the benefit of humankind.

Sec. 2. *Research.* The Secretary of Health and Human Services (Secretary), through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.

Sec. 3. *Guidance.* Within 120 days from the date of this order, the Secretary, through the Director of NIH, shall review existing NIH guidance and other widely recognized guidelines on human stem cell research, including provisions establishing appropriate safeguards, and issue new NIH guidance on such research that is consistent with this order. The Secretary, through NIH, shall review and update such guidance periodically, as appropriate.

Sec. 4. *General Provisions.* (a) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.

(b) Nothing in this order shall be construed to impair or otherwise affect:

(i) authority granted by law to an executive department, agency, or the head thereof; or

(ii) functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(c) This order is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity, by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.

Sec. 5. *Revocations.* (a) The Presidential statement of August 9, 2001, limiting Federal funding for research involving human embryonic stem cells, shall have no further effect as a statement of governmental policy.

(b) Executive Order 13435 of June 20, 2007, which supplements the August 9, 2001, statement on human embryonic stem cell research, is revoked.

THE WHITE HOUSE,
March 9, 2009.

[FR Doc. E9–5441
Filed 3–10–09; 11:15 am]
Billing code 3195–W9–P

Federal Register

Friday,
June 22, 2007

Part III

The President

Executive Order 13435—Expanding Approved Stem Cell Lines in Ethically Responsible Ways

Federal Register
Vol. 72, No. 120
Friday, June 22, 2007

Presidential Documents

Title 3—

The President

Executive Order 13435 of June 20, 2007

Expanding Approved Stem Cell Lines in Ethically Responsible Ways

By the authority vested in me as President by the Constitution and the laws of the United States of America, and to provide leadership with respect to research on pluripotent stem cells derived by ethically responsible techniques so that the potential of pluripotent stem cells can be explored without violating human dignity or demeaning human life, it is hereby ordered as follows:

Section 1. *Research on Alternative Sources of Pluripotent Stem Cells.* (a) The Secretary of Health and Human Services (Secretary) shall conduct and support research on the isolation, derivation, production, and testing of stem cells that are capable of producing all or almost all of the cell types of the developing body and may result in improved understanding of or treatments for diseases and other adverse health conditions, but are derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus.

(b) Within 90 days of this order, the Secretary, after such consultation with the Director of the National Institutes of Health (Director), shall issue a plan, including such mechanisms as requests for proposals, requests for applications, program announcements and other appropriate means, to implement subsection (a) of this section, that:

(i) specifies and reflects a determination of the extent to which specific techniques may require additional basic or animal research to ensure that any research involving human cells using these techniques is clearly consistent with the standards established under this order and applicable law;

(ii) prioritizes research with the greatest potential for clinical benefit;

(iii) takes into account techniques outlined by the President's Council on Bioethics, and any other appropriate techniques and research, provided they clearly meet the standard set forth in subsection (a) of this section;

(iv) renames the ''Human Embryonic Stem Cell Registry'' the ''Human Pluripotent Stem Cell Registry;'' and

(v) adds to the registry new human pluripotent stem cell lines that clearly meet the standard set forth in subsection (a) of this section.

(c) Not later than December 31 of each year, the Secretary shall report to the President on the activities carried out under this order during the past fiscal year, including a description of the research carried out or supported by the Department of Health and Human Services, including the National Institutes of Health, and other developments in the science of pluripotent stem cells not derived from human embryos.

Sec. 2. *Policy.* The activities undertaken and supported by and under the direction of the Secretary shall be clearly consistent with the following policies and principles:

(a) the purposes of this order are (i) to direct the Department of Health and Human Services, including the National Institutes of Health, to intensify peer reviewed research that may result in improved understanding of or treatments for diseases and other adverse health conditions, and (ii) to promote the derivation of human pluripotent stem cell lines from a variety

of alternative sources while clearly meeting the standard set forth in section 1(a) of this order;

(b) it is critical to establish moral and ethical boundaries to allow the Nation to move forward vigorously with medical research, while also maintaining the highest ethical standards and respecting human life and human dignity;

(c) the destruction of nascent life for research violates the principle that no life should be used as a mere means for achieving the medical benefit of another;

(d) human embryos and fetuses, as living members of the human species, are not raw materials to be exploited or commodities to be bought and sold; and

(e) the Federal Government has a duty to exercise responsible stewardship of taxpayer funds, both supporting important medical research and respecting ethical and moral boundaries.

Sec. 3. *Interpretation of this Order.* (a) For purposes of this order, the term ''human embryo'' shall mean any organism, not protected as a human subject under 45 CFR 46 as of the date of this order, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.

(b) For purposes of this order, the term ''subjecting to harm a human embryo'' shall mean subjecting such an embryo to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)) as of the date of this order.

(c) Nothing in this order shall be construed to affect any policy, guideline, or regulation regarding embryonic stem cell research, human cloning by somatic cell nuclear transfer, or any other research not specifically authorized by this order, or to forbid the use of existing stem cell lines deemed eligible for other federally funded research in accordance with the presidential policy decision of August 9, 2001, for research specifically authorized by this order.

Sec. 4. *General Provisions.* (a) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.

(b) This order is not intended to, and does not, create any right, benefit, or privilege, substantive or procedural, enforceable at law or in equity, by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.

THE WHITE HOUSE,
June 20, 2007.

[FR Doc. 07–3112
Filed 6–21–07; 11:09 am]
Billing code 3195–01–P

a path to return to peace negotiations based on United Nations Security Council Resolutions 242, 338, and the Madrid Conference. To get to Mitchell, the parties need to resume effective security cooperation and work together to stop terrorism and violence.

I call upon the leaders of the Palestinian Authority and Israel to demonstrate foresight and responsibility by choosing the path toward a better future for their people.

Address to the Nation on Stem Cell Research From Crawford, Texas

August 9, 2001

Good evening. I appreciate you giving me a few minutes of your time tonight so I can discuss with you a complex and difficult issue, an issue that is one of the most profound of our time.

The issue of research involving stem cells derived from human embryos is increasingly the subject of a national debate and dinner table discussions. The issue is confronted every day in laboratories as scientists ponder the ethical ramifications of their work. It is agonized over by parents and many couples as they try to have children or to save children already born. The issue is debated within the church, with people of different faiths, even many of the same faith, coming to different conclusions. Many people are finding that the more they know about stem cell research, the less certain they are about the right ethical and moral conclusions.

My administration must decide whether to allow Federal funds, your tax dollars, to be used for scientific research on stem cells derived from human embryos. A large number of these embryos already exist. They are the product of a process called in vitro fertilization, which helps so many couples conceive children. When doctors match sperm and egg to create life outside the womb, they usually produce more embryos than are implanted in the mother. Once a couple successfully has children, or if they are unsuccessful, the additional embryos remain frozen in laboratories. Some will not survive during long storage; others are destroyed. A number have been donated to science and used to create privately funded stem cell lines. And a few have been implanted in an adoptive mother and born and are today healthy children.

Based on preliminary work that has been privately funded, scientists believe further research using stem cells offers great promise that could help improve the lives of those who suffer from many terrible diseases, from juvenile diabetes to Alzheimer's, from Parkinson's to spinal cord injuries. And while scientists admit they are not yet certain, they believe stem cells derived from embryos have unique potential.

You should also know that stem cells can be derived from sources other than embryos, from adult cells, from umbilical cords that are discarded after babies are born, from human placentas. And many scientists feel research on these types of stem cells is also promising. Many patients suffering from a range of diseases are already being helped with treatments developed from adult stem cells. However, most scientists, at least today, believe that research on embryonic stem cells offer the most promise because these cells have the potential to develop in all of the tissues in the body.

Scientists further believe that rapid progress in this research will come only with Federal funds. Federal dollars help attract the best and brightest scientists. They ensure new discoveries are widely shared at the largest number of research facilities and that the research is directed toward the greatest public good.

The United States has a long and proud record of leading the world toward advances in science and medicine that improve human life. And the United States has a long and proud record of upholding the highest standards of ethics as we expand the limits of science and knowledge. Research on embryonic stem cells raises profound ethical questions, because extracting the stem cell destroys the embryo and thus destroys its potential for life. Like a snowflake, each of these embryos is unique, with the unique genetic potential of an individual human being.

As I thought through this issue, I kept returning to two fundamental questions: First, are these frozen embryos human life and, therefore, something precious to be protected? And second, if they're going to be

destroyed anyway, shouldn't they be used for a greater good, for research that has the potential to save and improve other lives?

I've asked those questions and others of scientists, scholars, bioethicists, religious leaders, doctors, researchers, Members of Congress, my Cabinet, and my friends. I have read heartfelt letters from many Americans. I have given this issue a great deal of thought, prayer, and considerable reflection. And I have found widespread disagreement.

On the first issue, are these embryos human life? Well, one researcher told me he believes this 5-day-old cluster of cells is not an embryo, not yet an individual, but a preembryo. He argued that it has the potential for life, but it is not a life because it cannot develop on its own. An ethicist dismissed that as a callous attempt at rationalization. "Make no mistake," he told me, "that cluster of cells is the same way you and I, and all the rest of us, started our lives. One goes with a heavy heart if we use these," he said, "because we are dealing with the seeds of the next generation."

And to the other crucial question, if these are going to be destroyed anyway, why not use them for good purpose, I also found different answers. Many argue these embryos are byproducts of a process that helps create life, and we should allow couples to donate them to science so they can be used for good purpose instead of wasting their potential. Others will argue there's no such thing as excess life and the fact that a living being is going to die does not justify experimenting on it or exploiting it as a natural resource.

At its core, this issue forces us to confront fundamental questions about the beginnings of life and the ends of science. It lies at a difficult moral intersection, juxtaposing the need to protect life in all its phases with the prospect of saving and improving life in all its stages.

As the discoveries of modern science create tremendous hope, they also lay vast ethical minefields. As the genius of science extends the horizons of what we can do, we increasingly confront complex questions about what we should do. We have arrived at that brave new world that seemed so distant in 1932, when Aldous Huxley wrote about human beings created in test tubes in what he called a "hatchery." In recent weeks, we learned that scientists have created human embryos in test tubes solely to experiment on them. This is deeply troubling and a warning sign that should prompt all of us to think through these issues very carefully.

Embryonic stem cell research is at the leading edge of a series of moral hazards. The initial stem cell researcher was at first reluctant to begin his research, fearing it might be used for human cloning. Scientists have already cloned a sheep. Researchers are telling us the next step could be to clone human beings to create individual designer stem cells, essentially to grow another you, to be available in case you need another heart or lung or liver.

I strongly oppose human cloning, as do most Americans. We recoil at the idea of growing human beings for spare body parts, or creating life for our convenience. And while we must devote enormous energy to conquering disease, it is equally important that we pay attention to the moral concerns raised by the new frontier of human embryo stem cell research. Even the most noble ends do not justify any means.

My position on these issues is shaped by deeply held beliefs. I'm a strong supporter of science and technology and believe they have the potential for incredible good, to improve lives, to save life, to conquer disease. Research offers hope that millions of our loved ones may be cured of a disease and rid of their suffering. I have friends whose children suffer from juvenile diabetes. Nancy Reagan has written me about President Reagan's struggle with Alzheimer's. My own family has confronted the tragedy of childhood leukemia. And like all Americans, I have great hope for cures.

I also believe human life is a sacred gift from our Creator. I worry about a culture that devalues life and believe as your President I have an important obligation to foster and encourage respect for life in America and throughout the world. And while we're all hopeful about the potential of this research, no one can be certain that the science will live up to the hope it has generated.

Eight years ago, scientists believed fetal tissue research offered great hope for cures and treatments, yet the progress to date has

not lived up to its initial expectations. Embryonic stem cell research offers both great promise and great peril. So I have decided we must proceed with great care.

As a result of private research, more than 60 genetically diverse stem cell lines already exist. They were created from embryos that have already been destroyed, and they have the ability to regenerate themselves indefinitely, creating ongoing opportunities for research. I have concluded that we should allow Federal funds to be used for research on these existing stem cell lines, where the life and death decision has already been made.

Leading scientists tell me research on these 60 lines has great promise that could lead to breakthrough therapies and cures. This allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life.

I also believe that great scientific progress can be made through aggressive Federal funding of research on umbilical cord, placenta, adult, and animal stem cells which do not involve the same moral dilemma. This year, your Government will spend $250 million on this important research.

I will also name a President's council to monitor stem cell research, to recommend appropriate guidelines and regulations, and to consider all of the medical and ethical ramifications of biomedical innovation. This council will consist of leading scientists, doctors, ethicists, lawyers, theologians, and others and will be chaired by Dr. Leon Kass, a leading biomedical ethicist from the University of Chicago. This council will keep us apprised of new developments and give our Nation a forum to continue to discuss and evaluate these important issues.

As we go forward, I hope we will always be guided by both intellect and heart, by both our capabilities and our conscience. I have made this decision with great care, and I pray it is the right one.

Thank you for listening. Good night, and God bless America.

NOTE: The President spoke at 8:01 p.m. at the Bush Ranch.

Digest of Other White House Announcements

The following list includes the President's public schedule and other items of general interest announced by the Office of the Press Secretary and not included elsewhere in this issue.

August 4

In the morning, the President traveled to Bethesda, MD, where he had his annual physical examination at Bethesda Naval Hospital. In the afternoon, he traveled to the Bush Ranch in Crawford, TX.

August 7

In the morning, the President traveled to Waco, TX, and later returned to Crawford.

The White House announced that the President will send U.S. Trade Representative Robert Zoellick to Indonesia on August 10–11 to meet with President Megawati.

August 8

In the morning, the President traveled to Waco, TX, and later returned to Crawford.

August 9

In the morning, the President had a telephone conversation with Secretary of Health and Human Services Tommy G. Thompson concerning the President's decision on stem cell research. In the afternoon, he had a telephone conversation with Dr. Leon Kass of the University of Chicago, also concerning the President's decision on stem cell research.

August 10

The President announced his intention to nominate Ralph Leo Boyce to be Ambassador to Indonesia.

The President announced his intention to nominate John D. Ong to be Ambassador to Norway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Disease, Disability, and Injury Prevention and Control Special Emphasis Panel (SEP): Sexually Transmitted Disease (STD) Faculty Expansion Program, Program Announcement #02005

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), the Centers for Disease Control and Prevention (CDC) announces the following meeting.

Name: Disease, Disability, and Injury Prevention and Control Special Emphasis Panel (SEP): Sexually Transmitted Disease (STD) Faculty Expansion Program, Program Announcement #02005.

Times and Date: 9 a.m.–9:30 a.m., November 29, 2001 (Open). 9:30 a.m.–4:30 p.m., November 29, 2001 (Closed).

Place: Centers for Disease Control and Prevention, National Center for HIV, STD, and TB Prevention, 10 Corporate Square Blvd, Conference Room 1304, Atlanta, Georgia 30329.

Status: Portions of the meeting will be closed to the public in accordance with provisions set forth in section 552b(c)(4) and (6), Title 5 U.S.C., and the Determination of the Deputy Director for Program Management, CDC, pursuant to Pub. L. 92–463.

Matters to be Discussed: The meeting will include the review, discussion, and evaluation of applications received in response to Program Announcement 02005.

CONTACT PERSON FOR MORE INFORMATION: Elizabeth A. Wolfe, Prevention Support Office, National Center for HIV, STD, and TB Prevention, CDC, Corporate Square Office Park, 8 Corporate Square Boulevard, M/S E07, Atlanta, Georgia 30329, telephone 404/639–8025.

The Director, Management Analysis and Services office has been delegated the authority to sign Federal Register notices pertaining to announcements of meetings and other committee management activities, for both the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry.

Dated: November 2, 2001.

John C. Burckhardt,

Acting Director, Management Analysis and Services Office, Centers for Disease Control and Prevention CDC.

[FR Doc. 01–28436 Filed 11–13–01; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells

ACTION: Notice; withdrawal of NIH Guidelines for Research Using Pluripotent Stem Cells Derived from Human Embryos (published August 25, 2000, 65 FR 51976, correctedNovember 21, 2000, 65 FR 69951).

SUMMARY: The National Institutes of Health (NIH) announces the withdrawal of those sections of the NIH Guidelines for Research Using Human Pluripotent Stem Cells, *http://www.nih.gov/news/stemcell/stemcellguidelines.htm.* (NIH Guidelines), that pertain to research involving human pluripotent stem cells derived from human embryos that are the result of *in vitro* fertilization, are in excess of clinical need, and have not reached the stage at which the mesoderm is formed.

The President has determined the criteria that allow Federal funding for research using existing embryonic stem cell lines, *http://www.whitehouse.gov/news/releases/2001/08/print/20010809-1.html.* Thus, the NIH Guidelines as they relate to human pluripotent stem cells derived from human embryos are no longer needed.

FOR FURTHER INFORMATION CONTACT: NIH Office of Extramural Research, NIH, 1 Center Drive, MSC 0152, Building 1, Room 146, Bethesda, MD 20892, or e-mail *DDER@nih.gov.*

Dated: November 2, 2001.

Ruth L. Kirschstein,

Acting Director, National Institutes of Health.

[FR Doc. 01–28426 Filed 11–13–01; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF THE INTERIOR

Office of the Secretary

Invasive Species Advisory Committee; Notice

AGENCY: Office of the Secretary, Interior.

ACTION: Request for nominations for the Invasive Species Advisory Committee—Extension of Deadline for Nomination Submissions.

SUMMARY: This is an extension of the deadline for nomination submissions due to ongoing delays in surface mail processing in the Washington, DC Metropolitan Area.

DATES: Extended Deadline—Tuesday, November 27, 2001 (6 p.m. EST).

ADDRESSES: Nominations should be sent to Lori Williams, Executive Director, National Invasive Species Council, 1951 Constitution Ave., NW., Room 320, Washington, DC 20240.

FOR FURTHER INFORMATION CONTACT: Kelsey Passé, Program Analyst, at (202) 208–6336, fax: (202) 208–1526, or by e-mail at *Kelsey_Passe@ios.doi.gov.*

SUPPLEMENTARY INFORMATION:

Advisory Committee Scope and Objectives

The purpose and role of the ISAC are to provide advice to the Invasive Species Council (Council), as authorized by Executive Order 13112, on a broad array of issues including preventing the introduction of invasive species, providing for their control, and minimizing the economic, ecological, and human health impacts that invasive species cause. The Council is Co-chaired by the Secretaries of the Interior, Agriculture, and Commerce. The duty of the Council is to provide national leadership regarding invasive species issues. Pursuant to the Executive Order, the Council developed a National Invasive Species Management Plan. The Plan is available on the web at *www.invasivespecies.gov.* The Council is responsible for effective implementation of the Plan. The Council coordinates Federal agency activities concerning invasive species; prepares, revises and issues the National Invasive Species Management Plan; encourages planning and action at local, tribal, State, regional and ecosystem-based levels; develops recommendations for international cooperation in addressing invasive species; facilitates the development of a coordinated network to document, evaluate, and monitor impacts from invasive species; and facilitates establishment of an information-sharing system on invasive species that utilizes, to the greatest extent practicable, the Internet.

The role of ISAC is to maintain an intensive and regular dialogue regarding the aforementioned issues. ISAC provides advice in cooperation with stakeholders and existing organizations addressing invasive species. The ISAC meets up to four (4) times per year.

Terms for current members of the ISAC expire at the end of 2001. Current members of the ISAC are eligible for reappointment. The Secretary of the Interior will appoint members to ISAC in consultation with the Secretaries of Agriculture and Commerce. The Secretary of Interior actively solicits

pharmacokinetic imaging in a non-invasive manner after non-toxic infusion of the spin probe.

However, the disadvantage of EPRI is the lack of proper orientation of the physiological image with respect to anatomy. On the contrary, Magnetic Resonance Imaging (MRI) methods are excellent for providing images with fine anatomical detail, but are often not possible methods that provide physiological information co-registered with anatomy with clinically relevant resolution.

The current invention complements a MRI with EPRI methods to solve each method's problem described above. A low-field MRI(5–30 mT) module is integrated into an EPRI(5—20 mT) system to provide an MRI scout image to properly orient the EPRI physiological information with respect to anatomy (A common magnet/gradient coil assembly is used for both MRI and EPRI scans).

Therefore, the EPR images contain spectral information regarding the local physiological conditions such as oxygen status. This data, when overlaid with anatomical images of MRI (Magnetic Resonance Imaging), co-register anatomical MR images and EPR physiological images.

Dated: November 13, 2000.

Jack Spiegel,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 00–29717 Filed 11–20–00; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells; Correction

ACTION: Notice; correction.

SUMMARY: The National Institutes of Health published in the **Federal Register** on August 25, 2000, the final National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells (65 FR 51976). The final Guidelines contained incorrect citations and other errors. The final Guidelines, with the corrections made in this notice, are available on the NIH stem cell information web site at:(*http://www.nih.gov/news/stemcell/index.htm*). For additional information on human pluripotent stem cells, refer to this web site.

FOR FURTHER INFORMATION CONTACT: NIH Office of Science Policy, Attention: HPSCRG, Building 1, Room 218, MSC 0166, 9000 Rockville Pike, Bethesda, MD 20892, (301) 594–7741 or e-mail *stemcell@mail.nih.gov.*

Corrections

1. In Section II.A.2.d of the Guidelines (65 FR 51980, first column), change ''human pluripotent stem cells,'' at the end of the section, to ''embryo.''

2. In Section II.B.1.a. of the Guidelines (65 FR 51980, second column), change ''Section II.A.2'' to ''Section II.B.2.''

3. In Section II.B.2.a. of the Guidelines (65 FR 51980, third column), add the following at the end of the section: ''and with 42 U.S.C. § 289g–2(b).''

4. In Section IV.B. of the Guidelines (65 FR 51981, first column), change ''applications shall'' in the first sentence to ''documentation of compliance with the Guidelines will'' and insert after ''by HPSCRG and'' the words, ''all applications will be reviewed''.

Dated: November 15, 2000.

Ruth L. Kirschstein,

Principal Deputy Director, NIH.

[FR Doc. 00–29791 Filed 11–20–00; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. FR–4565–N–31]

Notice of Proposed Information Collection: Comment Request; Section 203(k) Rehabilitation Mortgage Insurance Program

AGENCY: Office of the Assistant Secretary for Housing, HUD.

ACTION: Notice.

SUMMARY: The proposed information collection requirement described below will be submitted to the Office of Management and Budget (OMB) for review, as required by the Paperwork Reduction Act. The Department is soliciting public comments on the subject proposal.

DATES: *Comments Due Date:* January 22, 2000.

ADDRESSES: Interested persons are invited to submit comments regarding this proposal. Comments should refer to the proposal by name and/or OMB Control Number and should be sent to: Wayne Eddins, Reports Management Officer, Department of Housing and Urban Development, 451 7th Street, SW, L'Enfant Plaza Building, Room 8001, Washington, DC 20410.

FOR FURTHER INFORMATION CONTACT: Vance T. Morris, Director, Office of Single Family Program Development, Department of Housing and Urban Development, 451 7th Street SW, Washington, DC 20410, telephone (202) 708–2121 (this is not a toll free number) for copies of the proposed forms and other available information.

SUPPLEMENTARY INFORMATION: The Department is submitting the proposed information collection to OMB for review, as required by the Paperwork Reduction Act of 1995 (44 U.S.C. Chapter 35, as amended).

This notice is soliciting comments from members of the public and affected agencies concerning the proposed collection of information to: (1) Evaluate whether the proposed collection is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) Evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information; (3) Enhance the quality, utility, and clarity of the information to be collected; and (4) Minimize the burden of the collection of information on those who are to respond; including the use of appropriate automated collection techniques or other forms of information technology, e.g., permitting electronic submission of responses.

This Notice also lists the following information:

Title of Proposal: 203(k) Rehabilitation Mortgage Insurance.

OMB Control Number, if applicable: 2502–0527.

Description of the need for the information and proposed use: This request for OMB review involves a reinstatement of a previously approved information collection for 203(k) Rehabilitation Mortgage insurance (OMB control number 2502–0527) that expired on October 31, 2000. The information collection implements recommendations to mitigate program abuses that were cited in an Audit Report of HUD's Office of Inspector General. The information collection focuses on the loan origination process and requires (1) certifications and disclosures concerning identity–of–interest borrowers and program participants, and (2) proficiency testing of home inspectors/consultants. Periodic reporting of the collected information is not required.

Agency form numbers, if applicable: HUD–92700 & HUD–9746–A.

Estimation of the total numbers of hours needed to prepare the information collection including number of respondents, frequency of response, and

Federal Register

Friday,
August 25, 2000

Part IV

Department of Health and Human Services

National Institutes of Health

National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells and Notification of Request for Emergency Clearance; Modification of OMB No. 0925–0001/Exp. 2/01, "PHS 398 Research and Research Training Grant Applications and Related Forms"; Notices

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells

SUMMARY: The National Institutes of Health (NIH) is hereby publishing final ''National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells.'' The Guidelines establish procedures to help ensure that NIH-funded research in this area is conducted in an ethical and legal manner.

EFFECTIVE DATE: These Guidelines are effective on August 25, 2000. The moratorium on research using human pluripotent stem cells derived from human embryos and fetal tissue put in place by the Director, NIH, in January 1999, will be lifted on August 25, 2000.

SUMMARY OF PUBLIC COMMENTS ON DRAFT GUIDELINES: On December 2, 1999 (64 FR 67576), the NIH published Draft Guidelines for research involving human pluripotent stem cells (hPSCs) in the **Federal Register** for public comment. The comment period ended on February 22, 2000.

The NIH received approximately 50,000 comments from members of Congress, patient advocacy groups, scientific societies, religious organizations, and private citizens. This Notice presents the final Guidelines together with NIH's response to the substantive public comments that addressed provisions of the Guidelines.

Scope of Guidelines and General Issues

Respondents asked for clarification of terminology used in the Guidelines and some commented that the language was not appropriate or was too technical, particularly the informed consent sections. The NIH agrees that these Guidelines should be clear and understandable. Changes, including some reorganization of the sections, were made to this end. The Guidelines are written primarily for the purpose of informing investigators of the conditions that must be met in order to receive NIH funding for research using hPSCs and, therefore, some technical language is required. The Guidelines do not define the precise language that should appear in informed consent documents because these should be developed by the investigator/clinician specifically for a particular study protocol or procedure for which the consent is being sought. Existing regulatory provisions require (45 CFR 46.116) that the language in informed consent documents be understandable to prospective participants in the study.

Respondents suggested that NIH funding for research using hPSCs would be in violation of the DHHS appropriations law and that derivation of hPSCs cannot be distinguished from their use. For this reason, a number of respondents asked that the NIH withdraw the draft Guidelines. The NIH sought the opinion of the DHHS General Counsel, who determined that ''federally funded research that utilizes hPSCs would not be prohibited by the HHS appropriations law prohibiting human embryo research, because such cells are not human embryos.'' Comments questioning this conclusion did not present information or arguments that justify reconsideration of the conclusion.

Respondents commented that the Guidelines are too restrictive or that there is no need for Federal Guidelines for this arena of research. Comments asserted that federally funded research using hPSCs should go forward without formal requirements, in the same manner as in the private sector. In order to help ensure that the NIH-funded research using hPSCs is conducted in an ethical and legal manner, the NIH felt it was advisable to develop and implement guidelines. To this end, the NIH Director convened a Working Group of the Advisory Committee to the Director, NIH (ACD), to advise the ACD on the development of guidelines and an oversight process for research involving hPSCs. The NIH Director charged the Working Group with developing appropriate guidelines to govern research involving the derivation and use of hPSCs from fetal tissue and research involving the use of hPSCs derived from human embryos that are in excess of clinical need.

Respondents commented regarding the sources of stem cells. Some respondents stated that research on hPSCs was unnecessary because stem cells from adults, umbilical cords, and placentas could be used instead. Other respondents asked the NIH to restrict Federal funding for hPSC research to those cells derived from fetal and adult tissue but not embryos. Other respondents asked that the Guidelines encompass research using stem cells from adult tissues.

As stated under Section I. *Scope of Guidelines*, the Guidelines apply to the use of NIH funds for research using hPSCs derived from human embryos or human fetal tissue. The Guidelines do not impose requirements on Federal funding of research involving stem cells from human adults, umbilical cords, or placentas.

Given the enormous potential of stem cells to the development of new therapies for the most devastating diseases, it is important to simultaneously pursue all lines of promising research. It is possible that no single source of stem cells is best or even suitable/usable for all therapies. Different types or sources of stem cells may be optimal for treatment of specific conditions. In order to determine the very best source of many of the specialized cells and tissues of the body for new treatments and even cures, it is vitally important to study the potential of adult stem cells for comparison to that of hPSCs derived from embryos and fetuses. Unless all stem cell types are studied, the differences between adult stem cells and embryo and fetal-derived hPSCs will not be known.

Moreover, there is evidence that adult stem cells may have more limited potential than hPSCs. First, stem cells for all cell and tissue types have not yet been found in the adult human. Significantly, cardiac stem cells or pancreatic islet stem cells have not been identified in adult humans.

Second, stem cells in adults are often present in only minute quantities, are difficult to isolate and purify, and their numbers may decrease with age. For example, brain cells from adults that may be neural stem cells have been obtained only by removing a portion of the brain of an adult with epilepsy, a complex and invasive procedure that carries the added risk of further neurological damage. Any attempt to use stem cells from a patient's own body for treatment would require that stem cells would first have to be isolated from the patient and then grown in culture in sufficient numbers to obtain adequate quantities for treatment. This would mean that for some rapidly progressing disorders, there may not be sufficient time to grow enough cells to use for treatment.

Third, in disorders that are caused by a genetic defect, the genetic error likely would be present in the patient's stem cells, making cells from such a patient inappropriate for transplantation. In addition, adult stem cells may contain more DNA abnormalities caused by exposure to daily living, including sunlight, toxins, and errors made during DNA replication than will be found in fetal or embryonic hPSCs.

Fourth, there is evidence that stem cells from adults may not have the same capacity to multiply as do younger cells. These potential weaknesses may limit the usefulness of adult stem cells.

Respondents were concerned that these are guidelines and not requirements or regulations. Although these are guidelines and not regulations, they prescribe the documentation and assurances that must accompany requests for NIH funding for research utilizing hPSCs. If the funding requests do not contain the prescribed information, funding for hPSC research will not be provided. Compliance with the Guidelines will be imposed as a condition of grant award.

Respondents commented that there had not been enough widespread public disclosure/discussion of this research or the Guidelines. Prior to the development of draft Guidelines, there were two Congressional hearings on hPSCs. In a further effort to ensure substantial discussion and comment, the NIH convened a Working Group of the Advisory Committee to the Director, NIH (ACD), to advise the ACD on the development of these Guidelines. The Working Group was composed of scientists, patients and patient advocates, ethicists, clinicians, and lawyers. The Working Group met in public session on April 8, 1999, and heard from members of the public, as well as professional associations and Congress. In developing the draft Guidelines, the NIH also considered advice from the National Bioethics Advisory Commission (NBAC). Draft Guidelines were published for public comment in the **Federal Register** on December 2, 1999, for 60 days, and, in response to public interest, the comment period was extended an additional 28 days. Approximately 50,000 comments were received. NIH issued a national press release announcing the **Federal Register** notice and many of the Nation's newspapers carried articles on this area of research and on the Guidelines. Patient groups, scientific societies, and religious organizations convened meetings and discussion groups and disseminated materials about this area of research and about the Guidelines.

Comment was received about whether the Guidelines apply to hPSC lines developed outside of the United States. The Guidelines make no distinction based upon the country in which an hPSC line is developed. All lines to be used in hPSC cell research funded by NIH must meet the same requirements.

Derivation and Use of hPSCs From Fetal Tissue

Respondents made the point that the NIH has specified certain requirements for the use of human fetal tissue to derive hPSCs in addition to those imposed on other areas of human fetal tissue research. These respondents suggested that the section of the Guidelines pertaining to fetal tissue sources be omitted. In order to ensure uniformity in NIH's oversight of research using hPSCs, the Guidelines were extended to govern hPSCs derived from both human embryos and fetal tissue.

Use of hPSCs Derived From Human Embryos

Respondents suggested that the Guidelines refer to ''fertility treatment'' rather than to ''infertility treatment'' in order to clarify that they allow the use of human embryos from treatments that employ assisted reproductive technologies to facilitate reproduction in fertile, as well as in infertile, individuals. The Guidelines have been changed accordingly.

Respondents suggested dropping the word ''early'' throughout the document or more clearly defining ''early.'' The word ''early'' in reference to human embryos has been deleted; the Guidelines make it clear that NIH funding of research using hPSCs derived in the private sector from human embryos can involve only embryos that have not reached the stage at which the mesoderm is formed.

Some respondents were concerned that embryos might be created for research purposes. Other respondents stated there should be no distinction between embryos created for research purposes and those created for fertility treatment. Investigators seeking NIH funds for research using hPSCs are required to provide documentation, prior to the award of any NIH funds, that embryos were created for the purposes of fertility treatment. President Clinton, many members of Congress, the NIH Human Embryo Research Panel, and the NBAC have all embraced the distinction between embryos created for research purposes and those created for reproductive purposes.

Respondents were concerned about the creation of a ''black market'' for human embryos, and expressed concerns that individuals will be coerced into donating embryos. The Guidelines state that there can be no incentives for donation and that a decision to donate must be made free of coercion. In addition, the Guidelines set forth conditions that will help ensure all donations are voluntary. For example, with regard to hPSCs derived from embryos, research using Federal funds may only be conducted if the cells were derived from frozen embryos that were created for the purpose of fertility treatment and that were in excess of clinical need.

Respondents commented on the requirement that human embryos be frozen in order to qualify for derivation of hPSCs to be used in NIH-funded research. Respondents suggested that the freezing requirement would preclude the use of hPSCs derived from embryos that are genetically and chromosomally abnormal, since such embryos are usually not frozen for reproductive purposes. While the NIH acknowledges that research on hPSCs derived from such embryos could yield important scientific information, limiting research to hPSCs derived from frozen human embryos will help ensure that the decision to donate the embryo for hPSC research is distinct and separate from the fertility treatment.

Financial Issues

Respondents expressed concern regarding the sale of fetal tissue for profit and whether hPSC research would encourage such activity. Respondents also were concerned about whether clinics or doctors would profit from the derivation of hPSCs and/or their sale. Section 498B of the Public Health Service Act prohibits any individual from knowingly acquiring or selling human fetal tissue for ''valuable consideration.'' In addition, the Guidelines prohibit any inducement for the donation of human embryos for research purposes. The Guidelines also call for an assurance that the hPSCs to be used in NIH-funded research were obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the hPSCs. All grantees must sign an assurance that they are in compliance with all applicable Federal, State, and local laws. Each funded research institution is responsible for monitoring compliance by individual investigators with any such applicable laws.

Respondents questioned the prohibition against embryo donors benefitting financially from their donation. This clause was retained in the final Guidelines to help ensure that the donating individuals are offered no inducements to donate and that all donations are voluntary.

Respondents suggested that the Guidelines be strengthened to include a waiver of intellectual property rights. This proposed change would be inconsistent with 45 CFR 46.116 of the regulation for the protection of human subjects of research, which provides that no informed consent may include

language through which the subject waives or appears to waive any of the subject's legal rights.

Respondents questioned the reference in the requirements for informed consent related to the commercial potential of donated material. The paragraphs providing for disclosure in the informed consent of the possibility that the donated material could have commercial potential were modified. The reference in these paragraphs to ''donated material'' did not accurately reflect the intent of the provision. The Guidelines now make clear that the ''results of research on the human pluripotent stem cells may have commercial potential.''

Ineligible Research

Respondents objected to the areas of research that the NIH has deemed ineligible, particularly research that is not restricted by statute or regulation, such as research utilizing hPSCs that were derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human egg. The NIH determined that, at this time, research using hPSCs derived from such sources has not received adequate discussion and consideration by the public and is, therefore, ineligible for NIH funding.

Separation of Fertility Treatment and Abortion From Research

Respondents were concerned that hPSC research would encourage abortion. The law and the Guidelines guard against encouraging abortion by requiring that the decision to have an abortion be made apart from and prior to the decision to donate tissue.

Respondents objected to the condition in the Guidelines that the fertility physician could not be the same person as the researcher deriving stem cells. Some respondents stated that the Institutional Review Board (IRB) or an independent physician would be able to guard against this conflict of interest. The restriction was designed so that the person treating the individuals seeking fertility treatment, who is involved in decisions such as how many embryos to produce, is not the person seeking to derive hPSCs. This separation will help ensure that embryos will not be created in numbers greater than necessary for fertility treatment.

Respondents suggested that the clauses regarding donation of fetal tissue or human embryos for derivation of stem cells for eventual use in transplantation be changed explicitly to prevent directed donation. This change has been made.

Identifiers

Respondents were concerned about removing identifiers. There was concern that the investigator would not be able to document compliance with the Guidelines requirements without identifiers, or that the removal of identifiers would make it impossible to conduct certain genetic studies or develop therapeutic materials. The Guidelines have been modified to clarify that the term ''identifier'' refers to any information from which the donor(s) can be identified, directly or through identifiers linked to the donors. However, since information identifying the donor(s) may be necessary if the tissue or cells are to be used in transplantation, the Guidelines have also been modified to state that the informed consent should notify donor(s) whether or not identifiers will be retained.

Respondents commented that DNA is an identifier and that all donors of human embryos or fetal tissue should be told that identifiers such as DNA will be retained with the samples. Although DNA can be used to determine the individual from whom a tissue sample was taken, this can be done only when one has a sample from both the tissue in question and the putative donor; it cannot be used to identify an individual out of a population. Moreover, it is difficult to identify a donor using tissue derived from a fetus or embryo, since the tissue is not genetically identical to the donor.

Informed Consent and IRB Review

Respondents asked why investigators were expected to provide documentation of IRB review of derivation from human embryos, but not for derivation from fetal tissue. Respondents suggested that the requirements be changed so that protocols for both sources of hPSCs must be approved by an IRB. The Guidelines have been changed to make clear that the IRB review requirements regarding the derivation of cells from fetal tissue and human embryos are the same.

Comment was received expressing concern that the informed consent explicitly state that the donor will have no dispositional authority over derived pluripotent stem cells. The Guidelines state that donation of human embryos should have been made without any restriction regarding the individual(s) who may be the recipient of the cells derived from the hPSCs for transplantation. Such a statement is consistent with the statutory provision applicable to the donor informed consent for the use of fetal tissue for transplantation. The Guidelines now provide for the inclusion of a statement to this effect in the informed consent.

Respondents urged that the Guidelines be revised to remove the prohibition on potential donors receiving information regarding subsequent testing of donated tissue in the situation when physicians deem disclosure to be in the donors' best interest. This change has been made.

Respondents requested clarification regarding the persons from whom consent for donation of embryos for research must be obtained. The Guidelines call for informed consent from individual(s) who have sought fertility treatment. Only the individual(s) who were part of the decision to create the embryo for reproductive purposes should have been part of the decision to donate for the derivation of hPSCs.

Respondents urged that fertility clinics should be able to discuss with patients the option of donating embryos for research at the beginning of the IVF process. The Guidelines do not delineate the timeframe during which the general option of donating embryos for research can be discussed. However, according to the Guidelines, obtaining consent for donation of embryos for the purpose of deriving hPSCs should not occur until after the embryos are determined to be in ''excess of clinical need.''

Oversight

Respondents stated that the NIH's oversight in this area of research was very important to the legal and ethical conduct of this research, and asked for more information regarding the oversight process. Information about the operations of the Human Pluripotent Stem Cell Review Group (HPSCRG) can be found in the final Guidelines and on the NIH Web page.

Respondents were concerned about whether and how NIH would monitor research after a researcher receives NIH funds. Compliance with the Guidelines will be largely determined prior to the award of funds. Follow-up to ensure continued compliance with the Guidelines will be conducted in the same manner as for all other conditions of all other NIH grant awards. It is the responsibility of the investigator to file progress reports, and it is the responsibility of the funded institution to ensure compliance with the NIH Guidelines. NIH staff will also monitor the progress of these investigators as part of their regular duties.

Respondents asked about penalties for not following the Guidelines. The following actions may be taken by the NIH when there is a failure to comply with the terms and conditions of any award: (1) Under 45 CFR 74.14, the NIH can impose special conditions on an award, including increased oversight/monitoring/reporting requirements for an institution, project or investigator; and (2) under 45 CFR 74.62, if a grantee materially fails to comply with the terms and conditions of the award, the NIH may withhold funds pending correction of the problem or, pending more severe enforcement action, disallow all or part of the costs of the activity that was not in compliance, withhold further awards for the project, or suspend or terminate all or part of the funding for the project. Individuals and institutions may be debarred from eligibility for all Federal financial assistance and contracts under 45 CFR Part 76 and 48 CFR Subpart 9.4, respectively. Because these sanctions pertain to all conditions of grant award, the NIH did not reiterate them in the Guidelines.

Respondents suggested that the HPSCRG hold periodic Stem Cell Policy Conferences (similar to the Gene Therapy Policy Conferences conducted by the Recombinant DNA Advisory Committee (''RAC'')) in order to solicit and consider public comment from interested parties on the scientific, medical, legal, and ethical issues arising from stem cell research. Members of the HPSCRG will serve as a resource for recommending to the NIH any need for Human Pluripotent Stem Cell Policy Conferences.

Other Changes

Because compliance materials may be made public prior to funding decisions, we have added a sentence requiring the principal investigator's written consent to the disclosure of such material necessary to carry out public review and other oversight procedures.

The draft Guidelines required HPSCRG review of proposals from investigators planning to derive hPSCs from fetal tissue. Because the Guidelines address proposals for NIH funding for the use of hPSCs, this requirement has been removed from the Guidelines.

The text of the final Guidelines follows.

National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells

I. Scope of Guidelines

These Guidelines apply to the expenditure of National Institutes of Health (NIH) funds for research using human pluripotent stem cells derived from human embryos (technically known as human embryonic stem cells) or human fetal tissue (technically known as human embryonic germ cells). For purposes of these Guidelines, ''human pluripotent stem cells'' are cells that are self-replicating, are derived from human embryos or human fetal tissue, and are known to develop into cells and tissues of the three primary germ layers. Although human pluripotent stem cells may be derived from embryos or fetal tissue, such stem cells are not themselves embryos. NIH research funded under these Guidelines will involve human pluripotent stem cells derived: (1) From human fetal tissue; or (2) from human embryos that are the result of *in vitro* fertilization, are in excess of clinical need, and have not reached the stage at which the mesoderm is formed.

In accordance with 42 Code of Federal Regulations (CFR) 52.4, these Guidelines prescribe the documentation and assurances that must accompany requests for NIH funding for research using human pluripotent stem cells from: (1) Awardees who want to use existing funds; (2) awardees requesting an administrative or competing supplement; and (3) applicants or intramural researchers submitting applications or proposals. NIH funds may be used to derive human pluripotent stem cells from fetal tissue. NIH funds may not be used to derive human pluripotent stem cells from human embryos. These Guidelines also designate certain areas of human pluripotent stem cell research as ineligible for NIH funding.

II. Guidelines for Research Using Human Pluripotent Stem Cells That Is Eligible for NIH Funding

A. Utilization of Human Pluripotent Stem Cells Derived From Human Embryos

1. Submission to NIH

Intramural or extramural investigators who are intending to use existing funds, are requesting an administrative supplement, or are applying for new NIH funding for research using human pluripotent stem cells derived from human embryos must submit to NIH the following:

a. An assurance signed by the responsible institutional official that the pluripotent stem cells were derived from human embryos in accordance with the conditions set forth in section II.A.2 of these Guidelines and that the institution will maintain documentation in support of the assurance;

b. A sample informed consent document (with patient identifier information removed) and a description of the informed consent process that meet the criteria for informed consent set forth in section II.A.2.e of these Guidelines;

c. An abstract of the scientific protocol used to derive human pluripotent stem cells from an embryo;

d. Documentation of Institutional Review Board (IRB) approval of the derivation protocol;

e. An assurance that the stem cells to be used in the research were or will be obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells;

f. The title of the research proposal or specific subproject that proposes the use of human pluripotent stem cells;

g. An assurance that the proposed research using human pluripotent stem cells is not a class of research that is ineligible for NIH funding as set forth in section III of these Guidelines; and

h. The Principal Investigator's written consent to the disclosure of all material submitted under Paragraph A.1 of this section, as necessary to carry out the public review and other oversight procedures set forth in section IV of these Guidelines.

2. Conditions for the Utilization of Human Pluripotent Stem Cells Derived From Human Embryos

Studies utilizing pluripotent stem cells derived from human embryos may be conducted using NIH funds only if the cells were derived (without Federal funds) from human embryos that were created for the purposes of fertility treatment and were in excess of the clinical need of the individuals seeking such treatment.

a. To ensure that the donation of human embryos in excess of the clinical need is voluntary, no inducements, monetary or otherwise, should have been offered for the donation of human embryos for research purposes. Fertility clinics and/or their affiliated laboratories should have implemented specific written policies and practices to ensure that no such inducements are made available.

b. There should have been a clear separation between the decision to create embryos for fertility treatment and the decision to donate human embryos in excess of clinical need for research purposes to derive pluripotent stem cells. Decisions related to the creation of embryos for fertility treatment should have been made free

from the influence of researchers or investigators proposing to derive or utilize human pluripotent stem cells in research. To this end, the attending physician responsible for the fertility treatment and the researcher or investigator deriving and/or proposing to utilize human pluripotent stem cells should not have been one and the same person.

c. To ensure that human embryos donated for research were in excess of the clinical need of the individuals seeking fertility treatment and to allow potential donors time between the creation of the embryos for fertility treatment and the decision to donate for research purposes, only frozen human embryos should have been used to derive human pluripotent stem cells. In addition, individuals undergoing fertility treatment should have been approached about consent for donation of human embryos to derive pluripotent stem cells only at the time of deciding the disposition of embryos in excess of the clinical need.

d. Donation of human embryos should have been made without any restriction or direction regarding the individual(s) who may be the recipients of transplantation of the cells derived from the human pluripotent stem cells.

e. Informed Consent

Informed consent should have been obtained from individuals who have sought fertility treatment and who elect to donate human embryos in excess of clinical need for human pluripotent stem cell research purposes. The informed consent process should have included discussion of the following information with potential donors, pertinent to making the decision whether or not to donate their embryos for research purposes.

Informed consent should have included:

(i) A statement that the embryos will be used to derive human pluripotent stem cells for research that may include human transplantation research;

(ii) A statement that the donation is made without any restriction or direction regarding the individual(s) who may be the recipient(s) of transplantation of the cells derived from the embryo;

(iii) A statement as to whether or not information that could identify the donors of the embryos, directly or through identifiers linked to the donors, will be removed prior to the derivation or the use of human pluripotent stem cells;

(iv) A statement that derived cells and/or cell lines may be kept for many years;

(v) Disclosure of the possibility that the results of research on the human pluripotent stem cells may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development;

(vi) A statement that the research is not intended to provide direct medical benefit to the donor; and

(vii) A statement that embryos donated will not be transferred to a woman's uterus and will not survive the human pluripotent stem cell derivation process.

f. Derivation protocols should have been approved by an IRB established in accord with 45 CFR 46.107 and 46.108 or FDA regulations at 21 CFR 56.107 and 56.108.

B. Utilization of Human Pluripotent Stem Cells Derived From Human Fetal Tissue

1. Submission to NIH

Intramural or extramural investigators who are intending to use existing funds, are requesting an administrative supplement, or are applying for new NIH funding for research using human pluripotent stem cells derived from fetal tissue must submit to NIH the following:

a. An assurance signed by the responsible institutional official that the pluripotent stem cells were derived from human fetal tissue in accordance with the conditions set forth in section II.A.2 of these Guidelines and that the institution will maintain documentation in support of the assurance;

b. A sample informed consent document (with patient identifier information removed) and a description of the informed consent process that meet the criteria for informed consent set forth in section II.B.2.b of these Guidelines;

c. An abstract of the scientific protocol used to derive human pluripotent stem cells from fetal tissue;

d. Documentation of IRB approval of the derivation protocol;

e. An assurance that the stem cells to be used in the research were or will be obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells;

f. The title of the research proposal or specific subproject that proposes the use of human pluripotent stem cells;

g. An assurance that the proposed research using human pluripotent stem cells is not a class of research that is ineligible for NIH funding as set forth in section III of these Guidelines; and

h. The Principal Investigator's written consent to the disclosure of all material submitted under Paragraph B.1 of this section, as necessary to carry out the public review and other oversight procedures set forth in section IV of these Guidelines.

2. Conditions for the Utilization of Human Pluripotent Stem Cells Derived From Fetal Tissue.

a. Unlike pluripotent stem cells derived from human embryos, DHHS funds may be used to support research to derive pluripotent stem cells from fetal tissue, as well as for research utilizing such cells. Such research is governed by Federal statutory restrictions regarding fetal tissue research at 42 U.S.C. 289g–2(a) and the Federal regulations at 45 CFR 46.210. In addition, because cells derived from fetal tissue at the early stages of investigation may, at a later date, be used in human fetal tissue transplantation research, it is the policy of NIH to require that all NIH-funded research involving the derivation or utilization of pluripotent stem cells from human fetal tissue also comply with the fetal tissue transplantation research statute at 42 U.S.C. 289g–1.

b. Informed Consent

As a policy matter, NIH-funded research deriving or utilizing human pluripotent stem cells from fetal tissue should comply with the informed consent law applicable to fetal tissue transplantation research (42 U.S.C. 289g–1) and the following conditions. The informed consent process should have included discussion of the following information with potential donors, pertinent to making the decision whether to donate fetal tissue for research purposes.

Informed consent should have included:

(i) A statement that fetal tissue will be used to derive human pluripotent stem cells for research that may include human transplantation research;

(ii) A statement that the donation is made without any restriction or direction regarding the individual(s) who may be the recipient(s) of transplantation of the cells derived from the fetal tissue;

(iii) A statement as to whether or not information that could identify the donors of the fetal tissue, directly or through identifiers linked to the donors, will be removed prior to the derivation or the use of human pluripotent stem cells;

(iv) A statement that derived cells and/or cell lines may be kept for many years;

(v) Disclosure of the possibility that the results of research on the human pluripotent stem cells may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development; and

(vi) A statement that the research is not intended to provide direct medical benefit to the donor.

c. Derivation protocols should have been approved by an IRB established in accord with 45 CFR 46.107 and 46.108 or FDA regulations at 21 CFR 56.107 and 56.108.

III. Areas of Research Involving Human Pluripotent Stem Cells That Are Ineligible for NIH Funding

Areas of research ineligible for NIH funding include:

A. The derivation of pluripotent stem cells from human embryos;

B. Research in which human pluripotent stem cells are utilized to create or contribute to a human embryo;

C. Research utilizing pluripotent stem cells that were derived from human embryos created for research purposes, rather than for fertility treatment;

D. Research in which human pluripotent stem cells are derived using somatic cell nuclear transfer, *i.e.,* the transfer of a human somatic cell nucleus into a human or animal egg;

E. Research utilizing human pluripotent stem cells that were derived using somatic cell nuclear transfer, *i.e.,* the transfer of a human somatic cell nucleus into a human or animal egg;

F. Research in which human pluripotent stem cells are combined with an animal embryo; and

G. Research in which human pluripotent stem cells are used in combination with somatic cell nuclear transfer for the purposes of reproductive cloning of a human.

IV. Oversight

A. The NIH Human Pluripotent Stem Cell Review Group (HPSCRG) will review documentation of compliance with the Guidelines for funding requests that propose the use of human pluripotent stem cells. This working group will hold public meetings when a funding request proposes the use of a line of human pluripotent stem cells that has not been previously reviewed and approved by the HPSCRG.

B. In the case of new or competing continuation (renewal) or competing supplement applications, all applications shall be reviewed by HPSCRG and for scientific merit by a Scientific Review Group. In the case of requests to use existing funds or applications for an administrative supplement or in the case of intramural proposals, Institute or Center staff should forward material to the HPSCRG for review and determination of compliance with the Guidelines prior to allowing the research to proceed.

C. The NIH will compile a yearly report that will include the number of applications and proposals reviewed and the titles of all awarded applications, supplements or administrative approvals for the use of existing funds, and intramural projects.

D. Members of the HPSCRG will also serve as a resource for recommendations to the NIH with regard to any revisions to the NIH Guidelines for Research Using Human Pluripotent Stem Cells and any need for human pluripotent stem cell policy conferences.

Dated: August 17, 2000.

Ruth L. Kirschstein,

Principal Deputy Director, NIH.

[FR Doc. 00–21760 Filed 8–23–00; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Notification of Request for Emergency Clearance; Modification of OMB No. 0925–0001/Exp. 2/01, ''PHS 398 Research and Research Training Grant Applications and Related Forms''

SUMMARY: In accordance with section 3507(j) of the Paperwork Reduction Act of 1995, the National Institutes of Health (NIH) hereby publishes notification of a request for Emergency Clearance for modification of the information collection related to the National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells, published elsewhere in today's **Federal Register**. The currently approved information collection OMB No. 0925–0001 permits the NIH to request from applicant institutions information related to application, award, and continued compliance with the terms of Federal assistance for research and research-related training. The approval also covers the information collection authorized in accordance with 42 CFR 52, specifically the obtaining of ''[o]ther pertinent information the Secretary may require to evaluate the proposed project.'' (42 CFR 52.4(f))

The final National Institutes of Health Guidelines for Research Using Pluripotent Stem Cells requires submission of additional documentation in the form of additional institutional records from a limited number of institutions to enable an independent panel of non-Government experts to ascertain institutional compliance with the Guidelines. Compliance with the requirements of existing law and regulations is authorized under OMB No. 0925–0418, Exp. 1/01, ''Protection of Human Subjects: Assurance Identification/Certification/ Declaration.''

The present modification relates to the added reporting requirement of submission of documentation to permit the agency to exercise the oversight responsibility established under the Guidelines.

This modification is essential to the mission of NIH (42 USC 241 and 282(b)) and is of the highest scientific priority as determined by both internal review and external review by a panel of scientific and other experts in the field of stem cell research. After extensive consultation with the public and a public meeting, the NIH published proposed National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells in the **Federal Register** on December 2 , 1999 (**Federal Register**, Vol. 64, No. 231, pages 67576–67579). The comment period was extended to February 22, 2000. (**Federal Register**, February 3, 2000, Vol. 65, No. 23, page 539). Following the period of comment, NIH has proceeded to finalize the Guidelines, which are published elsewhere in this issue of the **Federal Register**.

These Guidelines are essential to ensure that NIH-funded research in this area is conducted in an ethical and legal manner. The NIH has determined that the oversight process stipulated in the Guidelines will achieve this objective. The Guidelines will require that institutions requesting or using NIH funds for research using human pluripotent stem cells submit additional documentation to the NIH in the form of institutional records that will permit NIH oversight in accordance with the Guidelines.

NIH has taken all practicable steps to consult with the scientific community and the public, through the process described above and through the careful consideration of all comments received from the public.

In view of the extensive period of comment and the thorough consideration of all views, both prior to the publication of the proposed Guidelines in December 1999 and subsequently, NIH is herewith requesting that OMB approve the modification of the collection of information simultaneously with the publication of the **Federal Register**

2008 AMENDMENTS

THE NATIONAL ACADEMIES' GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH

Human Embryonic Stem Cell Research Advisory Committee

Board on Life Sciences
Division on Earth and Life Studies

Board on Health Sciences Policy
Institute of Medicine

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by The Ellison Medical Foundation, The Greenwall Foundation, and the Howard Hughes Medical Institute. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

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Cover: A cluster of motor neurons and neural fibers derived from human embryonic stem cells in the lab of University of Wisconsin–Madison stem cell researcher and neurodevelopmental biologist Su-Chan Zhang. The motor neurons are shown in red, neural fibers appear green, and the blue specks indicate DNA in cell nuclei. These motor neurons were developed from one of James Thomson's original human embryonic stem cell lines. Copyright for the photograph is held by the University of Wisconsin's Board of Regents.

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Advisers to the Nation on Science, Engineering, and Medicine

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The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

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Acknowledgments

The Committee acknowledges the input received from members of the stem cell research and oversight communities and the speakers and participants in its meetings.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

George Q. Daley, Children's Hospital Boston and Harvard Medical School
Norman Fost, University of Wisconsin–Madison
Henry T. Greely, Stanford Law School
Geoffrey Lomax, California Institute for Regenerative Medicine
Gail R. Martin, University of California, San Francisco
P. Pearl O'Rourke, Partners HealthCare System
James Thomson, University of Wisconsin–Madison
Laurie Zoloth, Northwestern University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions

or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Janet Rowley**, University of Chicago Medical Center, and **Floyd Bloom**, Scripps Research Institute (retired). Appointed by the National Research Council, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Contents

Appendixes

2008 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research

INTRODUCTION

The National Academies' report *Guidelines for Human Embryonic Stem Cell Research* (NRC and IOM, 2005) was developed by the Committee on Guidelines for Human Embryonic Stem Cell Research and released in April 2005. The body of the report provided the background and rationale for the choices involved in formulating the Guidelines, which were compiled in its final chapter. Because human embryonic stem (hES) cell research touches on many ethical, legal, scientific, and policy issues, the Guidelines are intended to make explicit how research with hES cells can be pursued most responsibly. The Guidelines are intended to address researchers primarily in the United States, but they may be applicable internationally as well.

The 2005 publication of the Guidelines offered a common set of ethical standards for a field that, because of the absence of comprehensive federal funding, was lacking national standards for research. Although the Guidelines have proved useful since 2005, it was recognized soon after their initial issuance that some aspects of them needed clarification in light of experience and that they must be kept up to date given the rapid pace of scientific developments in the field of stem cell research. The National Academies established the Human Embryonic Stem Cell Research Advisory Committee for that purpose in 2006 with support from the Ellison Medical Foundation, the Greenwall Foundation, and the Howard Hughes Medical Institute. It issued its first set of amendments to the Guidelines in 2007 (NRC and IOM, 2007).

Statement of Task of the
Human Embryonic Stem Cell Research Advisory Committee

The Advisory Committee will meet 2 to 3 times per year over a period of 36 months to (1) monitor and review scientific developments and changing ethical, legal, and policy issues related to human embryonic stem cell research, (2) discuss the need for revisions to the Guidelines for Human Embryonic Stem Cell Research, and (3) prepare periodic reports to update the Guidelines as needed. Minimal but necessary changes may be issued as letter reports, but more extensive modifications may necessitate the preparation of traditional reports to fully provide the rationale for the changes.

Sources of information that will be considered by the Advisory Committee will include public symposia organized by the Committee to review developments in stem cell science and how these impact the ethical and policy issues surrounding hES cell research.

The Human Embryonic Stem Cell Research Advisory Committee continues to engage in a number of efforts to gather information about the need, if any, for revision of the Guidelines. For example, the Committee conducted three regional meetings (in southern California, Chicago, and the Boston area) in the first half of 2007 for those involved in institutional Embryonic Stem Cell Research Oversight (ESCRO) committees to hear from people in the field about their experiences in implementing the Guidelines and any problems they have encountered. In addition, the Committee participated in a day-long session on ESCRO committees at the annual meeting of Public Responsibility in Medicine and Research (PRIM&R) in December 2007 to gather more feedback from the community.

The Committee also met in March and August 2007 and in February 2008 to hear from invited speakers who addressed issues that the Committee has taken under consideration for potential further amendments to the Guidelines. Finally, the Committee is planning a second symposium (its first was held in November 2006) for November 2008 to hear invited speakers review the latest scientific developments, describe how the developments might affect analyses of associated ethical issues, and identify possible effects on the workability or justifiability of the current Guidelines. The meeting will

focus in part on recent developments in moving toward clinical translation of stem cell therapeutics. The Committee has also established an electronic mailing list for ESCRO committee members and staff to communicate and share questions and answers, and members of the Committee have been actively soliciting input from their colleagues and receiving comments via a Web site[1] established for the purpose.

As it did in 2007, the Committee identified issues that appeared to warrant consideration of revisions of the Guidelines. The present report addresses those issues in a second brief set of amendments. Most important, the Committee is issuing this second set of amendments to address new scientific developments in reprogramming of somatic cells to pluripotency by adding a new section (Section 7) and revising other relevant sections of the Guidelines. It is also issuing several other minor amendments to

- Clarify the obligations of investigators to notify and obtain approval from their institutions' ESCRO committees before initiating any hES cell experiments and to provide for the possibility of "expedited review" of some hES cell experimental protocols—Section 1.3(a)[2], Section 6.1, and Section 6.2.

- Clarify what is included in "direct expenses" for allowable reimbursements to women donating oocytes—Section 3.4(b).

- Further enumerate the registration and auditing responsibilities of institutions conducting hES cell research to improve public access to information and ensure that ESCRO committees are carrying out their responsibilities appropriately—Section 2.0.

In addition, inconsistencies in the original numbering of the Guidelines have led to some confusion. Various sections of the Guidelines, particularly within Section 1, have been renumbered in these amendments for greater clarity.

Future deliberations of the Committee will address items for which additional information-gathering and more extensive debate and discussion may be necessary. For example, based on the National Institutes of Health (NIH) determination that the pre-2001 "presidential" lines were derived from embryos donated with informed consent and without financial induce-

[1]http://www.nationalacademies.org/stemcells

[2]Formerly Section 1.2(a). As explained below, several sections of the Guidelines, particularly within Section 1, are being renumbered in these amendments for greater clarity.

ment (NIH, 2001), the 2007 Guidelines deemed those lines to have been acceptably derived (see Sections 1.4 and 1.5 and associated discussion in NRC and IOM, 2007). In light of questions raised when the present report was already near completion about the derivation or use of some of those lines (Streiffer, 2008), and as per its charge, the Committee will monitor developments as to the ethics and policy regarding the lines in question in order to consider whether any future changes in the Guidelines are warranted. Stem cell research oversight committees are, of course, free to set their own policies about the use of these lines according to the principles outlined in Section 1.6 of the Guidelines (as renumbered in this document). The Committee is also aware that the scientific and oversight communities desire additional guidance on how to evaluate research that requires the development of chimeras. In response, the Committee has added some text in the new Section 7.3(c) [as well as 1.3(b)] and also plans to address research involving chimeras at the meeting it is organizing for November 2008.

These amended Guidelines supersede those issued in 2005 and 2007 by the Committee on Guidelines for Human Embryonic Stem Cell Research and the Human Embryonic Stem Cell Research Advisory Committee, respectively. It is important that the clarifications and amendments presented here be interpreted in the context of the complete set of amended Guidelines, which is included at the end of this report (Appendix A). In addition, the glossary included in the 2005 *Guidelines for Human Embryonic Stem Cell Research* (NRC and IOM, 2005) has been amended by adding definitions for the terms *hPS cells* and *multipotent*, and the entire glossary is reprinted as Appendix B.

APPLICABILITY OF THE GUIDELINES TO NON-EMBRYONIC HUMAN PLURIPOTENT STEM CELLS

The original Guidelines released in 2005 were addressed specifically to research with hES cell lines, although institutions and investigators conducting research on human adult stem cells or fetal stem cells were encouraged to "consider which individual provisions of these guidelines are relevant to their research." Because the Guidelines were developed primarily for research with hES cells, however, it was not made explicit which provisions of the Guidelines might apply to other types of stem cells.

There have been several recent reports on reprogramming of somatic cells to pluripotency (for definitions see glossary, Appendix B). In light of the production of so-called induced pluripotent stem (iPS) cell lines derived

by introducing sets of genes into, first, murine somatic cells (Takahashi and Yamanaka, 2006) and, later, human somatic cells (Takahashi et al., 2007; Yu et al., 2007; Park et al., 2008), it seems prudent to consider more explicitly which provisions of the Guidelines should apply also to stem cells of types other than hES cells. This is not to suggest that the need for research with hES cells is supplanted by the availability of other pluripotent stem cells. It is far from clear at this point which cell types will prove to be the most useful for regenerative medicine, and it is likely that each will have some utility. Such iPS cells are currently derived by introduction of retroviruses that carry the inducing genes. This derivation procedure raises serious issues about their potential for use in therapy, inasmuch as it is known that inserted retroviruses can cause cancer, and research will be necessary to develop alternative means to derive iPS cells or to circumvent the potential tumorigenicity. Furthermore, the demonstration that iPS cells are indeed pluripotent relies on careful comparisons with hES cells; for either cell type to be used therapeutically in regenerative medicine, methods need to be developed to promote their differentiation into specialized cell types and to evaluate the safety of introducing cell populations that may contain some pluripotent cells into patients. Much further research will be required on both hES and iPS cells to develop the required procedures, including drawing appropriate comparisons between them. Understanding of the potential for differentiation of hES cells, iPS cells, or, indeed, adult multipotent (capable of differentiation into a limited spectrum of differentiated cell types)[3] stem cells will require testing in animals and screening for potential tumorigenicity. Therefore, issues arising from such human-animal chimera experiments pertain to all these cell types.

For those reasons and in response to inquiries from the scientific community, the Human Embryonic Stem Cell Research Advisory Committee has consulted with experts and carefully considered potential modifications of the Guidelines to cover other pluripotent and multipotent stem cells, which the Committee presents herein. The intention is not to extend unnecessarily the oversight of stem cell research where it is already adequately monitored under existing regulations and guidelines. For example, derivation of human pluripotent stem cell lines from sources other than embryos does not involve ethical or policy issues beyond those normally encountered in sampling any tissue from human subjects, although *use* of such cells may raise issues similar to those for embryonically derived cells. Derivation of iPS cells and

[3]A multipotent stem cell can give rise to other types of cells but it is limited in its ability to differentiate. An example is found in the multipotent stem cells in bone marrow that give rise to all blood cells but not other cell types.

of other non-embryonic human pluripotent stem cells (hereafter referred to as hPS cells) does not require special stem cell expertise and is adequately covered by current Institutional Review Board (IRB) regulations. It does not require additional review by an ESCRO committee. The Committee notes in particular that under federal regulations, even IRBs would not be required to review the generation of hPS cells from existing anonymized somatic cells from surgical waste, tissue banks, or commercial entities that provide tissue for research, nor would they be required to review the generation of hPS cells from cadaveric tissue, whether or not it is anonymized. Similarly, with few exceptions, purely *in vitro* experiments with hPS cells do not raise ethical concerns beyond those encountered with any human cell line and also do not require ESCRO committee review.

However, as mentioned above, introduction of any hPS cells and introduction of some multipotent stem cells (such as neural stem cells) into animals raises issues similar to those pertaining to hES cells. The earlier versions of the Guidelines placed responsibility for review of such experiments with hES cells in the hands of ESCRO committees and Institutional Animal Care and Use Committees (IACUCs), and it is logical to do the same for hPS cells and for stem cells with more limited potential for differentiation. The revisions presented in this document provide guidance on the levels of review for various categories of experiments with iPS and other hPS cells and on categories of research for which such review is not necessary. Most of the changes appear in a new Section 7, "Recommendations for Research on Non-Embryo-Derived Human Pluripotent Stem Cells (hPS Cells)", although some provisions of Sections 1, 3, 4, and 5 are also affected, as follows (new or revised wording is underlined, and deleted text appears in ~~strikeout~~ form):

From Section 1

1.1 What These Guidelines Cover

1.1(a) These guidelines cover all derivation of hES cell lines and all research that uses hES cells derived from

(i) blastocysts made for reproductive purposes and later obtained for research from *in vitro* fertilization (IVF) clinics,
(ii) blastocysts made specifically for research using IVF,
(iii) somatic cell nuclear transfer (NT) into oocytes.

1.1(b) ~~Many, but not all,~~ Some of the ~~guidelines and~~ concerns addressed in this report are common to other ~~areas~~ types of human stem cell research; as such, certain of these Guidelines should also apply to those other types of research. For example, ~~such as~~

(i) research that uses human adult stem cells.

(ii) research that uses fetal stem cells or embryonic germ cells derived from fetal tissue; such research is covered by federal statutory restrictions at 42 USC 289g-2(a) and federal regulations at 45 CFR 46.210.

(iii) research that uses human pluripotent stem (hPS) cells derived from non-embryonic sources, such as spermatogonial stem cells and "induced pluripotent" stem cells derived from somatic cells by introduction of genes or otherwise (so-called iPS cells), and other pluripotent cells yet to be developed.

Recommendations as to which guidelines apply to other hPS cells are collected in Section 7 below. Institutions and investigators conducting research ~~using such materials~~ with adult and fetal stem cells should also consider which individual provisions of these guidelines are relevant to their research.

1.1(c) The guidelines do not cover research that uses nonhuman stem cells.

From Section 3

3.1 An IRB, as described in federal regulations at 45 CFR 46.107, should review all new procurements of all gametes, blastocysts, or somatic cells for the purpose of generating new hES or hPS cell lines. This includes the procurement of blastocysts in excess of clinical need from infertility clinics; blastocysts made through IVF specifically for research purposes; ~~and~~ oocytes, sperm, and somatic cells donated for development of hES cell lines derived

through NT or by parthenogenesis or androgenesis; and hPS cells derived by any means and that require human subjects review.

3.6 In the context of donation of gametes, blastocysts, or somatic cells for hES cell research, or for hPS cell research that requires human subjects review, the informed-consent process should, at a minimum, provide the following information:

(a) A statement that the blastocysts, gametes, or somatic cells will be used to derive hES or hPS cells for research that may include research on human transplantation.
(b) A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation.
(c) A statement as to whether the identities of the donors will be readily ascertainable to those who derive or work with the resulting hES or hPS cell lines.
(d) If the identities of the donors are retained (even if coded), a statement as to whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines.
(e) An assurance that participants in research projects will follow applicable and appropriate best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of stem cells. (Traceable information, however, must be secured to ensure confidentiality.)
(f) A statement that derived hES or hPS cells and/or cell lines might be kept for many years.
(g) A statement that the hES or hPS cells and/or cell lines might be used in research involving genetic manipulation of the cells or mixing of human and nonhuman cells in animal models.
(h) Disclosure of the possibility that the results of study of the hES or hPS cells may have commercial potential and a statement that the donor will not receive financial or any other benefits from any future commercial development.
(i) A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation.

(j) A statement that embryos will be destroyed in the process of deriving hES cells.
(k) A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors.
(l) A statement of the risks involved to donors.

In addition, donors could be offered the option of agreeing to some forms of hES cell research but not others. For example, donors might agree to have their materials used for deriving new hES cell lines but not want their materials used, for example, for NT. The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored. Investigators and stem cell banks are, of course, free to choose which cell lines to accept, and are not obligated to accept cell lines for which maintaining information about specific research use prohibitions would be unduly burdensome.

New derivations of stem cell lines from banked tissues obtained prior to the adoption of these guidelines are permissible provided that the original donations were made in accordance with the legal requirements in force at the place and time of donation. This includes gametes, blastocysts, adult stem cells, somatic cells, or other tissue. In the event that these banked tissues retain identifiers linked to living individuals, human subjects protections may apply.

From Section 4

4.6 Investigators must document how they will characterize, validate, store, and distribute any new hES cell lines and how they will maintain the confidentiality of any coded or identifiable information associated with the lines (see Section 5.0 below). Investigators are encouraged to apply the same procedures and standards for characterization, validation, storage, and distribution to hPS cell lines.

From Section 5

5.0 BANKING AND DISTRIBUTION OF hES CELL LINES

There are several models for the banking of human biological materials, including hES cells. The most relevant is the U.K. Stem Cell Bank. The guidelines developed by this and other groups generally adhere to key ethical principles that focus on the need for consent of donors and a system for monitoring adherence to ethical, legal, and scientific requirements. As hES cell research advances, it will be increasingly important for institutions that are obtaining, storing, and using cell lines to have confidence in the value of stored cells—that is, that they were obtained ethically and with the informed consent of donors, that they are well characterized and screened for safety, and that the conditions under which they are maintained and stored meet the highest scientific standards. Institutions engaged in hES research should seek mechanisms for establishing central repositories for hES cell lines—through partnerships or augmentation of existing quality research cell line repositories—and should adhere to high ethical, legal, and scientific standards. At a minimum, an institutional registry of stem cell lines should be maintained. Institutions are encouraged to consider the use of the same procedures for banking and distribution of hPS cell lines.

Section 7

7.0 RECOMMENDATIONS FOR RESEARCH ON NON-EMBRYO-DERIVED HUMAN PLURIPOTENT STEM CELLS (hPS CELLS)

7.1 Derivation

Because non-embryo-derived hPS cells are derived from human material, their derivation is covered by existing IRB regulations concerning review and informed consent. No ESCRO committee review is necessary, although the IRB may always seek the advice of an ESCRO committee if it seems desirable. The IRB review

should consider proper consent for use of the derived hPS cells. Some of the recommendations for informed consent that apply to hES cells also apply to hPS cells (see Section 3.6), including informed consent to genetic manipulation of resulting pluripotent stem cells and their use for transplantation into animals and humans and, potentially, in future commercial development.

7.2 Use in *in Vitro* Experiments

Use of hPS cells in purely *in vitro* experiments need not be subject to any review beyond that necessary for any human cell line except that any experiments designed or expected to yield gametes (oocytes or sperm) should be subject to ESCRO committee review.

7.3 Use in Experiments Involving Transplantation of hPS Cells into Animals at Any Stage of Development or Maturity

7.3(a) Research involving transplantation of pluripotent human cells derived from non-embryonic sources into nonhuman animals at any stage of embryonic, fetal, or postnatal development should be reviewed by ESCRO committees and IACUCs, as are similar experiments that use hES cells.

7.3(b) ESCRO committees should review the provenance of hPS cells as they review the provenance of hES cells (see Section 1.6) to ensure that the cell lines were derived according to ethical procedures of informed consent as monitored by an IRB or equivalent oversight body.

7.3(c) Proposals for the use of hPS cells in animals should be considered in one of the following categories:

(i) Permissible after currently mandated reviews and proper documentation [see Section 1.3(a)]: experiments that are exempt from full ESCRO committee review but not IACUC review (experiments that involve only transplantation into postnatal animals with no likelihood of contributing to the central nervous system or germ line).

(ii) Permissible after additional review by an ESCRO committee, as described in Section 2.0 of the Guidelines [see Section 1.3(b)]: experiments in which there is a significant possibility that the implanted hPS cells could give rise to neural or gametic cells and tissues. Such experiments need full ESCRO committee and IACUC review and would include generation of all preimplantation chimeras and neural transplantation into embryos or perinatal animals. Particular attention should be paid to at least three factors: the extent to which the implanted cells colonize and integrate into the animal tissue; the degree of differentiation of the implanted cells; and the possible effects of the implanted cells on the function of the animal tissue.

(iii) Should not be conducted at this time [see Section 1.3(c)]:

(1) Experiments that involve transplantation of hPS cells into human blastocysts.

(2) Research in which hPS cells are introduced into nonhuman primate embryos, pending further research that will clarify the potential of such introduced cells to contribute to neural tissue or to the germ line.

7.4 Multipotent Neural Stem Cells

It is also relevant to note that neural[4] stem cells, although not pluripotent, are multipotent and may have the potential to contribute to neural tissue in chimeric animals. ESCRO committees should decide whether they wish to review and monitor such experiments with neural stem cells in a similar fashion.

7.5 Prohibition on Breeding

No animal into which hPS cells have been introduced such that they could contribute to the germ line should be allowed to breed.

[4]Referring to cells of the nervous system that give rise to both neurons and glia.

7.6 Guidance for Banking and Distribution

Institutions should consider the value of banking and distributing hPS cells using the guidance and rules that are already in place for hES cells and the value of including hPS cell lines in their registries.

CLARIFICATION OF THE MEANING OF "PROPER NOTIFICATION"

Section 1.3 (formerly Section 1.2) of the Guidelines specifies research that is "permissible after currently mandated review and *proper notification* of the relevant research institution" (emphasis added). Section 1.3(a) clarifies which documentation is required for determining the provenance of the cell lines, but it does not address what "proper notification" entails. Similarly, Sections 6.1 and 6.2 concerning research use of hES cell lines refer to "notification" and "notice" but do not specify what notification entails.

Use of the word "notification" has led some ESCRO committee representatives to ask whether the Guidelines intend that investigators fulfill this requirement by merely informing ESCRO committees that the research would be occurring (that is, the investigator would determine and inform, but the ESCRO committee would have no role). That is not what was intended. The discussion in the 2005 report states that the "ESCRO committee should ensure that the procurement process has been appropriate by requiring documentation that it was approved by an IRB and adhered to basic principles of ethically responsible procurement" (NRC and IOM, 2005, pp. 54-55). Thus, the ESCRO committee—not the investigator—must decide whether the proposed research is purely *in vitro* research with existing hES cell lines that meet appropriate standards for procurement.

The original Guidelines Committee intended that notification involve the ESCRO committee but allow expedited review procedures, such as those used in the context of IRBs. The federal regulations for IRBs outline the procedure as follows (45 CFR 46.110[5]):

> Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may ex-

[5]http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.110.

> ercise all of the authorities of the IRB except that the reviewers may not disapprove the research. . . .
>
> (c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

ESCRO committees are therefore called on to establish procedures for reviewing purely *in vitro* research that uses previously and appropriately derived hES cell lines; these reviews may be expedited at the discretion of an ESCRO committee. The former Section 1.2(a) [renumbered as 1.3(a)] of the Guidelines is therefore revised to clarify this point.

1.3(a) hES cell research permissible after currently mandated reviews

Purely *in vitro* hES cell research that uses previously derived hES cell lines is permissible provided that the ESCRO committee or equivalent body designated by the investigator's institution (see Section 2.0) receives documentation of the provenance of the cell lines, including (i) documentation of the use of an acceptable informed-consent process that was approved by an Institutional Review Board (IRB) or foreign equivalent for their derivation (consistent with Section 3.6) and (ii) documentation of compliance with any additional required review by an Institutional Animal Care and Use Committee (IACUC), Institutional Biosafety Committee (IBC), or other institutionally mandated review. To determine whether the proposed research meets the requirements of this section, the ESCRO committee may choose to conduct an *expedited review* of such research proposals. In this context, "expedited review" means that the ESCRO committee chair or others designated by the committee chair can act on behalf of the committee to determine that the hES cells have been acceptably derived (see Section 1.6) and report to the entire committee.

In addition, Sections 6.1 and 6.2 are revised to be consistent with the changes in the newly revised and renumbered 1.3(a):

6.1 Institutions should require documentation of the provenance of all hES cell lines, whether the cells were imported into the institution or generated locally. ~~Notice to~~ The institution should obtain ~~include~~ evidence of IRB approval of the procurement process and of adherence to basic ethical and legal principles of procurement as described in Sections 1.3(a) and 1.6. In the case of lines imported from another institution, documentation that these criteria were met at the time of derivation will suffice.

6.2 *In vitro* experiments involving the use of already derived and coded hES cell lines will not need review beyond the ~~notification required~~ review described in Sections 1.3(a) and ~~in Section~~ 6.1.

PUBLIC OPENNESS AND ESCRO COMMITTEE AUDITS

Research that uses hES cells remains controversial in the United States and is still subject to intense political scrutiny. Therefore, it is important to sustain public confidence in the integrity of the institutions and researchers conducting hES cell research; this is one of the reasons that the Guidelines were developed. The Human Embryonic Stem Cell Research Advisory Committee continues to believe that it is in the interests of researchers and their institutions to ensure that the Guidelines of the National Academies or other relevant bodies (such as state regulations and guidelines of the International Society for Stem Cell Research) are being appropriately implemented to ensure that both the public and policy-makers may have a high level of confidence that institutions and their researchers are conducting the research responsibly. As part of this assurance, the public should have reasonable access to information on the types of hES cell research being conducted at an institution and evidence that the research conforms to the requirements of the guidelines being followed by that institution.

For those reasons, the committee is amending the Guidelines in two ways. First, Section 2.0 calls for registries of hES cell research to be maintained by institutional ESCRO committees. Although the original intent was that the information in a registry be available to the public, this intent was not explicit in the Guidelines. The committee is therefore amending the wording of Section 2.0 to make that clear. Second, although the committee cannot impose legally enforceable requirements, it is adding a strong suggestion that institutions at which hES cell research is being conducted carry out pe-

riodic audits (for example, every 3-5 years) of their ESCRO committees to ensure that these groups are performing their duties as intended as a good management practice. The emphasis of the audits should be on documenting decisions regarding the acceptability of research proposals and on verifying that cell lines in use at the institution were acceptably derived. Institutions should also make at least the general findings and preferably the details of the audits available to the public. The amended wording (underlined) of Section 2.0 is as follows:

2.0 ESTABLISHMENT OF AN INSTITUTIONAL EMBRYONIC STEM CELL RESEARCH OVERSIGHT COMMITTEE

To provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES cell research, each institution should have activities involving hES cells overseen by an Embryonic Stem Cell Research Oversight (ESCRO) committee. This committee could be internal to a single institution or established jointly with one or more other institutions. Alternatively, an institution may have its proposals reviewed by an ESCRO committee of another institution, or by an independent ESCRO committee. An ESCRO committee should include independent representatives of the lay public as well as persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hES cell research. It must have suitable scientific, medical, and ethical expertise to conduct its own review and should have the resources needed to coordinate the management of the various other reviews required for a particular protocol. A pre-existing committee could serve the functions of the ESCRO committee provided that it has the ~~recommended~~ expertise recommended here and representation to perform the various roles described in this report. For example, an institution might elect to constitute an ESCRO committee from among some members of an IRB. But the ESCRO committee should not be a subcommittee of the IRB, as its responsibilities extend beyond human subject protections. Furthermore, much hES cell research does not require IRB review. The ESCRO committee should

(a) Provide oversight over all issues related to derivation and use of hES cell lines.
(b) Review and approve the scientific merit of research protocols.
(c) Review compliance of all in-house hES cell research with all relevant regulations and these guidelines.
(d) Maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators. An institution conducting stem cell research should make information from the registries (including, but not necessarily limited to, project abstracts and sources of funding) available to the public and the media through the institution's Web site.
(e) Facilitate education of investigators involved in hES cell research.

An institution that maintains its own ESCRO committee should conduct periodic audits of the committee to verify that it is carrying out its responsibilities appropriately. Auditable records include documentation of decisions regarding the acceptability of research proposals and verification that cell lines in use at the institution were acceptably derived (see Section 1.6). Institutions should make the results of the audits available to the public.

An institution that uses an external ESCRO committee should nevertheless ensure that the registry and educational functions of an internal ESCRO committee are carried out by the external ESCRO committee on its behalf or internally by other administrative units. Those institutions that use external ESCRO committees are also responsible for ensuring that these committees are likewise carrying out their responsibilities appropriately.

CLARIFICATION OF POLICY REGARDING REIMBURSEMENT OF OOCYTE DONORS

It was pointed out in the report *Guidelines for Human Embryonic Stem Cell Research* (NRC and IOM, 2005) that although there is widespread consensus that donors should not be paid for blastocysts donated for research,

there is less of a consensus about inducements for women to donate oocytes or for men to donate sperm for research purposes. Oocyte donation solely for research purposes is the issue of most concern because of its invasiveness, its inconvenience, and the risks posed by the procedure (reviewed in IOM and NRC, 2007). If the need for oocytes in hES cell research increases, however, it is possible that donations from clinical procedures or for nonfinancial motives may prove insufficient to meet the demand. In such cases, investigators might want to recruit oocyte donors, and it is from this circumstance that the issue of whether such donors should be paid arises.

Guidelines for Human Embryonic Stem Cell Research contained a long discussion (Chapter 5) of the arguments for and against payment of oocyte donors, which will not be repeated here. In short, one side argues for fair and just remuneration of participants in research, in which inducements are commonly provided for competent adult research subjects provided that the research risks are reasonable in relation to the potential research benefits. Furthermore, because payment is legal and widely practiced for egg donation for reproductive purposes, many find the forbidding of payment in the research context difficult to justify. Others, however, oppose any payment, whether for research or reproduction. Typically, they caution against any form of payment that may create an "undue inducement" that could compromise a prospective donor's evaluation of the risks posed by donation or the voluntariness of her choices. Furthermore, opponents of payment often embed their objections in a larger set of concerns about the "commodification of life," which also apply to payment for human tissue of any sort and to the patenting of genes and other issues. Complicating these principled debates are more pragmatic concerns: whether (and how much) payment is needed to ensure a sufficient supply of oocytes for nuclear transfer and other forms of specialized stem cell research, and the interchangeability of cell lines, material transfers, and the future of collaborative stem cell research if various state and national jurisdictions have different rules regarding reimbursement and compensation for oocyte donors.

The recommendation made by the Committee on Guidelines for Human Embryonic Stem Cell Research in 2005 was that women who undergo hormonal induction to generate oocytes specifically for research purposes should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an Institutional Review Board. Thus, the National Academies' Guidelines prohibit cash or in-kind payments for donating oocytes for research purposes. As pointed out in the earlier report (NRC and IOM,

2005) that position was based in part on the recognition that payments to oocyte donors raise concerns that might undermine public confidence in the responsible management of hES cell research. The report also noted that the recommendation was intended to ensure consistency between procurement practices in the United States and in other countries that have major hES cell research programs and with the limitations enacted in specific states, facilitating collaboration among investigators in the United States and abroad. Since that time, however, California has provided a useful model in its finalized regulations (Title 17 CA Code of Regulations, Section 100020) that allows reimbursement of oocyte donors for "permissible expenses," which are clearly defined to include "actual lost wages." The state of Massachusetts has a similar policy. Although the original National Academies' Guidelines did not specifically mention lost wages as a reimbursable category of direct expenses, institutions and states that perform or support hES cell research should view the National Academies' Guidelines as open to the interpretation that "lost wages" is a legitimate category of reimbursable expenses. To make that explicit, the wording of Section 3.4(b) is modified as follows (new wording underlined):

> 3.4(b) Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for NT) should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an IRB. Direct expenses may include costs associated with travel, housing, child care, medical care, health insurance, and actual lost wages. No payments beyond reimbursements, cash or in-kind, should be provided for donating oocytes for research purposes. Similarly, no payments beyond reimbursements should be made for donations of sperm for research purposes or of somatic cells for use in NT.

The committee does not find persuasive the argument that this change has the effect of assigning differing values to the oocytes of different women based on their relative salaries. Reimbursement for lost wages is not a "price" being paid for oocytes. The intent is to leave all donors no better off, but also no worse off.

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Appendix A

National Academies' Guidelines for Human Embryonic Stem Cell Research Amended as of September 2008[1]

1.0 INTRODUCTION

In this chapter we collect all the recommendations made throughout the report and translate them into a series of formal guidelines. These guidelines focus on the derivation, procurement, banking, and use of human embryonic stem (hES) cell lines. They provide an oversight process that will help to ensure that research with hES cells is conducted in a responsible and ethically sensitive manner and in compliance with all regulatory requirements pertaining to biomedical research in general. The National Academies are issuing

[1]New or modified wording is indicated by underlining, deleted text by ~~strikeout~~.

these guidelines for the use of the scientific community, including researchers in university, industry, or other private-sector research organizations.

1.1 What These Guidelines Cover

1.1(a) These guidelines cover all derivation of hES cell lines and all research that uses hES cells derived from

(i) blastocysts made for reproductive purposes and later obtained for research from *in vitro* fertilization (IVF) clinics,
(ii) blastocysts made specifically for research using IVF,
(iii) somatic cell nuclear transfer (NT) into oocytes.

1.1(b) Some of the ~~guidelines and~~ concerns addressed in this report are common to other ~~areas~~ types of human stem cell research; as such, certain of these Guidelines should also apply to those other types of research. For example, ~~such as~~

(i) research that uses human adult stem cells,

(ii) research that uses fetal stem cells or embryonic germ cells derived from fetal tissue; such research is covered by federal statutory restrictions at 42 U.S.C. 289g-2(a) and federal regulations at 45 CFR 46.210,

(iii) research using human pluripotent stem (hPS) cells derived from non-embryonic sources, such as spermatogonial stem cells and "induced pluripotent" stem cells derived from somatic cells by introduction of genes or otherwise (so-called iPS cells), as well as other pluripotent cells yet to be developed.

Recommendations as to which guidelines apply to other hPS cells are collected in Section 7 below. Institutions and investigators conducting research ~~using such materials~~ with adult and fetal stem cells should also consider which individual provisions of these guidelines are relevant to their research.

1.1(c) The guidelines do not cover research that uses nonhuman stem cells.

1.2 Reproductive Uses of NT

These guidelines also do not apply to reproductive uses of nuclear transfer (NT), which are addressed in the 2002 report *Scientific and Medical Aspects of Human Reproductive Cloning*, in which the National Academies recommended that "Human reproductive cloning should not now be practiced. It is dangerous and likely to fail." Although these guidelines do not specifically address human reproductive cloning, it continues to be the view of the National Academies that research aimed at the reproductive cloning of a human being should not be conducted at this time.

1.3 Categories of hES Cell Research

These guidelines specify categories of research that:

- Are permissible after currently mandated reviews and proper notification of the relevant research institution.
- Are permissible after additional review by an Embryonic Stem Cell Research Oversight (ESCRO) committee, as described in Section 2.0 of the guidelines.
- Should not be conducted at this time.

Because of the sensitive nature of some aspects of hES cell research, these guidelines in many instances set a higher standard than is required by laws or regulations with which institutions and individuals already must comply.

1.3(a) hES cell research permissible after currently mandated reviews

Purely *in vitro* hES cell research that uses previously derived hES cell lines is permissible provided that the ESCRO committee or equivalent body designated by the investigator's institution (see Section 2.0) receives documentation of the provenance of the cell lines including (i) documentation of the use of an acceptable informed consent process that was approved by an Institutional Review Board (IRB) or foreign equivalent for their derivation (consistent with Section 3.6) and (ii) documentation of compliance with any additional required review by an Institutional Animal Care and Use Committee (IACUC), Institutional Biosafety Committee (IBC), or other institutionally mandated review. To determine whether the proposed research meets the requirements of this section, the ESCRO committee may choose to conduct an *expedited review* of such research proposals. In this context, "expedited review" means that the ESCRO committee chair or others des-

ignated by the committee chair act on behalf of the committee to determine that the hES cells have been acceptably derived (see Section 1.6) and report to the entire committee.

1.3(b) hES cell research permissible only after additional review and approval

(i) Generation of new lines of hES cells by whatever means.

(ii) Research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development. Particular attention should be paid to at least three factors: the extent to which the implanted cells colonize and integrate into the animal tissue; the degree of differentiation of the implanted cells; and the possible effects of the implanted cells on the function of the animal tissue.

(iii) Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable or might become known to the investigator.

1.3(c) hES cell research that should not be permitted at this time

The following types of research should not be conducted at this time:

(i) Research involving *in vitro* culture of any intact human embryo, regardless of derivation method, for longer than 14 days or until formation of the primitive streak begins, whichever occurs first.

(ii) Research in which hES cells are introduced into nonhuman primate blastocysts or in which any embryonic stem cells are introduced into human blastocysts.

In addition:

(iii) No animal into which hES cells have been introduced such that they could contribute to the germ line should be allowed to breed.

1.4 Obligations of Investigators and Institutions

All scientific investigators and their institutions, regardless of their field, bear the ultimate responsibility for ensuring that they conduct themselves in accordance with professional standards and with integrity. In particular, people whose research involves hES cells should work closely with oversight bodies, demonstrate respect for the autonomy and privacy of those who donate gametes, blastocysts, or somatic cells and be sensitive to public concerns about research that involves human embryos.

1.5 Use of NIH-Approved hES Cell Lines

1.5(a) It is acceptable to use hES cell lines that were approved in August 2001 for use in U.S. federally funded research.

1.5(b) ESCRO committees should include on their registry a list of NIH-approved cell lines that have been used at their institution in accord with the requirement in Section 2.0 of the Guidelines.

1.5(c) Presence on the list of NIH-approved cell lines constitutes adequate documentation of provenance, as per Section 6.1 of the Guidelines.

1.6 Acceptability of Research Using hES Cell Lines Imported from Other Institutions or Jurisdictions

1.6(a) Before approving use of hES and hPS cell lines imported from other institutions or jurisdictions, ESCRO committees should consider whether such cell lines have been "acceptably derived."

1.6(b) "Acceptably derived" means that the cell lines were derived from gametes or embryos for which

(i) the donation protocol was reviewed and approved by an IRB or, in the case of donations taking place outside the United States, a substantially equivalent oversight body;
(ii) consent to donate was voluntary and informed;
(iii) donation was made with reimbursement policies consistent with these Guidelines; and
(iv) donation and derivation complied with the extant legal requirements of the relevant jurisdiction.

1.6(c) ESCRO committees should include on their registry a list of cell lines that have been imported from other institutions or jurisdictions and information on the specific guidelines, regulations, or statutes under which the derivation of the imported cell lines was conducted. This is in accord with the requirement in Section 2.0 of the Guidelines that calls for ESCRO committees to maintain registries listing the cell lines in use at their institutions.

2.0 ESTABLISHMENT OF AN INSTITUTIONAL EMBRYONIC STEM CELL RESEARCH OVERSIGHT COMMITTEE

To provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES cell research, each institution should have activities involving hES cells overseen by an Embryonic Stem Cell Research Oversight (ESCRO) committee. This committee could be internal to a single institution or established jointly with one or more other institutions. Alternatively, an institution may have its proposals reviewed by an ESCRO committee of another institution, or by an independent ESCRO committee. An ESCRO committee should include independent representatives of the lay public as well as persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hES cell research. It must have suitable scientific, medical, and ethical expertise to conduct its own review and should have the resources needed to coordinate the management of the various other reviews required for a particular protocol. A pre-existing committee could serve the functions of the ESCRO committee provided that it has the ~~recommended~~ expertise recommended here and representation to perform the various roles described in this report. For example, an institution might elect to constitute an ESCRO committee from among some members of an IRB. But the ESCRO committee should not be a subcommittee of the IRB, as its responsibilities extend beyond human subject protections. Furthermore, much hES cell research does not require IRB review. The ESCRO committee should:

(a) Provide oversight over all issues related to derivation and use of hES cell lines.
(b) Review and approve the scientific merit of research protocols.
(c) Review compliance of all in-house hES cell research with all relevant regulations and these guidelines.
(d) Maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators.

An institution conducting stem cell research should make information from the registries (including, but not necessarily limited to, project abstracts and source of funding) available to the public and the media through the institution's Web site.

(e) Facilitate education of investigators involved in hES cell research.

An institution that maintains its own ESCRO committee should also conduct periodic audits of the committee to verify that it is carrying out its responsibilities appropriately. Auditable records include documentation of decisions regarding the acceptability of research proposals and verification that cell lines in use at the institution were acceptably derived (see Section 1.6). Institutions should make the results of these audits available to the public.

An institution that uses an external ESCRO committee should nevertheless ensure that the registry and educational functions of an internal ESCRO committee are carried out by the external ESCRO committee on its behalf or internally by other administrative units. Those institutions that use external ESCRO committees are also responsible for ensuring that these committees are likewise carrying out their responsibilities appropriately.

2.1 For projects that involve more than one institution, review of the scientific merit, justification, and compliance status of the research may be carried out by a single ESCRO committee if all participating institutions agree to accept the results of the review.

3.0 PROCUREMENT OF GAMETES, BLASTOCYSTS, OR CELLS FOR hES GENERATION

3.1 An IRB, as described in federal regulations at 45 CFR 46.107, should review all new procurements of all gametes, blastocysts, or somatic cells for the purpose of generating new hES or hPS cell lines. This includes the procurement of blastocysts in excess of clinical need from infertility clinics; blastocysts made through IVF specifically for research purposes; ~~and~~ oocytes, sperm, and somatic cells donated for development of hES cell lines derived through NT or by parthenogenesis or androgenesis; and hPS cells derived by any means that require human subjects review.

3.2 Consent for donation should be obtained from each donor at the time of donation. Even people who have given prior indication of their intent to donate to research any blastocysts that remain after clinical care should

nonetheless give informed consent at the time of donation. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

3.3 When donor gametes have been used in the IVF process, resulting blastocysts may not be used for research without consent of all gamete donors.

3.4 Payment and Reimbursement

3.4(a) No payments, cash or in-kind, may be provided for donating blastocysts in excess of clinical need for research purposes. People who elect to donate stored blastocysts for research should not be reimbursed for the costs of storage prior to the decision to donate.

3.4(b) Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for NT) should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an IRB. Direct expenses may include costs associated with travel, housing, child care, medical care, health insurance, and actual lost wages. No payments beyond reimbursements, cash or in-kind, should be provided for donating oocytes for research purposes. Similarly, no payments beyond reimbursements should be made for donations of sperm for research purposes or of somatic cells for use in NT.

3.5 To facilitate autonomous choice, decisions related to the creation of embryos for infertility treatment should be free of the influence of investigators who propose to derive or use hES cells in research. Whenever it is practicable, the attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hES cells should not be the same person.

3.6 In the context of donation of gametes, blastocysts, or somatic cells for hES cell research or for hPS cell research that requires human subjects review, the informed-consent process, should, at a minimum, provide the following information.

(a) A statement that the blastocysts, gametes, or somatic cells will be used to derive hES or hPS cells for research that may include research on human transplantation.
(b) A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation.

(c) A statement as to whether the identities of the donors will be readily ascertainable to those who derive or work with the resulting hES or hPS cell lines.
(d) If the identities of the donors are retained (even if coded), a statement as to whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines.
(e) An assurance that participants in research projects will follow applicable and appropriate best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of stem cells. (Traceable information, however, must be secured to ensure confidentiality.)
(f) A statement that derived hES or hPS cells and/or cell lines might be kept for many years.
(g) A statement that the hES or hPS cells and/or cell lines might be used in research involving genetic manipulation of the cells or the mixing of human and nonhuman cells in animal models.
(h) Disclosure of the possibility that the results of study of the hES or hPS cells may have commercial potential and a statement that the donor will not receive financial or any other benefits from any future commercial development.
(i) A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation.
(j) A statement that embryos will be destroyed in the process of deriving hES cells.
(k) A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors.
(l) A statement of the risks involved to the donor.

In addition, donors could be offered the option of agreeing to some forms of hES cell research but not others. For example, donors might agree to have their materials used for deriving new hES cell lines but might not want their materials used, for example, for NT. The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored. Investigators and stem cell banks are, of course, free to choose which cell lines to accept, and are not obligated to accept cell lines for which maintaining information about specific research use prohibitions would be unduly burdensome.

New derivations of stem cell lines from banked tissues obtained prior to the adoption of these guidelines are permissible provided that the original dona-

tions were made in accordance with the legal requirements in force at the place and time of donation. This includes gametes, blastocysts, adult stem cells, somatic cells, or other tissue. In the event that these banked tissues retain identifiers linked to living individuals, human subjects protections may apply.

3.7 Clinical personnel who have a conscientious objection to hES cell research should not be required to participate in providing donor information or securing donor consent for research use of gametes or blastocysts. That privilege should not extend to the care of a donor or recipient.

3.8 Researchers may not ask members of the infertility treatment team to generate more oocytes than necessary for the optimal chance of reproductive success. An infertility clinic or other third party responsible for obtaining consent or collecting materials should not be able to pay for or be paid for the material obtained (except for specifically defined cost-based reimbursements and payments for professional services).

4.0 DERIVATION OF hES CELL LINES

4.1 Requests to the ESCRO committee for permission to attempt derivation of new hES cell lines from donated embryos or blastocysts must include evidence of IRB approval of the procurement process (see Section 3.0 above).

4.2 The scientific rationale for the need to generate new hES cell lines, by whatever means, must be clearly presented, and the basis for the numbers of embryos and blastocysts needed should be justified.

4.3 Research teams should demonstrate appropriate expertise or training in derivation or culture of either human or nonhuman ES cells before permission to derive new lines is given.

4.4 When NT experiments involving either human or nonhuman oocytes are proposed as a route to generation of ES cells, the protocol must have a strong scientific rationale. Proposals that include studies to find alternatives to donated oocytes in this research should be encouraged.

4.5 Neither blastocysts made using NT (whether produced with human or nonhuman oocytes) nor parthenogenetic or androgenetic human embryos

may be transferred to a human or nonhuman uterus or cultured as intact embryos *in vitro* for longer than 14 days or until formation of the primitive streak, whichever occurs first.

4.6 Investigators must document how they will characterize, validate, store, and distribute any new hES cell lines and how they will maintain the confidentiality of any coded or identifiable information associated with the lines (see Section 5.0 below). Investigators are encouraged to apply the same procedures and standards for characterization, validation, storage, and distribution to hPS cell lines.

5.0 BANKING AND DISTRIBUTION OF hES CELL LINES

There are several models for the banking of human biological materials, including hES cells. The most relevant is the U.K. Stem Cell Bank. The guidelines developed by this and other groups generally adhere to key ethical principles that focus on the need for consent of donors and a system for monitoring adherence to ethical, legal, and scientific requirements. As hES cell research advances, it will be increasingly important for institutions that are obtaining, storing, and using cell lines to have confidence in the value of stored cells—that is, that they were obtained ethically and with the informed consent of donors, that they are well characterized and screened for safety, and that the conditions under which they are maintained and stored meet the highest scientific standards. Institutions engaged in hES research should seek mechanisms for establishing central repositories for hES cell lines—through partnerships or augmentation of existing quality research cell line repositories and should adhere to high ethical, legal, and scientific standards. At a minimum, an institutional registry of stem cell lines should be maintained. Institutions are encouraged to consider the use of the same procedures for banking and distribution of hPS cell lines.

5.1 Institutions that are banking or plan to bank hES cell lines should establish uniform guidelines to ensure that donors of material give informed consent through a process approved by an IRB and that meticulous records are maintained about all aspects of cell culture. Uniform tracking systems and common guidelines for distribution of cells should be established.

5.2 Any facility engaged in obtaining and storing hES cell lines should consider the following standards:

(a) Creation of a committee for policy and oversight purposes and creation of clear and standardized protocols for banking and withdrawals.

(b) Documentation requirements for investigators and sites that deposit cell lines, including
  (i) A copy of the donor consent form.
  (ii) Proof of Institutional Review Board approval of the procurement process.
  (iii) Available medical information on the donors, including results of infectious-disease screening.
  (iv) Available clinical, observational, or diagnostic information about the donor(s).
  (v) Critical information about culture conditions (such as media, cell passage, and safety information).
  (vi) Available cell line characterization (such as karyotype and genetic markers).

A repository has the right of refusal if prior culture conditions or other items do not meet its standards.

(c) A secure system for protecting the privacy of donors when materials retain codes or identifiable information, including but not limited to
  (i) A schema for maintaining confidentiality (such as a coding system).
  (ii) A system for a secure audit trail from primary cell lines to those submitted to the repository.
  (iii) A policy governing whether and how to deliver clinically significant information back to donors.

(d) The following standard practices:
  (i) Assignment of a unique identifier to each sample.
  (ii) A process for characterizing cell lines.
  (iii) A process for expanding, maintaining, and storing cell lines.
  (iv) A system for quality assurance and control.
  (v) A Web site that contains scientific descriptions and data related to the cell lines available.
  (vi) A procedure for reviewing applications for cell lines.
  (vii) A process for tracking disbursed cell lines and recording their status when shipped (such as number of passages).
  (viii) A system for auditing compliance.

(ix) A schedule of charges.
(x) A statement of intellectual property policies.
(xi) When appropriate, creation of a clear Material Transfer Agreement or user agreement.
(xii) A liability statement.
(xiii) A system for disposal of material.

(e) Clear criteria for distribution of cell lines, including but not limited to evidence of approval of the research by an embryonic stem cell research oversight committee or equivalent body at the recipient institution.

6.0 RESEARCH USE OF hES CELL LINES

Once hES cell lines have been derived, investigators and institutions, through ESCRO committees and other relevant committees (such as an IACUC, an IBC, or a radiation safety committee) should monitor their use in research.

6.1 Institutions should require documentation of the provenance of all hES cell lines, whether the cells were imported into the institution or generated locally. ~~Notice to~~ The institution should obtain ~~include~~ evidence of IRB approval of the procurement process and of adherence to basic ethical and legal principles of procurement as described in Sections 1.3(a) and 1.6. In the case of lines imported from another institution, documentation that these criteria were met at the time of derivation will suffice.

6.2 *In vitro* experiments involving the use of already derived and coded hES cell lines will not need review beyond the ~~notification required~~ review described in Sections 1.3(a) and ~~in Section~~ 6.1.

6.3 Each institution should maintain a registry of its investigators who are conducting hES cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding the use of hES cells.

6.4 All protocols involving the combination of hES cells with nonhuman embryos, fetuses, or adult animals must be submitted to the local IACUC for review of animal welfare issues and to the ESCRO committee for consideration of the consequences of the human contributions to the resulting chimeras. (See also Section 1.3(c)(iii) concerning breeding of chimeras.)

6.5 Transplantation of differentiated derivatives of hES cells or even hES cells themselves into adult animals will not require extensive ESCRO committee review. If there is a possibility that the human cells could contribute in a major organized way to the brain of the recipient animal, however, the scientific justification for the experiments must be strong, and proof of principle using nonhuman (preferably primate) cells, is desirable.

6.6 Experiments in which hES cells, their derivatives, or other pluripotent cells are introduced into nonhuman fetuses and allowed to develop into adult chimeras need more careful consideration because the extent of human contribution to the resulting animal may be higher. Consideration of any major functional contributions to the brain should be a main focus of review. (See also Section 1.3(c)(iii) concerning breeding of chimeras.)

6.7 Introduction of hES cells into nonhuman mammalian blastocysts should be considered only under circumstances in which no other experiment can provide the information needed. (See also Sections 1.3(c)(ii) and 1.3(c)(iii) concerning restrictions on breeding of chimeras and production of chimeras with nonhuman primate blastocysts.)

6.8 Research use of existing hES cells does not require IRB review unless the research involves introduction of the hES cells or their derivatives into patients or the possibility that the identity of the donors of the blastocysts, gametes, or somatic cells is readily ascertainable or might become known to the investigator.

7.0 RECOMMENDATIONS FOR RESEARCH ON NON-EMBRYO-DERIVED HUMAN PLURIPOTENT STEM CELLS (hPS CELLS)

7.1 Derivation

Because non-embryo-derived hPS cells are derived from human material, their derivation is covered by existing IRB regulations concerning review and informed consent. No ESCRO committee review is necessary, although the IRB may always seek the advice of an ESCRO committee if it seems desirable. The IRB review should consider proper consent for use of the derived hPS cells. Some of the recommendations for informed consent that apply to hES cells also apply to hPS cells (see Section 3.6), including informed consent to genetic manipulation of resulting pluripotent stem cells and their

use for transplantation into animals and humans and, potentially, in future commercial development.

7.2 Use in *in Vitro* Experiments

Use of hPS cells in purely *in vitro* experiments need not be subject to any review beyond that necessary for any human cell line except that any experiments designed or expected to yield gametes (oocytes or sperm) should be subject to ESCRO committee review.

7.3 Use in Experiments Involving Transplantation of hPS Cells into Animals at Any Stage of Development or Maturity

7.3(a) Research involving transplantation of pluripotent human cells derived from non-embryonic sources into nonhuman animals at any stage of embryonic, fetal, or postnatal development should be reviewed by ESCRO committees and IACUCs, as are similar experiments that use hES cells.

7.3(b) ESCRO committees should review the provenance of hPS cells as they review the provenance of hES cells (see Section 1.6) to ensure that the cell lines were derived according to ethical procedures of informed consent as monitored by an IRB or equivalent oversight body.

7.3(c) Proposals for use of hPS cells in animals should be considered in one of the following categories:

> (i) Permissible after currently mandated reviews and proper documentation [see Section 1.3(a)]: experiments that are exempt from full ESCRO committee review but not IACUC review (experiments that involve only transplantation into postnatal animals with no likelihood of contributing to the central nervous system or germ line).
>
> (ii) Permissible after additional review by an ESCRO committee, as described in Section 2.0 of the Guidelines [see Section 1.3(b)]: experiments in which there is a significant possibility that the implanted hPS cells could give rise to neural or gametic cells and tissues. Such experiments need full ESCRO committee and IACUC review and would include generation of all preimplantation chimeras and neural transplantation into embryos or perinatal animals. Particular attention should be paid to at least three factors: the extent to which the

implanted cells colonize and integrate into the animal tissue; the degree of differentiation of the implanted cells; and the possible effects of the implanted cells on the function of the animal tissue.

(iii) Should not be conducted at this time [see Section 1.3(c)]:

(1) Experiments that involve transplantation of hPS cells into human blastocysts.
(2) Research in which hPS cells are introduced into nonhuman primate embryos, pending further research that will clarify the potential of such introduced cells to contribute to neural tissue or to the germ line.

7.4 Multipotent Neural Stem Cells

It is also relevant to note that neural stem cells, although not pluripotent, are multipotent and may have the potential to contribute to neural tissue in chimeric animals. ESCRO committees should decide whether they wish to review and monitor such experiments with neural stem cells in a similar fashion.

7.5 Prohibition on Breeding

No animal into which hPS cells have been introduced such that they could contribute to the germ line should be allowed to breed.

7.6 Guidance for Banking and Distribution

Institutions should consider the value of banking and distributing hPS cells using the guidance and rules that are already in place for hES cells and the value of including hPS cell lines in their registries.

8.0 INTERNATIONAL COLLABORATION

If a U.S.-based investigator collaborates with an investigator in another country, the ESCRO committee may determine that the procedures prescribed by the foreign institution afford protections consistent with these guidelines, and the ESCRO committee may approve the substitution of some of or all of the foreign procedures for its own.

9.0 CONCLUSION

The substantial public support for hES cell research and the growing trend by many nonfederal funding agencies and state legislatures to support this field requires a set of guidelines to provide a framework for hES cell research. In the absence of the oversight that would come with unrestricted federal funding of this research, these guidelines will offer reassurance to the public and to Congress that the scientific community is attentive to ethical concerns and is capable of self-regulation while moving forward with this important research.

To help ensure that these guidelines are taken seriously, stakeholders in hES cell research—sponsors, funding sources, research institutions, relevant oversight committees, professional societies, and scientific journals, as well as investigators—should develop policies and practices that are consistent with the principles inherent in these guidelines. Funding agencies, professional societies, journals, and institutional review panels can provide valuable community pressure and impose appropriate sanctions to ensure compliance. For example, ESCROs and IRBs should require evidence of compliance when protocols are reviewed for renewal, funding agencies should assess compliance when reviewing applications for support, and journals should require that evidence of compliance accompanies publication of results.

As individual states and private entities move into hES cell research, it will be important to initiate a national effort to provide a formal context in which the complex moral and oversight questions associated with this work can be addressed on a continuing basis. Both the state of hES cell research and clinical practice and public policy surrounding these topics are in a state of flux and are likely to be so for several years. Therefore, the committee believes that a national body should be established to assess periodically the adequacy of the policies and guidelines proposed in this document and to provide a forum for a continuing discussion of issues involved in hES cell research. New policies and standards may be appropriate for issues that cannot now be foreseen. The organization that sponsors this body should be politically independent and without conflicts of interest, should be respected in the lay and scientific communities, and able to call on suitable expertise to support this effort.

Appendix B

Glossary[1]

Adult stem cell—An undifferentiated cell found in a differentiated tissue that can renew itself and (with limitations) differentiate to yield the specialized cell types of the tissue from which it originated.

Androgenesis—Development in which the embryo contains only paternal chromosomes.

Autologous transplant—Transplanted tissue derived from the intended recipient of the transplant. Such a transplant helps to avoid complications of immune rejection.

Blastocoel—The cavity in the center of a blastocyst.

Blastocyst—A preimplantation embryo of 50–250 cells depending on age. The blastocyst consists of a sphere made up of an outer layer of cells (the trophectoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass).

Blastomere—A single cell from a morula or early blastocyst, before the differentiation into trophectoderm and inner cell mass.

Bone marrow—The soft, living tissue that fills most bone cavities and contains hematopoietic stem cells, from which all red and white blood cells evolve. The bone marrow also contains mesenchymal stem cells from which a number of cell types arise, including chondrocytes, which produce cartilage, and fibroblasts, which produce connective tissue.

[1]New or modified wording is indicated by underlining, deleted text by ~~strikeout~~.

Chimera—An organism composed of cells derived from at least two genetically different cell types. The cells could be from the same or separate species.

Differentiation—The process whereby an unspecialized early embryonic cell acquires the features of a specialized cell, such as a heart, liver, or muscle cell.

DNA—Deoxyribonucleic acid, a chemical found primarily in the nucleus of cells. DNA carries the instructions for making all the structures and materials the body needs to function.

Ectoderm—The outermost of the three primitive germ layers of the embryo; it gives rise to skin, nerves, and brain.

Egg cylinder—An asymmetric embryonic structure that helps to determine the body plan of the mouse.

Electroporation—Method of introducing DNA into a cell.

Embryo—An animal in the early stages of growth and differentiation that are characterized by cleavage, laying down of fundamental tissues, and the formation of primitive organs and organ systems; especially the developing human individual from the time of implantation to the end of the eighth week after conception, after which stage it becomes known as a fetus.[2]

Embryoid bodies (EBs)—Clumps of cellular structures that arise when embryonic stem cells are cultured. Embryoid bodies contain tissue from all three germ layers: endoderm, mesoderm, and ectoderm. Embryoid bodies are not part of normal development and occur only in vitro.

Embryonic disk—A group of cells derived from the inner cell mass of the blastocyst, which later develops into an embryo. The disk consists of three germ layers known as the endoderm, mesoderm, and ectoderm.

Embryonic germ (EG) cells—Cells found in a specific part of the embryo or fetus called the gonadal ridge that normally develop into mature gametes. The germ cells differentiate into the gametes (oocytes or sperm).

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[2]http://www.nlm.nih.gov/medlineplus/mplusdictionary.html. In common parlance, "embryo" is used more loosely and variably to refer to all stages of development from fertilization until some ill-defined stage when it is called a fetus. There are strictly defined scientific terms such as "zygote," "morula," and "blastocyst" that refer to specific stages of preimplantation development (see Chapter 2 of NRC and IOM, 2005). In this report, we have used the more precise scientific terms where relevant but have used the term "embryo" where more precision seemed likely to confuse rather than clarify.

Embryonic stem (ES) cells—Primitive (undifferentiated) cells derived from the early embryo that have the potential to become a wide variety of specialized cell types.

Endoderm—Innermost of the three primitive germ layers of the embryo; it later gives rise to the lungs, liver, and digestive organs.

Enucleated cell—A cell whose nucleus has been removed.

Epidermis—The outer cell layers of the skin.

Epigenetic—Refers to modifications in gene expression that are controlled by heritable but potentially reversible changes in DNA methylation or chromatin structure without involving alteration of the DNA sequence.

Epithelium—Layers of cells in various organs, such as the epidermis of the skin or the lining of the gut. These cells serve the general functions of protection, absorption, and secretion, and play a specialized role in moving substances through tissue layers. Their ability to regenerate is excellent; the cells of an epithelium may replace themselves as frequently as every 24 hours from the pools of specialized stem cells.

Feeder cell layer—Cells that are used in culture to maintain pluripotent stem cells. Feeder cells usually consist of mouse embryonic fibroblasts.

Fertilization—The process whereby male and female gametes unite to form a zygote (fertilized egg).

Fibroblasts—Cells from many organs that give rise to connective tissue.

Gamete—A mature male or female germ cell, that is, sperm or oocyte, respectively.

Gastrulation—The procedure by which an animal embryo at an early stage of development produces the three primary germ layers: ectoderm, mesoderm, and endoderm.

Gene—A functional unit of heredity that is a segment of DNA located in a specific site on a chromosome. A gene usually directs the formation of an enzyme or other protein.

Gene targeting—A procedure used to produce a mutation in a specific gene.

Genital ridge—Anatomic site in the early fetus where primordial germ cells are formed.

Genome—The complete genetic material of an organism.

Genotype—Genetic constitution of an individual.

Germ cell—A sperm or egg or a cell that can become a sperm or egg. All other body cells are called somatic cells.

Germ layer—In early development, the embryo differentiates into three distinct germ layers (ectoderm, endoderm, and mesoderm), each of which gives rise to different parts of the developing organism.

Germ line—The cell lineage from which the oocyte and sperm are derived.

Gonadal ridge—Anatomic site in the early fetus where primordial germ cells (PGCs) are formed.

Gonads—The sex glands—testis and ovary.

Hematopoietic—Blood-forming.

Hematopoietic stem cell (HSC)—A stem cell from which all red and white blood cells evolve and that may be isolated from bone marrow or umbilical cord blood for use in transplants.

Hepatocyte—Liver cell.

Heterologous—From genetically different individuals.

hES cell—Human embryonic stem cell; a type of pluripotent stem cell.

Histocompatibility antigens—Glycoproteins on the surface membranes of cells that enable the body's immune system to recognize a cell as native or foreign and that are determined by the major histocompatibility complex.

Homologous recombination—Recombining of two like DNA molecules, a process by which gene targeting produces a mutation in a specific gene.

hPS cells—Human pluripotent stem cells derived from non-embryonic sources.

Hybrid—An organism that results from a cross between gametes of two different genotypes.

Immune system cells—White blood cells, or leukocytes, that originate in the bone marrow. They include antigen-presenting cells, such as dendritic cells, T and B lymphocytes, macrophages, and neutrophils, among many others.

Immunodeficient mice—Genetically altered mice used in transplantation experiments because they usually do not reject transplanted tissue.

Immunogenic—Related to or producing an immune response.

Immunosuppressive—Suppressing a natural immune response.

Implantation—The process in which a blastocyst implants into the uterine wall, where a placenta forms to nurture the growing fetus.

Inner cell mass—The cluster of cells inside the blastocyst that give rise to the embryonic disk of the later embryo and, ultimately, the fetus.

Interspecific—Between species.

In utero—In the uterus.

In vitro—Literally, "in glass," in a laboratory dish or test tube; in an artificial environment.

***In vitro* fertilization (IVF)**—An assisted reproductive technique in which fertilization is accomplished outside the body.

In vivo—In the living subject; in a natural environment.

Karyotype—The full set of chromosomes of a cell arranged with respect to size, shape, and number.

Leukemia inhibitory factor (LIF)—A growth factor necessary for maintaining mouse embryonic stem cells in a proliferative, undifferentiated state.

Mesenchymal stem cells—Stem cells found in bone marrow and elsewhere from which a number of cell types can arise, including chondrocytes, which produce cartilage, and fibroblasts, which produce connective tissue.

Mesoderm—The middle layer of the embryonic disk, which consists of a group of cells derived from the inner cell mass of the blastocyst; it is formed at gastrulation and is the precursor to bone, muscle, and connective tissue.

Morula—A solid mass of 16–32 cells that resembles a mulberry and results from the cleavage (cell division without growth) of a zygote (fertilized egg).

Mouse embryonic fibroblast (MEF)—Cells used as feeder cells in culturing pluripotent stem cells.

Multipotent—Capable of differentiation into a limited spectrum of differentiated cell types.

Neural stem cell (NSC)—A stem cell found in adult neural tissue that can give rise to neurons, astrocytes, and oligodendrocytes.

Nuclear transfer (NT)—Replacing the nucleus of one cell with the nucleus of another cell.

Oocyte—Developing egg; usually a large and immobile cell.

Ovariectomy—Surgical removal of an ovary.

Parthenogenesis—Development in which the embryo contains only maternal chromosomes.

Passage—A round of cell growth and proliferation in culture.

Phenotype—Visible properties of an organism produced by interaction of genotype and environment.

Placenta—The oval or discoid spongy structure in the uterus from which the fetus derives its nourishment and oxygen.

Pluripotent cell—A cell that has the capability of developing into cells of all germ layers (endoderm, ectoderm, and mesoderm).

Precursor cells—In fetal or adult tissues, partly differentiated cells that divide and give rise to differentiated cells. Also known as progenitor cells.

Preimplantation genetic diagnosis (PGD)—A procedure applied to IVF embryos to determine which ones carry deleterious mutations predisposing to hereditary diseases.

Primary germ layers—The three initial embryonic germ layers—endoderm, mesoderm, and ectoderm—from which all other somatic tissue types develop.

Primordial germ cell—A cell appearing during early development that is a precursor to a germ cell.

Primitive streak—The initial band of cells from which the embryo begins to develop. The primitive streak establishes and reveals the embryo's head-tail and left-right orientations.

Pseudopregnant—Refers to a female primed with hormones to accept a blastocyst for implantation.

Somatic cell—Any cell of a plant or animal other than a germ cell or germ cell precursor.

Somatic cell nuclear transfer (SCNT)—The transfer of a cell nucleus from a somatic cell into an egg (oocyte) whose nucleus has been removed.

Stem cell—A cell that has the ability to divide for indefinite periods *in vivo* or in culture and to give rise to specialized cells.

Teratoma—A tumor composed of tissues from the three embryonic germ layers. Usually found in ovary or testis. Produced experimentally in animals by injecting pluripotent stem cells to determine the stem cells' abilities to differentiate into various types of tissues.

Tissue culture—Growth of tissue *in vitro* on an artificial medium for experimental research.

Transfection—A method by which experimental DNA may be put into a cultured cell.

Transgene—A gene that has been incorporated into a cell or organism and passed on to successive generations.

Transplantation—Removal of tissue from one part of the body or from one individual and its implantation or insertion into another, especially by surgery.

Trophectoderm—The outer layer of the developing blastocyst that will ultimately form the embryonic side of the placenta.

Trophoblast—The extraembryonic tissue responsible for negotiating implantation, developing into the placenta, and controlling the exchange of oxygen and metabolites between mother and embryo.

Undifferentiated—Not having changed to become a specialized cell type.

Xenograft or xenotransplant—A graft or transplant of cells, tissues, or organs taken from a donor of one species and grafted into a recipient of another species.

Zygote—A cell formed by the union of male and female germ cells (sperm and egg, respectively).

Appendix C

Committee Biographical Sketches

COCHAIRS

R. Alta Charo, JD, is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin–Madison, on the faculties of both the Law School and the Medical School. In 2006, she was Visiting Professor of Law the University of California, Berkeley Boalt Hall School of Law. Professor Charo is the author of nearly 100 articles, book chapters, and government reports on such topics as voting rights, environmental law, family planning and abortion law, medical genetics law, reproductive technology policy, science policy, and medical ethics. Professor Charo is a member of the boards of the Alan Guttmacher Institute and the Foundation for Genetic Medicine, a member of the National Medical Advisory Committee of the Planned Parenthood Federation of America, and a member of the ethics advisory boards of the International Society for Stem Cell Research, the Juvenile Diabetes Research Foundation, and WiCell. In 2005, she was appointed to the ethics standards working group of the California Institute for Regenerative Medicine and was elected a fellow of the Wisconsin Academy of Sciences, Arts and Letters. In 1994, Professor Charo served on the National Institutes of Health Human Embryo Research Panel; and from 1996 to 2001, she was a member of the presidential National Bioethics Advisory Commission and participated in drafting its reports *Cloning Human Beings* (1997), *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity* (1998), *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (1999), *Ethical Issues in Human Stem Cell Research* (1999), *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (2001), and *Ethical and Policy Issues in Research Involving Human Participants* (2001). She was a member of the National Academies' Board on Life Sciences from 2001 until 2007 and since 2006 has been a member of the Institute of Medicine (IOM) Board on

Population Health and Public Health Practices. Professor Charo was elected to IOM in 2006.

Richard O. Hynes, PhD, is the Daniel K. Ludwig Professor for Cancer Research at the David H. Koch Institute for Integrative Cancer Research and Department of Biology at MIT and a Howard Hughes Medical Institute Investigator. He was formerly head of the Biology Department and then director of the Center for Cancer Research at the Massachusetts Institute of Technology. His research focuses on fibronectins and integrins and the molecular basis of cellular adhesion, both in normal development and in pathological situations, such as cancer, thrombosis, and inflammation. Dr. Hynes's current interests are cancer invasion and metastasis, angiogenesis, and animal models of human disease states. He is a member of the National Academy of Sciences and the Institute of Medicine and is a fellow of the Royal Society of London and the American Academy of Arts and Sciences. In 1997, he received the Gairdner International Foundation Award. In 2000, he served as president of the American Society for Cell Biology and testified before Congress about the need for federal support and oversight of embryonic stem cell research. He cochaired the 2005 National Academies *Guidelines for Human Embryonic Stem Cell Research* and is a governor of the Wellcome Trust, UK.

MEMBERS

Eli Y. Adashi, MD, MS, FACOG, is professor of medical science and the former dean of medicine and biological sciences and the Frank L. Day Professor of Biology at the Warren Alpert Medical School of Brown University. Previously, Dr. Adashi served as the professor and chair of the Department of Obstetrics and Gynecology at the University of Utah Health Sciences Center. Dr. Adashi is a member of the Institute of Medicine, a member of the Association of American Physicians, and a fellow of the American Association for the Advancement of Science. Dr. Adashi is a former member of the Advisory Council of the National Institute of Child Health and Human Development and a former president of the Society for Reproductive Endocrinologists, the Society for Gynecologic Investigation, and the American Gynecological and Obstetrical Society. Dr. Adashi is also a former examiner and director of the Division of Reproductive Endocrinology of the American Board of Obstetrics and Gynecology. He is a founding member and treasurer and more recently chair of the advisory committee of the Geneva-based Bertarelli Foundation,

dedicated to promoting the welfare of the infertile couple and to addressing the current "epidemic" of high-order multiple gestations.

Brigid L.M. Hogan, PhD, is the George Barth Geller Professor and chair of the Department of Cell Biology, Duke University Medical Center. Before joining Duke, Dr. Hogan was an investigator of the Howard Hughes Medical Institute and Hortense B. Ingram Professor in the Department of Cell Biology at Vanderbilt University Medical Center. Dr. Hogan earned her PhD in biochemistry at the University of Cambridge. She was then a postdoctoral fellow in the Department of Biology at the Massachusetts Institute of Technology. Before moving to the United States in 1988, Dr. Hogan was head of the Molecular Embryology Laboratory at the National Institute for Medical Research in London. Her research focuses on the genetic control of embryonic development and morphogenesis, using the mouse as a model system. Her laboratory developed methods for deriving mouse pluripotential embryonic germ cell lines. She was cochair for science of the 1994 National Institutes of Health Human Embryo Research Panel and a member of the 2001-2002 National Academies Panel on Scientific and Medical Aspects of Human Cloning. Within the last few years, Dr. Hogan has been elected to the Royal Society of London, the American Academy of Arts and Sciences, the Institute of Medicine, and the National Academy of Sciences.

Marcia Imbrescia is the owner of Peartree Design, a landscape design firm, and was previously the media director for Drumbeater, a high-technology advertising agency. She holds BA degrees in marketing and journalism and a graduate certificate in landscape design. Ms. Imbrescia has a passion for health advocacy and helping people with illness and disability. She is a member of the Board of Trustees of the Arthritis Foundation (AF), for which she has participated as a volunteer at the chapter and national levels. She served as a member (1996-1998 and 2001) and chairperson (2002-2003) of AF's American Juvenile Arthritis Organization. In 1992, she received the Volunteer of the Year Award from the Massachusetts Chapter of AF. Her volunteer efforts include program development, conference planning, public speaking, fundraising, and advocacy. She served on the National Academies Committee on Guidelines for Human Embryonic Stem Cell Research in 2004-2005.

Terry Magnuson, PhD, is Sarah Graham Kenan Professor and chair of the Department of Genetics at the University of North Carolina. He also directs the Carolina Center for Genome Sciences and is the program director of cancer genetics at the Lineberger Comprehensive Cancer Center. Dr. Magnuson's

research interests include mammalian genetics, genomics, and development. His laboratory has developed a high-throughput system to study the effects of mutations on mouse development with mouse embryonic stem cells. He is particularly interested in the role of chromatin remodeling complexes in such processes as autosomal imprinting, X-inactivation, and anterior-posterior patterning of axial structures in mammals. He is an elected member of the American Academy of Arts and Sciences and was a member of the Board of Directors of the Genetics Society of America and of the Society for Developmental Biology.

Linda B. Miller, OTR, MS in hospital administration, is president of the Washington, DC–based Volunteer Trustees Foundation, a consortium of not-for-profit hospital governing boards. She has extensive experience in trustee education, advocacy, and the legal, ethical, and policy issues facing voluntary health care institutions. Recently, she has worked closely with the states' attorneys general in developing guidelines for protecting the community interest in the sale and conversion of nonprofit hospitals and in designing models for practice and legal oversight. She was elected to membership in the Institute of Medicine (IOM) in 1997.

Ms. Miller has been a frequent speaker on health-policy issues and has been published extensively in both the medical and popular press, including the *New England Journal of Medicine*, *Health Affairs*, *USA Today*, the *Washington Post,* and the *New York Times*. She served as a special assistant to the secretary of health, education, and welfare (now the Department of Health and Human Services) and on numerous health-related policy councils and advisory committees, including the National Institutes of Health's Consensus Panel on Liver Transplantation and, most recently, IOM's Committee on Spinal Cord Injury. Ms. Miller serves on the Advisory Board of the University of Louisville–based Institute for Cellular Therapeutics, headed by Suzanne Ildstad, which does research in adult bone marrow transplantation, and has been a member of several academic and health-care institutions' boards of governors, including those of Blythedale Children's Hospital in New York, Capital Hospice in the national capital region, and Cornell University's Alumni Council.

Jonathan D. Moreno, PhD, is the David and Lyn Silfen University Professor and professor of medical ethics and of the history and sociology of science at the University of Pennsylvania. He is also a senior fellow at the Center for American Progress. Until 2007, he was the Emily Davie and Joseph S. Kornfeld Professor of Biomedical Ethics at the University of Virginia, where

he also directed the Center for Biomedical Ethics. Dr. Moreno is a member of the Institute of Medicine. He is also a bioethics adviser for the Howard Hughes Medical Institute, a faculty affiliate of the Kennedy Institute of Ethics at Georgetown University, and a fellow of the Hastings Center. During 1995-1996, he was senior policy and research analyst for the President's Advisory Committee on Human Radiation Experiments; and during 1998-2000, he was a senior consultant for the National Bioethics Advisory Commission. He cochaired the 2005 National Academies Committee on Guidelines for Human Embryonic Stem Cell Research and is a consultant to the Ethical, Social and Cultural Program of the Bill & Melinda Gates Foundation Grand Challenges in Global Health initiative for ethical and regulatory issues related to stem cell research in China.

Pilar N. Ossorio, PhD, JD, is associate professor of law and bioethics at the University of Wisconsin–Madison and program faculty in the Graduate Program in Population Health at the university. Before taking her position there, she was director of the Genetics Section of the Institute for Ethics at the American Medical Association and taught as an adjunct faculty member at the University of Chicago Law School. For the 2006 calendar year, Professor Ossorio was a visiting professor of law at the University of California, Berkeley Boalt Hall School of Law.

Dr. Ossorio received her PhD in microbiology and immunology in 1990 from Stanford University. She went on to complete a postdoctoral fellowship in cell biology at Yale University School of Medicine. Throughout the early 1990s, Dr. Ossorio worked as a consultant for the federal program on the Ethical, Legal, and Social Implications (ELSI) of the Human Genome Project; in 1994, she took a full-time position with the Department of Energy's ELSI program. In 1993, she served on the Ethics Working Group for President Clinton's Health Care Reform Task Force. Dr. Ossorio received her JD from the Boalt Hall School of Law in 1997. While there, she was elected to the legal honor society Order of the Coif and received several awards for outstanding legal scholarship.

Dr. Ossorio is a fellow of the American Association for the Advancement of Science (AAAS), on the Editorial Board of the *American Journal of Bioethics*, an adviser to the National Human Genome Research Institute on ethical issues in large-scale sequencing, and a member of the University of Wisconsin's institutional review board for health-sciences research. She is a past member of AAAS's Committee on Scientific Freedom and Responsibility, a past member of the National Cancer Policy Board in the Institute of Medicine, and a past member or chair of several working groups on genet-

ics and ethics. She has published scholarly articles in bioethics, law, and molecular biology.

E. Albert Reece, MD, PhD, MBA, is dean of the University of Maryland School of Medicine and vice president for medical affairs at the University of Maryland, Baltimore. Previously, he was vice chancellor and dean of the University of Arkansas College of Medicine. Dr. Reece received his undergraduate degree from Long Island University, his MD (Magna Cum Laude) from New York University, his PhD in biochemistry from the University of the West Indies, and his MBA from the Fox School of Business and Management of Temple University. He completed a residency in obstetrics and gynecology at Columbia University–Presbyterian Hospital and a fellowship in maternal-fetal medicine at Yale University School of Medicine. He served on the faculty at Yale for 10 years and was the chairman of the Department of Obstetrics, Gynecology and Reproductive Sciences at Temple University. Dr. Reece has published over 400 journal articles, book chapters, and abstracts and nine textbooks, including *Diabetes in Pregnancy*, *Medicine of the Fetus & Mother*, and *Fundamentals of Obstetric & Gynecologic Ultrasound*. He is an editor for the *Journal of Maternal-Fetal Medicine* and a reviewer for several other scientific journals. His research focuses on diabetes in pregnancy, birth defects, and prenatal diagnosis. Dr. Reece is a member of the Institute of Medicine.

Joshua R. Sanes, PhD, is professor of molecular and cellular biology and the Paul J. Finnegan Family Director of the Center for Brain Science at Harvard University. He was previously Alumni Endowed Professor of Neurobiology at the Washington University School of Medicine. Dr. Sanes earned a BA in biochemistry and psychology at Yale and a PhD in Neurobiology at Harvard. He studies the formation of the synapses that interconnect nerve cells, including pioneering work on the signals exchanged between nerve cells and their target muscles as new connections are made. He is also using the vertebrate visual system to examine how nerve cells develop and migrate to the right location in the body. He was elected a fellow of the American Association for the Advancement of Science in 1992 and a member of the National Academy of Sciences in 2002.

Harold T. Shapiro, PhD, is president emeritus of both Princeton University and the University of Michigan and is currently professor of economics and public affairs at Princeton University. His research interests include bioethics, the social role of higher education, hospital and medical-center administra-

tion, university administration, econometrics, statistics, and economics. Dr. Shapiro chairs the Board of Trustees of the Alfred P. Sloan Foundation, is presiding director for the Dow Chemical Company, and is a member of numerous boards, including the Robert Wood Johnson Medical School, HCA, the Merck Vaccine Advisory Board, the Knight Foundation Commission on Intercollegiate Athletics, the U.S. Olympic Committee, and the Stem Cell Institute of New Jersey. He is a former chair of the Association of American Universities and the National Bioethics Advisory Committee and vice chair of the President's Council of Advisors on Science and Technology. He has also served on the Board of Directors of the National Bureau of Economic Research, Inc. and the Board of Trustees of the Universities Research Association, Inc. He has chaired and served on numerous National Academies committees, including the Committee on the Organizational Structure of the National Institutes of Health and the Committee on Particle Physics. Dr. Shapiro was named the 2006 American Association for the Advancement of Science William D. Carey Lecturer for his leadership in science policy. He earned a PhD in economics from Princeton University and holds 14 honorary doctorates.

John E. Wagner, Jr., MD, is a professor of pediatrics at the University of Minnesota Medical School. He is the first recipient of the Children's Cancer Research Fund/Hageboeck Family Chair in Pediatric Oncology and also holds the Variety Club Endowed Chair in Molecular and Cellular Therapy. He is the director of the Division of Pediatric Hematology/Oncology and Bone Marrow Transplantation and scientific director of clinical research of the Stem Cell Institute. Dr. Wagner is a member of numerous societies, including the American Society of Hematology, the International Society of Experimental Hematology, and the American Society of Blood and Marrow Transplantation. He is a member of several honorary societies, including Alpha Omega Alpha (1980), the American Society of Clinical Investigation (2000), and the Association of American Physicians (2006). Dr. Wagner holds a patent on the isolation of the pluripotential quiescent stem cell population. Dr. Wagner holds a BA in biological sciences and a BA in psychology from the University of Delaware and an MD from Jefferson Medical College. Dr. Wagner's research has focused on the development of novel cellular therapies for tissue repair and suppression of the immune response using subpopulations of neonatal umbilical cord blood and adult bone marrow and peripheral blood. His projects are funded by the National Institutes of Health and industry. In addition, Dr. Wagner pioneered the use of embryo selection to "create" a perfectly tissue-matched stem cell donor for the treat-

ment of genetic disease. Dr. Wagner has written more than 180 articles and book chapters on hematopoietic stem cell transplantation. He cochairs the Graft Sources and Manipulation Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR), serves on the Scientific Board of Directors of the National Marrow Donor Program, and is a member of the Scientific and Medical Accountability Standards Working Group of the California Institute of Regenerative Medicine. Dr. Wagner has previously served as a member of the Institute of Medicine's Committee on Establishing a National Cord Blood Stem Cell Banking Program.

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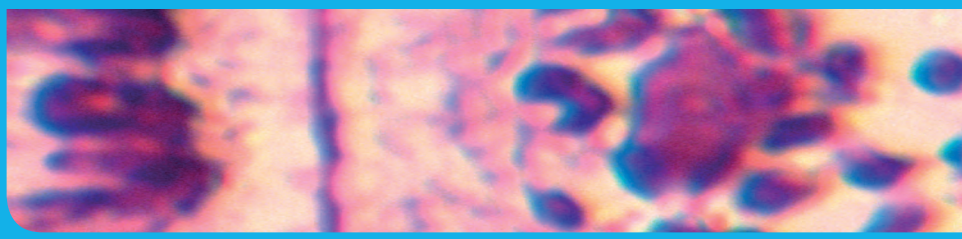

ETHICAL GUIDELINES ON THE USE OF ASSISTED REPRODUCTIVE TECHNOLOGY IN CLINICAL PRACTICE AND RESEARCH

2004 (AS REVISED IN 2007 TO TAKE INTO ACCOUNT THE CHANGES IN LEGISLATION)

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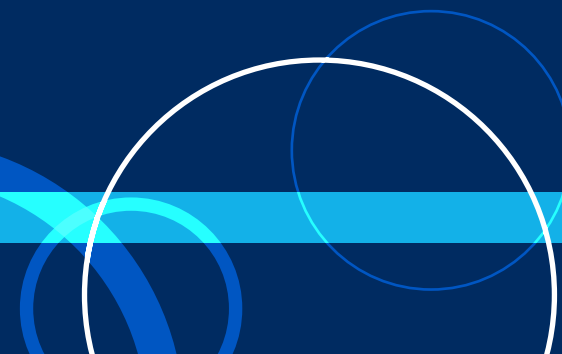

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CONTENTS

PREFACE

The previous version of this document was developed in 2004 to provide ethical guidelines for clinical practice and research involving assisted reproductive technology.

In addition, the guidelines were designed to take into account the legal requirements of the 2002 legislation, the *Research Involving Human Embryos Act 2002* and the *Prohibition of Human Cloning Act 2002*, in relation to prohibited and licensable activities.

In 2007, the guidelines have been revised only to the extent made necessary by amendments to those Acts and to account for changes to the *National Health and Medical Research Council Act 1992*. This revision to the guidelines, which included public consultation, was developed by AHEC and presented to the NHMRC Council on 12 June 2007. It was then referred to the Chief Executive Officer (CEO) of the NHMRC and is now issued.

The document will, in due course, be fully revised, in keeping with the NHMRC policy of 5-yearly reviews.

PART A

INTRODUCTION

1 BACKGROUND

ETHICAL GUIDELINES ON ASSISTED REPRODUCTIVE TECHNOLOGY

1.1 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*).

1.2 The 1996 ART guidelines 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, a committee established by the Fertility Society of Australia.

1.3 In the 1996 ART guidelines, 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. At the time of preparation of these current guidelines, uniform legislation has not been enacted.

1.4 In 2004, the NHMRC published *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research*. The guidelines revised and replaced the 1996 guidelines and also took account of the *Prohibition of Human Cloning Act 2002* (PHC Act) and the *Research Involving Human Embryos Act 2002* (RIHE Act).

NATIONAL LEGISLATION ON EMBRYO RESEARCH AND HUMAN CLONING

1.5 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.

1.6 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.[1] That report 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.[2] The latter 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.

1.7 In 2002, the Australian Parliament passed legislation banning human cloning (PHC Act). Through COAG, the states and territories agreed that each jurisdiction would introduce complementary laws and progressively amend or introduce new legislation to provide for corresponding prohibition on cloning humans and other unacceptable practices.

1.8 The Australian Parliament also passed legislation to regulate certain uses of embryos that have been deemed to be no longer needed in an ART program ('excess ART embryos'). The RIHE Act also established the Embryo Research Licensing Committee (referred to in these guidelines as the Licensing Committee) as a new principal committee of the NHMRC. The functions of the Licensing Committee include the consideration of applications for licences to conduct research on excess ART embryos, to grant licences in conformity with the RIHE Act, to appoint inspectors for monitoring and compliance, to maintain a public database and to report to the Australian Parliament on a regular basis.

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1 *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings*, AHEC, December 1998.

2 *Human Cloning: Scientific, Ethical and Regulatory Aspects of Human Cloning and Stem Cell Research*, House of Representatives Standing Committee on Legal and Constitutional Affairs, Canberra, August 2001 (Andrews Report).

1.9 The RIHE Act acknowledges the importance of the application of ethical principles to research involving human embryos in several ways. The RIHE Act requires that, 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 in the RIHE Act (s 8) as consent obtained in accordance with guidelines issued by the CEO of the NHMRC under the *National Health and Medical Research Council Act 1992* and prescribed by the regulations for the purposes of this definition.

1.10 The RIHE Act (s 21) states that the Licensing Committee must not issue a licence unless satisfied that the activity or project proposed in the application has been assessed and approved by a human research ethics committee (HREC) constituted in accordance with, and acting in compliance with, the National Statement *on Ethical Conduct in Research Involving Humans* (NHMRC 1999), now *The National Statement on Ethical Conduct in Human Research 2007*, referred to in these guidelines as the National Statement.

1.11 The PHC and RIHE Acts contain a requirement for review which was conducted in 2005. The report of that review, conducted by a committee chaired by the late Justice John Lockhart, was published in December 2005 as *Legislation Review: Prohibition of Human Cloning Act 2002 and Research Involving Human Embryos Act 2002*, (the Lockhart Review) and recommended changes to both Acts.

1.12 In 2006, the *Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006* (the Amendment Act) was enacted. The Amendment Act comes into effect on 12 June 2007. These amendments extend the range of licensable activities. The Amendment Act changed the title of the PHC Act to the *Prohibition of Human Cloning for Reproduction Act 2002* (PHCR Act).

REVISED ETHICAL GUIDELINES FOR THE USE OF ART (2007)

1.13 The current revision replaces the 2004 ART guidelines, to the extent necessitated by changes to the PHC Act and the RIHE Act brought about by the Amendment Act. With respect to clinical practice, the ART guidelines remain a key element in the accreditation processes for ART clinics. With respect to research, they will be used by HRECs and researchers who apply for ethical approval of any proposed research involving participants in ART, human eggs, sperm and/or embryos, and by researchers applying to the Licensing Committee for a licence.

1.14 In addition to these guidelines, researchers also need to refer to the National Statement and, in relevant circumstances, *Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research* (NHMRC 2003).

1.15 It is the responsibility of clinicians and researchers to be aware of any other relevant laws and regulations.

1.16 NHMRC ethical guidelines, in conjunction with the law, create a robust framework for the conduct of research or practice. For example, the National Statement sets ethical guidelines for the conduct of all human research.

1.17 This document contains revised ethical guidelines for the conduct of clinical practice or research in ART, including research involving human embryos. For an explanation of the role of these guidelines in relation to licensable activities, see Section 4.

2 INTRODUCTION TO THESE GUIDELINES

ETHICAL BASIS OF GUIDELINES

2.1 Ethics is sometimes thought to be merely a matter of individual preference or cultural convention. Although ethical judgments may indeed express personal preferences, and may be connected in complicated ways with cultural conventions, ethics itself is a form of rational inquiry that concerns how we should live and what we should do. Some ethical issues are matters of debate: people of goodwill can reason about them but still reach differing practical conclusions.

2.2 The best way of reasoning about ethical issues is itself a matter of debate. Some people emphasise the moral undesirability of *certain acts* (such as deliberate deception) in and of themselves and the moral desirability of *certain standards of conduct* (such as integrity in one's relationships with others) in and of themselves. Others emphasise the moral significance of anticipating the likely *consequences* of proposed acts (for example, the likely consequences for a woman who gestates a child for another woman).

2.3 Similarly, some people emphasise the *duties* we owe to each other (for example, the duty to respect another's personal autonomy). Others emphasise the *moral claims* we are entitled to make against each other (for example, a child's moral entitlement to knowledge of his or her genetic parents). All of these kinds of considerations matter, even if there can be reasonable disagreement among people about how they are to be balanced.

2.4 In preparing these guidelines, AHEC has tried to be sensitive to all the relevant ethical dimensions of ART: to recognise the basic human goods at stake; to distinguish goals and purposes from means chosen; to clarify relevant moral principles and motives; to distinguish the moral evaluation of human acts themselves from the moral evaluation of their likely consequences; to identify the virtues or character traits that facilitate responsible conduct in ART; and, to recognise that, while related in complicated ways, ethical questions cannot be wholly separated from social and political questions.

2.5 In these guidelines, AHEC has recognised that the welfare of people who may be born as a result of the use of ART is paramount.

2.6 AHEC has also taken into account the following issues:

- the autonomy and long-term welfare of individuals (both men and women) who take part in ART or research;
- the need for informed decision making;
- the importance of an ethical framework for the use of gametes and embryos in clinical practice, training and research; and
- the recognition in the strict licensing procedures imposed by National Legislation that the embryo warrants very serious moral consideration.

2.7 In addition, AHEC has recognised the potential benefits from the responsible pursuit of medical and scientific knowledge.

SCOPE

2.8 These guidelines cover all activities associated with ART as they occur in:

- ***clinical practice***, including:
  - routine practice associated with fertility treatment using ART
  - training, quality assurance and innovative practices
  - the use of excess embryos for training purposes
  - the creation or use of hybrid embryos for sperm testing, and
- ***research*** involving:
  - participants in ART
  - donors of human gametes or cells involved in embryo research
  - embryos that are intended for implantation
  - excess ART embryos
  - other human embryos (See Section 17).

2.9 These guidelines are primarily for ART practitioners, researchers, infertility clinic administrators, HRECs, and state and national government officials.

STRUCTURE AND USE OF THE GUIDELINES

2.10 These guidelines are divided into three parts:

- Part A provides introductory information about the development of the guidelines and their ethical and legal basis.
- Part B provides ethical guidelines for clinical practice involving ART.
- Part C provides ethical guidelines for research involving ART and other practices.

2.11 For all issues raised in the guidelines, clinicians and researchers must comply with relevant national and/or state/territory legislation.

2.12 In addition, AHEC has identified ethical principles that must inform the conduct of clinicians and researchers and the procedures developed in clinics and research facilities.

2.13 The ethical principles are supported by practical guidelines that clinicians and researchers should include in their standard operating procedures in order to ensure that they comply with the ethical principles. These practical guidelines should be followed unless there is an effective alternative option that is consistent with the relevant ethical principle.

2.14 To assist the reader, throughout Part B and Part C, the legal requirements and ethical principles (see paragraph 2.11 and 2.12), have first order paragraph numbering (for example, 14.1). The practical guidelines described in paragraph 2.13 all have second order paragraph numbering (for example, 14.1.1).

2.15 In addition, there are three appendices to the guidelines. Appendix A lists the members of AHEC, Appendix B relates to process matters in the preparation of the revised guidelines and Appendix C aims to stimulate community discussion about a number of issues that are controversial and may need consideration by legislators.

3 REGULATORY FRAMEWORK

3.1 Legislation

Clinical practice, research and all other activities referred to in these guidelines must comply with:

- relevant national legislation, including the PHCR Act, the RIHE Act and the *Privacy Act 1988*; and
- relevant state and territory legislation, including privacy legislation.

3.2 NHMRC licensing arrangements

Activities that require a licence are specified under the RIHE Act and must comply with the conditions of the licence and these guidelines.

3.3 Professional and accreditation standards

Clinical practice, research and all other related activities referred to in these guidelines must conform to standards established by the relevant professional and accreditation bodies, including certification and maintenance of appropriate professional standards, and maintenance of quality management systems for laboratory and clinical work.

3.4 NHMRC guidelines

Clinical practice, research and all other related activities using ART are to adhere to these ethical guidelines as follows:

- they must comply with all relevant legislation relating to the activities described in these guidelines;
- they must conform with ethical principles outlined in Parts B and C of the guidelines; and
- they should follow the practical guidelines provided in Parts B and C to ensure conformity with ethical principles (see paragraph 2.13).

Research using ART should also conform to the most recent editions of other relevant NHMRC guidelines (see 'Key information sources'), including:

- the National Statement*;*
- *Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research*; and
- *Australian Code for the Responsible Conduct of Research*.

3.5 Human research ethics committees

Activities that require a licence (see paragraph 4.2) and all proposals for human research must be approved by an HREC.

Other activities, such as some quality assurance and innovative practices, may also need to be considered and approved by an HREC. (See National Statement.)

3.6 Monitoring

Research institutions have the responsibility for monitoring all human research. See the section on monitoring approved research in the National Statement.

4 ETHICS AND LICENSABLE PRACTICES

INTRODUCTION

In general, ethical guidelines issued under the *NHMRC Act 1992* for human research provide guidance to researchers, HRECs and institutions. They are not, in themselves, legally binding. However, they have legal effect, for example, when the agreements with the Commonwealth bodies require compliance. In some areas of research, the ethical guidelines may be given legal force by State or Commonwealth statute, which is the case for research involving the formation or use of human embryos. The Fertility Society of Australia also endorses the NHMRC ART guidelines as part of its accreditation process.

The PHC and RIHE Acts in 2002 provided a list of prohibited practices. Accordingly, the 2004 guidelines did not contain any guidance for HRECs reviewing proposals involving these practices. Changes to these Acts have introduced exceptions by which certain otherwise prohibited practices are now permissible if authorised by a licence. This revised document includes ethical guidelines for the implementation of these changes to the Acts.

A condition of the issuing of a licence is that the proposal has been approved by an HREC. 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 has been assessed and approved by an HREC that is constituted in accordance with, and acting in compliance with, the National Statement. For research involving human gametes or embryos, the National Statement states that such research is governed by, and subject to the ART guidelines (see sections on human tissue samples and human stem cells).

In relation to clinical practice, the ART guidelines provide ethical guidance. However, in relation to licensable activities under the RIHE Act, compliance with the ART guidelines is also a legal requirement to the extent required by the Act.

Accordingly, AHEC has developed, and the CEO of the NHMRC issues, these revised ethical guidelines. Researchers, in the design and conduct of research, and HRECs, in their review of proposals, must apply these guidelines. In accordance with the National Statement, HRECs are required to have regard to the values and principles of ethical conduct: research merit and integrity, justice, beneficence and respect.

AHEC has developed guidelines on obtaining human ova and other aspects of research involving the formation and/or use of human embryos for research purposes. AHEC has not developed guidelines on the intrinsic issues involved in the formation of human embryos and human-animal hybrid embryos and their use in research. Whether these activities are ethically acceptable in the context of a specific research proposal is a judgement assigned by legislation to the HREC prior to the application for a licence.

4.1 *PROHIBITION OF HUMAN CLONING FOR REPRODUCTION ACT 2002*

Sections 9 to 21 of the PHCR Act prohibit certain practices under the following headings[3] as used in the Act:

- placing a human embryo clone in the human body or the body of an animal [s 9];
- importing or exporting a human embryo clone [s 10];
- creating a human embryo for a purpose other than achieving pregnancy in a woman [s 12];
- creating or developing a human embryo by fertilisation that contains genetic material provided by more than 2 persons [s 13];
- developing a human embryo outside the body of a woman for more than 14 days [s 14];
- heritable alterations to genome [s 15];
- collecting a viable human embryo from the body of a woman [s 16];
- creating a chimeric embryo [s 17];
- developing a hybrid embryo [s 18];
- placing of an embryo [s 19] ;
- importing, exporting or placing a prohibited embryo [s 20][4]; and
- commercial trading in human eggs, human sperm or human embryo [s 21].

Sections 22 to 23B of the PHCR Act prohibit certain practices unless authorised by a licence, under the following headings:

- creating a human embryo other than by fertilisation, or developing such an embryo [s 22];
- creating or developing a human embryo containing genetic material provided by more than 2 persons [s 23];
- using precursor cells from a human embryo or a human foetus to create a human embryo, or developing such an embryo [s 23A];
- creating a hybrid embryo [s 23B – Note: a licence to create or develop a hybrid embryo can only be issued under the RIHE Act (s 21) and only for prescribed purposes].

[3] The full definition of the practices can be found in the identified sections of the PHCR Act.

[4] See 'Explanation of key terms' for definition of a prohibited embryo.

4.2 *RESEARCH INVOLVING HUMAN EMBRYOS ACT 2002*[5]

Sections 10 and 11 of the RIHE Act state that the following uses of excess ART embryos are exempt and therefore do not require a licence:

- storage;
- removal from storage;
- transport;
- observation (see 'Explanation of key terms');
- allowing the embryo to succumb;
- use by an accredited ART centre of an embryo that is not suitable to be placed in the body of the woman for whom it was created (where suitability is determined only on the basis of its biological fitness for implantation), and the use forms part of diagnostic investigations conducted in connection with the ART treatment of the woman for whom the embryo was created; or
- use carried out by an accredited ART centre and for the purposes of achieving a pregnancy in a woman other than the woman for whom the excess ART embryo was created.

Sections 10A and 10B of the RIHE Act state that the following practices are prohibited unless authorised by a licence:

- using a human embryo:
  - created by a process other than the fertilisation of a human egg by a human sperm; or
  - created by a process other than fertilisation that contains genetic material of more than 2 persons; or
  - created using precursor cells taken from a human embryo or human foetus, or
- using a hybrid embryo; and
- undertaking research or training involving the fertilisation of a human egg by a human sperm up to, but not including, the first mitotic division, outside the body of a woman for the purposes of research or training in ART.

Section 11 of the RIHE Act prohibits the use, outside the body of a woman, of a human embryo created by fertilisation of a human egg by a human sperm that is not an excess ART embryo for a purpose unrelated to the ART treatment of a woman.

[5] The following summarises sections 10, 11, 10A and 10B of the RIHE Act.

PART B

ETHICAL GUIDELINES FOR THE CLINICAL PRACTICE OF ART

5 ETHICAL PRINCIPLES FOR CLINICAL PRACTICE OF ART

5.1 Respect all participants

Assisted reproductive technology (ART) procedures must be conducted in a way that is respectful of all involved. Clinical decisions must respect, primarily, the interests and welfare of the persons who may be born, as well as the long-term health and psychosocial welfare of all participants, including gamete donors.

5.1.1 According to the National Statement, any person whose gametes are used for research purposes is considered to be a research participant.

5.2 Respect human embryos

While there are different views held in our community about the moral status of a human embryo, one very widely shared view is that embryos warrant very serious moral consideration. At all times, any embryos created must be dealt with according to these guidelines and accepted standards of clinical and laboratory practice.

In the course of clinical practice, clinicians must limit the number of embryos created to those likely to be needed by the participants in the course of their treatment.

5.2.1 To limit the number of embryos created, clinicians should:

- minimise ovarian stimulation;
- limit the number of ova fertilised and embryos stored; and
- not start new treatment cycles for patients when clinically suitable embryos are in storage.

5.3 Use open and consistent decision making

Participants in ART are entitled to understand and participate in the decision making about their care. Clinics must use an open and consistent approach to ethical issues that arise in practice.

5.3.1 Clinics should maintain documented practices and procedures, identifying the line of responsibility for each. For example, specific protocols should be developed for the following:

- the range of treatments and laboratory procedures;
- access to, and eligibility for, treatment;
- gametes and embryo donation (including selection, counselling and screening of both recipients and donors);

- storage and disposal of gametes and embryos;
- information giving and counselling;
- obtaining consent to treatment;
- record keeping and data reporting;
- investigation and resolution of complaints.

5.4 Provide information and counselling

Participants in ART are entitled to detailed information about proposed procedures and any alternatives and to receive counselling about the consequences of those procedures. Clinicians must strive to ensure that all participants (and, where relevant, their spouses or partners) in ART are informed about all aspects of the procedures and receive professional counselling. Section 9 provides guidelines on information giving and counselling.

5.5 Obtain consent

Participants in ART have the right to decide for themselves whether or not to take part in the proposed procedures. Clinics must obtain the consent of all participants in ART procedures (and, where relevant, their spouse or partner). Section 9 provides guidelines on obtaining consent.

5.6 Maintain privacy and confidentiality

All participants in ART are entitled to privacy. Clinics must respect the privacy of participants and confidentiality of all records and must have a privacy policy that ensures compliance with relevant legislation and guidelines.

5.7 Keep detailed records

Good record keeping is an essential component of clinical practice and vital for ART because of the long-term consequences of procedures involving ART on the health and psychosocial wellbeing of the persons who are born and on the participants in ART procedures themselves (and their spouses and partners, if any). Clinics must keep accurate records of all gametes and embryos in their care in accordance with Section 10.

5.8 Collect and report outcomes data

Participants in ART are entitled to accurate information about the risks of the procedures they will undergo. To monitor the short-term and long-term risks of ART procedures, and to provide accurate information for prospective participants, clinics must collect and make public data on the outcomes of ART procedures in accordance with Section 10.

5.9 Respect conscientious objections

Conscientious objectors are not obliged to be involved in the procedures or programs to which they object. If any member of staff or student expresses a conscientious objection to the treatment of any individual patient or to any ART procedures conducted by the clinic, the clinic must allow him or her to withdraw from involvement in the procedure or program to which he or she objects. Clinics must also ensure that staff and students are not disadvantaged because of a conscientious objection.

6 USE OF GAMETES IN REPRODUCTIVE TREATMENT PROGRAMS

INTRODUCTION

The gametes used in ART can either be provided by the spouse or partner of the person receiving treatment or donated by a third party. In these guidelines, the term 'donated gametes' is used when the gametes are provided by a third person who, while being the genetic parent of the person born, will not be the social parent (see 'Explanation of key terms').

Most of the guidelines in this section refer to donated gametes. However, paragraphs 6.15 and 6.16 refer to collection of gametes from either a spouse or partner, or from a gamete donor, for use in ART procedures.

Gametes may be donated for use by anyone who is receiving ART treatment at the clinic where the donation is made ('unknown donation'). However, some gamete donors may donate their gametes for use only by certain individuals, such as those from a particular ethnic or social group ('unknown but directed donation'), or for use by a specified recipient who is known to the donor, such as a relative or friend ('known donation'). Most of the guidelines in this section refer to unknown donations, but some specific issues relating to unknown but directed donation and known donation are included in paragraphs 6.6 to 6.9.

Voluntary exchange of information between persons conceived using donated gametes, gamete donors and gamete recipients, with the consent of all parties, is desirable. The guidelines in this section specify the minimum level of information that should be accessible to participants in a donated gamete treatment program. Access to further information may occur only with the consent of all parties involved or as specified by the law.

DONATION OF GAMETES

6.1 Uphold the right to knowledge of genetic parents and siblings

Persons conceived using ART procedures are entitled to know their genetic parents. Clinics must not use donated gametes in reproductive procedures unless the donor has consented to the release of identifying information about himself or herself to the persons conceived using his or her gametes. Clinics must not mix gametes in a way that confuses the genetic parentage of the persons who are born.

6.1.1 Clinics should help potential gamete donors to understand and accept the significance of the biological connection that they have with the persons conceived using their gametes. Donors should be advised that the persons conceived are entitled to knowledge of their genetic parents and siblings.

6.1.2 Clinics should help prospective recipients to understand the significant biological connection that their children have with the gamete donor. Recipients should be advised that their children are entitled to knowledge of their genetic parents and siblings; they should therefore be encouraged to tell their children about their origins.

6.1.3 Working with relevant professional organisations, clinics should use forums for public information to encourage people who were donors before the introduction of these guidelines, and those previously conceived using donated gametes, to contact the clinic and register their consent to being contacted by their genetic children or genetic siblings and half-siblings, respectively.

6.1.4 Clinics should not use gametes or embryos collected before the introduction of these guidelines without the consent of the gamete donor (or gamete providers for donated embryos) to the release of identifying information for any future treatments (with the exception of the circumstances given in paragraph 6.1.5).

6.1.5 The only situations in which a reproductive procedure involving donor gametes may be considered without the consent of the donor to the release of identifying information are:

- where the recipient has a child who was born before the introduction of these guidelines using the same gamete donor; or
- where embryos created using donated gametes have been stored before the introduction of these guidelines but the donor cannot be contacted.

In such circumstances, the recipients should be given detailed information (and offered further counselling, if required) about the benefits and risks associated with this transitional arrangement for the persons conceived using donated gametes without consent to release of identifying information.

6.2 Use suitable gamete donations

In using gamete donations, clinicians must carefully consider the physical, psychological and social wellbeing of the person to be born and the participants.

Treatment in Australia using either gametes donated overseas or embryos created from gametes donated overseas must not take place unless all the relevant conditions of these guidelines and any relevant legislation have been fulfilled.

6.2.1 Children and young people (who are defined as 'minors' in each jurisdiction) should not be allowed to donate gametes for use by others in a reproductive procedure.

6.2.2 Clinics should not use gametes donated by older men and women unless the potential recipient understands the implications and increased risks of such an arrangement.

6.3 Limit the number of persons born from a single donor

Persons conceived using donor gametes, and the donors of gametes, need to be protected from the consequences of having many genetic siblings and offspring, respectively. Clinics must take all reasonable steps to reduce the numbers of genetic relatives created through donor gamete programs.

6.3.1 Gametes from one donor should be used in a limited number of families. In deciding the number of families, clinicians should take account of:

- the number of genetic relatives that the persons conceived using the donation will have;
- the risk of a person conceived with donor gametes inadvertently having a sexual relationship with a close genetic relative (with particular reference to the population and ethnic group in which the donation will be used);
- the consent of the donor for the number of families to be created; and
- whether the donor has already donated gametes at another clinic.

6.4 Minimise risk of infection

Clinics must take all appropriate steps to reduce the risk of transmission of infection.

6.4.1 Clinics should not accept donations from people at an increased risk of transmissible infections.

6.4.2 All donors of gametes should undergo appropriate infection control surveillance.

6.5 Do not trade in human gametes

Gamete donation must be altruistic. Commercial trading in human gametes and/or the use of direct or indirect inducements, must not be undertaken (see paragraph 17.21.2).

KNOWN DONATION

6.6 Respect the donor's wishes

If the donor specifies recipients he or she knows personally, clinics must respect the wishes of the donor.

6.7 Encourage careful consideration of donations from relatives

If clinics provide treatment involving gamete donation from a relative, they must encourage very careful consideration of all relevant issues (in particular, that it is unethical to mislead a child about the identity of his or her genetic parent(s), and that relationships within families can be confused by cross-generational donations).

6.8 Do not allow fertilisation of eggs from close relatives

Eggs must not be fertilised with sperm from a close genetic relative (that is, from a person for whom a sexual relationship with the female donor would legally be considered to be incest).

UNKNOWN BUT DIRECTED DONATION

6.9 Respect the donor's wishes

Some gamete donors may wish to donate their gametes for use only by certain individuals, such as those from a particular ethnic or social group. This type of directed donation is illegal in some jurisdictions. Clinics in those states must not accept such donations. In the remaining states and territories, clinics must not use the gametes in a way that is contrary to the wishes of the donor.

ENTITLEMENT TO INFORMATION

6.10 Provide gamete recipients with relevant medical history of gamete donor

Gamete recipients need information about gamete donors that is relevant for the care of their donor-conceived offspring. Clinics must allow recipients of donated gametes access, through either a medical practitioner or an appropriately qualified health professional, to at least the following information about gamete donors:

- details of past medical history, family history and any genetic test results that are relevant to the future health of the person born (or any subsequent offspring of that person) and the recipient of the donation;
- details of the physical characteristics of the gamete donor; and
- the number and sex of persons conceived using the gametes donated by the same gamete donor.

6.11 Provide donor-conceived persons with information about their gamete donor

People conceived using donated gametes are entitled to know their genetic parents. On request, clinics must arrange for either a medical practitioner, or an appropriately qualified health professional, to provide at least the following information, to a person conceived through ART procedures, provided that he or she has either reached the age of 18 years or acquired sufficient maturity to appreciate the significance of the request (including any implications for his or her younger siblings):

- all medical and family history information as specified in paragraph 6.10;
- identifying information about the gamete donor (subject to paragraph 6.1); and
- the number and sex of persons conceived using the gametes provided by the same gamete donor, the number of families involved, and any identifying information that these siblings have consented to being released (see paragraph 6.1.3).

6.12 Provide gamete donors with relevant information about their genetic offspring

Gamete donors are entitled to some information about the recipients of their gametes and the offspring born (in particular, to prepare them for future approaches by their genetic offspring). Clinics may provide gamete donors, on request, with nonidentifying information about gamete recipients, including the number and sex of persons born.

6.13 Respect the privacy of all persons involved in ART procedures

People have a right to privacy. Clinics must not release identifying information to another person without the consent of the person to be identified.

6.13.1 When approached by a person who was conceived using donated gametes and who now seeks identifying information about his or her genetic parents, the clinic should examine the consent form of the gamete donor and proceed as follows:

- If the consent form does not include permission for release of identifying information (because the donation was made before the introduction of these guidelines and the gamete donor has not come forward in response to the public information campaign outlined in paragraph 6.1.3), the clinic should make an appropriate effort, consistent with the original consent document and the privacy rights of the donor, to contact the gamete donor and obtain his or her consent to the release of information.

- If the consent form includes permission for release of identifying information, the clinic may notify the donor and release the information to the person requesting the information.

6.13.2 When a clinic is approached by a person who was conceived using donated gametes and who now seeks identifying information about his or her genetic siblings or half-siblings, it should check its register of consent for the release of such information (see paragraph 6.1.3) and proceed as follows:

- If consent has been registered by the siblings concerned, the information may be released.
- If consent has not been registered, clinics should not release identifying information or contact the siblings.

6.13.3 Acceptance of counselling services should be encouraged as part of the preparation for the release of identifying information.

RESPONSIBILITY FOR GAMETES AND RESULTING EMBRYOS

6.14 Maintain a consistent chain of responsibility

Participants in ART procedures involving donated gametes need to know who is responsible for the gametes and resulting embryos used in their treatment. At the same time, the right of the donor to withdraw his or her consent for donation also needs to be protected.

Clinics must maintain clear procedures for the transfer of responsibility for gametes and the resulting embryos at each stage of the program as follows:

- When the gamete donor has not specified a recipient for his or her gametes, the clinic has responsibility for decision making about the use, storage and disposal of the gametes, subject to any limitations expressed in the consent of the donor.
- When the gamete donor has specified a known recipient for his or her gametes, and consent for treatment has been given by the recipient, the recipient has responsibility for decision making about the use of the gametes in his or her own reproductive treatment, as well as storage and disposal, subject to any limitations expressed in the consent of the donor.
- At any time before insemination or fertilisation, gamete donors may vary or withdraw their consent to donation (see paragraph 9.6).
- Once fertilisation has taken place, the persons for whom the embryo has been created have responsibility for decision making about its use in their own reproductive treatment and the medical care of the embryo (both before and after implantation into the uterus), storage and disposal.

POSTHUMOUS USE OF GAMETES

6.15 Use of gametes from deceased or dying persons or from persons in postcoma unresponsive state

When either parent dies before the birth of a child, this is generally regarded by society as tragic in that the child will not know that parent. The facilitation of conception in circumstances where the child born will never know one of his or her genetic parents is, by analogy, a serious act of profound significance for the person born. In addition, state or territory legislation may prohibit the use of gametes after a person has died.

Clinics must not facilitate use of gametes to achieve pregnancy in such circumstances, unless all of the following conditions are met:

- a deceased person has left clearly expressed and witnessed directions consenting to the use of his or her gametes; or
- a person in a postcoma unresponsive state ('vegetative state') prepared clearly expressed and witnessed directions, before he or she entered the coma, consenting to the use of his or her gametes; or
- a dying person prepares clearly expressed and witnessed directions consenting to the use, after death, of his or her gametes; and
- the prospective parent received counselling about the consequences of such use; and
- the use does not diminish the fulfilment of the right of any child who may be born to knowledge of his or her biological parents.

6.15.1 As these situations arise infrequently and involve serious ethical issues, clinics should ensure that those involved seek advice and guidance from a clinical ethics committee on the ethical issues raised above and, if necessary, seek advice regarding the application of relevant laws.

6.16 Allow an appropriate period of time before attempting conception

The loss of a spouse or partner will be followed by a period of grief. Clinics must allow adequate time for this grieving process and ensure that counselling is available to the surviving spouse or partner before assisting in conception attempts using gametes collected from persons described in paragraph 6.15.

CREATION OF HYBRID EMBRYOS FOR PURPOSES OF TESTING SPERM QUALITY

6.17 Limit the formation of hybrid embryos to sperm testing in an accredited ART centre (see RIHE Act s 20(1)(f))

6.17.1 For the investigation of male infertility, sperm quality may be tested, under licence, by the fertilisation of an animal egg by a human sperm, and use of such embryo up to, but not including, the first mitotic division. Hybrid embryos may not be formed for any other purpose and their creation or use must occur in an accredited ART centre.

6.17.2 The consent to the use of the sperm to form a hybrid embryo must meet the provisions of Section 9, 'Information giving, counselling and consent'.

7 USE OF DONATED EMBRYOS

INTRODUCTION

Embryos that are no longer needed for reproductive treatment by the persons for whom they were created may be donated to another couple for their reproductive treatment (see 'Explanation of key terms'). The implications of embryo donation for the persons born and the donors are similar to those in adoption. Neither the birth mother nor the social father of the person born is the genetic parent.

Embryos may be donated for use by anyone who is receiving ART at the clinic where the donation is made ('unknown donation'). However, some embryo donors may donate their embryos for use only by certain individuals, such as those from a particular ethnic or social group ('unknown but directed donation') or for a specified person who is known to the donor, such as a relative or friend ('known donation').

Most of this section refers to unknown donations, but some specific issues relating to known donations (paragraphs 7.4 and 7.5) and to unknown but directed donations (paragraph 7.6) are included.

7.1 Uphold the right to knowledge of genetic parents and siblings

As for adopted people, persons born from reproductive procedures using donated embryos are entitled to know their genetic parents and of the existence of any genetically related siblings.

Donated embryos, or embryos created using donated gametes, must therefore only be used in an ART procedure to achieve a pregnancy if all the principles in Section 6 for donated gametes are followed both for the gamete providers whose gametes were used to create the embryo and for the recipients of the embryo.

The only situations in which a reproductive procedure involving donor embryos may be considered without the consent of the gamete providers to the release of identifying information are:

- where the recipient has a child who was born before the introduction of these guidelines using the same embryo donor(s); or
- where embryos created using donated gametes have been stored before the introduction of these guidelines but the donor cannot be contacted.

In such circumstances, the recipients should be given detailed information (and offered further counselling, if required) about the benefits and risks associated with this transitional arrangement for the person conceived using a donated embryo without consent to release of identifying information.

7.2 Maintain the integrity of genetic parenthood

Persons conceived by ART are entitled to know their genetic parents. Clinics must not use any procedures that allow the genetic parentage of persons conceived to be confused. For this reason, clinicians must not transfer embryos to the uterus of a woman from more than one source at any one time.

7.2.1 Because of the potential for difficulties in tracing genetic parents, and because of possible effects on the long-term psychosocial welfare of the persons born from embryos that have undergone serial donations, clinics should not facilitate the following procedures:

- donation of an embryo that has been created using a donated gamete or gametes; or
- on-donation of a donated embryo to another couple.

7.3 Ensure a consistent chain of responsibility

People undertaking ART procedures using donated embryos need to know who is responsible for the embryos involved in their treatment. At the same time, the right of the donors to withdraw their consent for donation also needs to be protected.

Clinics must maintain clear procedures for the transfer of responsibility for embryos at each stage of the program as follows:

- Once the embryo donors have specified a recipient who has accepted their embryo for implantation, the nominated embryo recipient (and her spouse or partner, if any) has responsibility for decision making about its use in her reproductive treatment and the embryo's medical care, storage and disposal, subject to any limitations expressed in the consent of the donor or imposed by law.
- If the embryo donors have not specified a recipient for their embryos, clinics should keep or place the embryos in storage until suitable recipients are selected by the clinic for treatment.
- At any time before transfer of the embryo into the uterus of the recipient, embryo donors may vary or withdraw their consent to donation (see paragraph 9.6).

KNOWN DONATIONS

7.4 Respect the donor's wishes

If the donor specifies recipients he or she knows personally, and who have indicated that they wish to accept the donation, clinics must respect the wishes of the donor.

7.5 Encourage careful consideration of donations from relatives

If clinicians provide treatment involving embryo donation from a relative, they must encourage careful consideration of all relevant issues (in particular, that it is unethical to mislead a child about the identity of his or her genetic parent(s), and that relationships within families can be confused by cross-generational donations).

UNKNOWN BUT DIRECTED DONATION

7.6 Respect the donor's wishes

Some embryo donors may wish to donate their embryos for use only by certain individuals, such as those from a particular ethnic or social group. This type of directed donation is illegal in some jurisdictions. Clinics in those states must not accept such donations. In the remaining states and territories, clinics must not use the embryos in a way that is contrary to the wishes of the donor.

8 STORAGE OF GAMETES AND EMBRYOS

STORAGE OF GAMETES

8.1 Explain options for use and disposal of stored gametes

The persons for whom gametes are stored are entitled to know the options for future use and disposal of their gametes. Clinics must ensure that, at the time that gametes are stored, the people who are responsible for them are given sufficient information to understand the future options they will have for the gametes.

8.2 Ensure safety and identity

Persons for whom gametes are stored and persons who use stored gametes are entitled to certainty about the safety and identity of the gametes. Clinics must therefore ensure the safe storage and accurate identification of all gametes.

8.2.1 The identity and location of any gametes or gonadal tissue in storage should be recorded in detail.

8.2.2 The labelling method should not be susceptible to unauthorised, undetectable or accidental alteration.

8.3 Limit storage

It is not desirable to leave gametes in storage indefinitely. Clinics must have clear policies that limit the duration of storage of gametes.

8.3.1 Gametes should be kept in safe storage for up to the maximum time specified in the consent (see paragraph 8.8), after which, if the gamete provider has not consented to further storage arrangements, clinics may dispose of the gametes.

8.3.2 In accepting gametes (including gonadal tissue) for storage, clinicians should clearly outline to each gamete provider his or her responsibilities and any circumstances under which the clinic may dispose of the gametes before the end of the consent period.

8.4 Do not store gametes from deceased or dying persons or from persons in a postcoma unresponsive state

The use of gametes for conception requires the consent of the gamete provider or donor. Clinics must not store or use gametes from deceased persons or from persons who are unable to consent to the procedure, for example, due to postcoma unresponsiveness ('vegetative state'), unless there is a clearly expressed and witnessed directive from the person that gives his or her consent to the use of the gametes.

If the clinic receives confirmation that a gamete provider or donor has died, it must dispose of the stored gametes, unless there is a clearly expressed and witnessed directive to the contrary.

STORAGE OF EMBRYOS

8.5 Discuss options for use or disposal of stored embryos

The persons for whom embryos are stored will, from time to time, have to make difficult decisions about the future of their embryos. Clinics must ensure that, at the time that embryos are stored, all the people who are responsible for them (including the persons for whom they are stored and the gamete providers for the embryos) are given sufficient information to understand the future options they will have for the embryos.

8.5.1 Clinics should provide information about the following options for the future use of stored embryos:

- use in reproductive treatment for the original participant;
- donation to another recipient for reproductive treatment, in which case clinics would explore options for the embryos to be used by other participants in reproductive procedures (see Section 7);
- removal from storage, in which case clinics would arrange for disposal of the embryo (see paragraph 8.9);
- use in research (see Section 17);
- use in training or quality assurance activities (see Section 14).

8.6 Ensure safety and identity

Persons for whom embryos are stored are entitled to certainty about the safety and identity of their embryos.

Clinics must therefore ensure the safety and accurate identification of all embryos stored.

8.6.1 The identity, number and location of any embryos in storage should be recorded in detail.

8.6.2 The labelling method used should not be susceptible to unauthorised, undetectable or accidental alteration.

8.7 Respect the wishes of the persons for whom the embryos are stored

At any time during the period of storage, the persons for whom the embryo is stored, in consultation with their clinician, may decide that the embryo is no longer needed for their treatment.

If the embryo is no longer needed for treatment, clinicians must obtain a declaration in writing that the embryo is no longer required for any clinical treatment. The other four options noted in paragraph 8.5.1 may then be offered.

8.7.1 If a dispute arises between the members of a couple for whom the embryo is stored, and either person requests continued storage, the embryo should be kept in storage until the dispute is resolved or until the maximum period of storage has been reached (see paragraph 8.8).

8.7.2 If both members of a couple for whom an embryo is stored die, any reasonable, clearly expressed and witnessed directive from them should be followed. If there is no such directive, or it cannot be followed, clinics should arrange for disposal of the embryo.

8.8 Limit duration of storage

It is not desirable to leave embryos in storage indefinitely.

Clinics must have clear policies that limit the duration of storage of embryos.

8.8.1 The maximum time for which embryos may be kept in storage should be five years with the option to renew consent for a further five years.

8.8.2 If, after the maximum period of storage, the embryos have not been used, donated or allowed for use in research (see paragraph 8.5), and no alternative arrangements have been made by the persons for whom the embryos are stored, clinics should arrange for the disposal of the embryos.

8.9 Dispose of embryos respectfully

Clinics must have protocols in place for the respectful disposal of embryos.

8.9.1 The wishes of the persons for whom the embryos are stored, as to the method of disposal, should be respected.

9 INFORMATION GIVING, COUNSELLING AND CONSENT

INFORMATION GIVING

9.1 Provide and discuss all relevant information with participants

To make informed decisions about their treatment, participants in ART need to understand all the procedures involved, including any health risks and psychosocial consequences associated with them. Clinics must give up-to-date, objective, accurate information about treatment options and the procedures involved to all potential participants in ART procedures and discuss it with them.

9.1.1 The information discussed should allow participants to develop an accurate understanding of the following issues:

- the likelihood of the woman becoming pregnant other than through ART;
- recent success and failure rates relevant to the particular participants;
- any significant risks involved in the proposed procedures;
- the likelihood and significance of potential short-term or long-term physical and psychosocial implications for the person born and the participants;
- the currently available published data on morbidity, and both long-term and short-term outcomes, for persons born through ART;
- whether the proposed procedure is accepted practice or an innovative procedure (see paragraph 14.1);
- options for use, storage, donation and disposal of gametes and embryos (see Sections 6, 7 and 8);
- an explanation of all costs involved;
- the clinic's privacy policy; and
- any planned or possible follow-up studies and/or the possibility of later contact and request to take part in such studies.

9.1.2 Clinics should provide and discuss information about storage of gametes (including gonadal tissue) and/or embryos. The information should include:

- the survival rate and suitability for transfer of gametes and embryos after freezing and thawing for the particular clinic;
- the live-birth rate following the use of the thawed gametes, tissues and embryos;
- available information about outcomes for persons conceived using stored gametes or embryos;
- any legal or other limitations to use, including posthumous use; and
- the maximum storage times.

9.1.3 Clinics should provide and discuss information in a way that is appropriate to, and sufficient for, informed decision making. The information should be given:

- verbally, supported by written information in plain language;
- with sensitivity to cultural diversity and religious beliefs;
- in a way that is accessible to those with low literacy or disability, and/or whose first language is not English;
- in a way that avoids any coercion or inducement; and
- without emotive imagery (such as images of babies and young children) or emotive language.

9.2 Consider the information needs of all parties in donated gamete or embryo programs

Donors and recipients in gamete or embryo donor programs (see Sections 6 and 7) each have complex information needs. Clinics must consider the information needs of both donors and recipients.

9.2.1 Clinics should provide and discuss information on the following issues:

- the possible implications and long-term psychosocial consequences of gamete or embryo donation for the donors, the recipients and the persons conceived;
- for participation in a donor oocyte program, the possibility that this may affect the ability of the donor to have children in the future;
- the arrangements of the clinic for collection, storage and release of identifying information;
- any difficulties in finding gamete or embryo donors, including meeting the requests of specific recipients;

- the scope of consent and the rights of each person involved to withdraw consent (see paragraphs 6.9 and 7.3);
- the responsibilities of each participant to all other participants in the proposed reproductive procedure;
- the legal status of the genetic and social parents of any persons conceived using donated gametes or embryos in the jurisdiction in which the clinic is located, or the gametes or embryos are used; and
- the options of donating embryos to other people or allowing them to be used for research (see paragraph 8.5). (For further details on allowing embryos to be used for research, see Section 17.)

COUNSELLING

9.3 Provide counselling services

ART involves complex decision making and participants may find it an emotional and stressful experience. Clinics must provide readily accessible services from accredited counsellors to support participants in making decisions about their treatment, before, during and after the procedures.

9.3.1 Clinics should therefore provide counselling services, with professionals who have appropriate training, skills, experience and accreditation necessary for their counselling role. The counselling services should:

- provide an opportunity to discuss and explore issues;
- explore the personal and social implications for the persons born and for the participants;
- provide personal and emotional support for participants, including help in dealing with unfavourable results;
- provide advice about additional services and support networks;
- reflect an integrated, multidisciplinary approach, including medical, nursing, scientific and counselling staff; and
- provide participants with information, when requested, about professional counsellors who are independent of the clinic.

9.3.2 For participants in a gamete or embryo donation program, counselling should include a detailed discussion of the complex issues relating to gamete or embryo donation, including the following specific aspects:

- the long-term psychosocial implications for each individual and each family involved;
- the psychosexual implications;
- the motives of the gamete or embryo provider for becoming involved in a donated gamete program;
- the need to ensure that gamete or embryo donors make their own independent decision to participate and that this decision is reached free from coercion in any form; and
- the right of persons born to have identifying information about their genetic parents and information about the possibility that they will make contact in the future.

CONSENT

9.4 Obtain consent from all participants in all procedures

Before clinical ART procedures are undertaken, clinicians must ensure that consent is obtained from all participants (and, where relevant, their spouses or partners), is informed, voluntary, competent, specific and documented, and remains current.

9.4.1 Consent should be obtained in writing, following the provision and discussion of information about the implications of proposed reproductive procedures, adequate time for consideration of the information and adequate opportunities for personal preparation (see paragraphs 9.1 to 9.3).

9.4.2 Clinics should have procedures to ensure that consent is voluntary and free from coercion.

9.4.3 Consent forms should include the following statements:

- that the participants have received the information provided about the proposed procedures;
- that counselling by a professional counsellor has been offered;
- that participants have had explained to them the procedures involved and the risks of complications and have had their questions answered;
- that participants have had explained to them any mandatory uses of data;

- whether or not the participants give permission for any additional (nonmandatory) uses or disclosures of identifying information or data collected about them;
- whether or not the participants give permission to be contacted in the future with a request for participation in follow-up research;
- the arrangements for storage and disposal of gametes or embryos;
- a signed statement by the supervising clinician that he or she has provided information about the proposed procedures; and
- that relevant participants consent to each proposed procedure.

9.5 Obtain consent from all participants in donated gamete or embryo programs

The donation of gametes or embryos is associated with a range of difficult ethical, social and legal considerations for participants. Clinics must obtain a separate consent form from each participant in gamete or embryo donation programs and their spouse or partner (if any).

9.5.1 Consent forms for the donation of gametes or embryos should include:

- full details of the agreed arrangements for any treatment involving donated gametes or embryos (see Sections 6 and 7);
- an acknowledgment that each participant (and spouse or partner, if any) has received and understood the information provided about gamete or embryo donation;
- a statement that the gamete or embryo donor understands and acknowledges his or her biological connection to any persons conceived using his or her donated gametes or embryos;
- a statement giving explicit permission to make the information specified in paragraphs 6.10 and 6.11 available to the recipients and any person conceived through the procedure, respectively;
- a description of the arrangements set out in paragraphs 6.14 and 7.3 for responsibility for the gametes or embryos after donation; and
- provision for signature by the participant (and his or her spouse or partner, if any).

9.5.2 Potential gamete or embryo donors and gamete or embryo recipients should be given adequate time between provision of information and obtaining consent to allow consideration of the complex issues involved.

9.6 Recognise the right of participants to withdraw or vary their consent

Clinics must recognise that, with the exception of some specific issues relating to the donation of gametes and embryos (see paragraphs 6.14 and 7.3), participants have the right to withdraw or vary their consent at any time.

9.7 Obtain consent for the storage of gametes or embryos

The storage of gametes or embryos is associated with a range of ethical, social and legal considerations for all participants. Clinics must obtain a separate consent form from persons responsible for stored gametes or embryos (and, where relevant, their spouses or partners).

9.7.1 Consent forms for the storage of gametes or embryos should include:

- the maximum period of storage; and
- for embryos, a clearly expressed and witnessed directive as to what should be done with the embryos if either or both the person(s) for whom they are stored die(s), become(s) incapable of varying or revoking the consent, or fail(s) to give further instructions at the expiry of the maximum period of storage.

9.8 Obtain consent to retrieve and store a child's or young person's gonadal tissue or gametes

The retrieval of gonadal tissue or gametes from a child or young person for storage in anticipation of their future need is associated with a range of difficult ethical, social and legal considerations. Decisions to permit the retrieval and storage of gonadal tissue or gametes for a child or young person are ethically acceptable only when:

- the risks and discomfort to the child or young person are minimal;
- storage is the only means of maintaining the benefit of the reproductive capacity of the child or young person;
- there is an independent judgement that the storage is in the child's or young person's overall best interests;
- the child or young person, if capable, and their parents or guardian agree to the storage;
- where required by law, a court or tribunal authorisation has been obtained to undertake a non-therapeutic procedure on the child or young person on the basis that the procedure is in their interests; and
- information about and consent to the retrieval and storage of gametes or gonadal tissue from a child or young person should follow the requirements of Section 9.4.

9.8.1 When the child or young person is not legally competent but sufficiently understands the issues, clinicians should encourage him or her to take part in the decision process.

9.8.2 Any research involving gametes from children or young people are subject to the National Statement (See the section on children and young people) and Section 16 of these guidelines.

9.9 Obtain consent to retrieve and store the gonadal tissue or gametes of people with impaired decision-making ability

The conditions in 9.8 apply to consent for the retrieval and storage of gonadal tissue for people with impaired decision-making ability, such as cognitive impairment, intellectual disability or a mental illness. (See relevant section of the National Statement).

9.10 Obtain separate consent to the use of an excess ART embryo in research

Under the RIHE Act and corresponding state or territory legislation, the persons responsible for embryos that are no longer required for ART treatment (ie those defined in the RIHE Act as 'excess ART embryos'), as well as other embryos, may consent to the use of those embryos in research.

Clinics must apply the principles in Section 15 and follow the procedures in Section 17 for consent to research involving embryos. Such consent must be separate from consent for any treatment and be obtained after the embryos have been deemed excess.

10 RECORD KEEPING AND DATA REPORTING

RECORD KEEPING

10.1 Maintain integrity and privacy of personal information

Clinical records contain sensitive personal information. Clinics must manage records so that the integrity and privacy of the information complies with all requirements of relevant national, state or territory legislation and accrediting bodies, and conforms with the ethical principles defined in these guidelines.

10.1.1 Clinics should have the following overall arrangements for record keeping:

- a privacy policy that complies with the requirements of the relevant national, state or territory privacy legislation;
- procedures to collect, record and report information about persons, treatments and results that ensure maximum security, integrity and effectiveness;
- arrangements to store relevant information about participants in a procedure involving the use of donated gametes or embryos in a way that is secure but accessible to the persons born as a result of the procedures, and the participants, under the conditions described in paragraphs 6.10 to 6.13;
- arrangements to ensure transfer of records to a suitable person or location when a clinic closes or a practitioner ceases to practise (such arrangements should ensure that records stay with the gametes and embryos to which they relate); and
- provision to keep records indefinitely (or at least for the expected lifetime of any persons born).

10.2 Observe, record, monitor and evaluate procedures and outcomes

Good record keeping is essential for short-term and long-term follow-up of procedures. Clinics must therefore keep detailed clinical and laboratory records that are appropriate to the practice of ART and allow monitoring of procedures and their short-term and long-term outcomes:

10.2.1 Clinics should record the following information:

- full names (including previous names) and contact details of all participants and, whenever possible, the names of persons born as a result of assisted reproductive technology;
- particulars of gametes and embryos to enable staff in the clinic to trace what happens to each individual embryo, egg or sperm sample from the date of collection;

- data about outcomes of procedures to allow the clinic or accrediting body to publish relevant information to assist participants to make informed decisions about treatment options (particularly in relation to any experimental or innovative procedures);
- data to facilitate monitoring of short-term outcomes, including the live birth rate per treatment cycle commenced, the occurrence of single and multiple pregnancies, spontaneous abortion, termination of pregnancy, ectopic pregnancy, stillbirth, genetic conditions, perinatal events and any adverse effects and other side effects for the participants during treatment; and
- data to facilitate long-term follow-up studies of persons born as a result of ART procedures, and the participants (eg rates of long-term adverse outcomes and subsequent fertility).

10.3 Record information about donation, use and storage of gametes and embryos

In order to facilitate the exchange of information between donors, recipients and the persons conceived by gamete or embryo donation (as required by paragraphs 6.10 to 6.12), clinics must have appropriate arrangements/systems for data collection, data storage and information release.

10.3.1 Clinics should collect the following information from gamete donors (or gamete providers for donated embryos):

- name, any previous name, date of birth and most recent address;
- details of past medical history, family history, and any genetic test results that are relevant to the future health of the person conceived by gamete donation (or any subsequent offspring of that person) or the recipient of the donation; and
- details of physical characteristics.

10.3.2 Clinics should tell gamete donors (or gamete providers for donated embryos) that it is their ethical responsibility to keep the clinic informed about any changes to their health that may be relevant to the persons born or the recipients of their donation, and about changes to their contact details.

10.3.3 Clinics should keep records of the number of persons born using gametes or embryos provided by the same person(s), the sex of each person born and the number of families into which they have been born. Clinics should ensure that gamete donors (or gamete providers for donated embryos) consent to this information being collected and released to the persons born and/or recipients, as appropriate.

10.3.4 Clinics should store all relevant information about participants in a donated gamete or embryo treatment program indefinitely (see 10.1.1), in a way that is secure but is accessible to all the participants under the conditions described in paragraphs 6.10 to 6.12).

10.4 Monitor the number of embryos created and stored

Clinics must limit the number of embryos created to those that are likely to be needed to achieve a pregnancy. Clinics must maintain records that are adequate to allow monitoring of the number of embryos created and stored (see paragraph 5.2) and to comply with requirements of legislation or relevant authorities (see paragraph 10.5.2).

10.4.1 Clinics should record the following data for each collection cycle:

- the number of eggs collected;
- the number of eggs exposed to sperm;
- the number of embryos created;
- the date that each embryo is created; and
- the number of embryos placed in storage.

10.4.2 Clinics should record the following data for each frozen embryo transfer:

- the number of embryos removed from storage for transfer into the woman for whom the embryos were stored;
- the number of embryos removed from storage for donation to another person for treatment;
- the number of embryos removed from storage for research purposes; and
- the number of embryos removed from storage and disposed of.

10.4.3 Clinics should collate the following data annually:

- mean number of eggs collected at egg collection cycles;
- proportion of egg collection cycles where more than 20 eggs were collected;
- mean number of eggs exposed to sperm in each fertilisation cycle;
- mean number of embryos created in each fertilisation cycle;
- total number of embryos put into storage following fertilisation cycles in the clinic during the previous calendar year; and
- total number of embryos removed from storage for frozen embryo transfer in the clinic during the previous calendar year.

REPORTING OF DATA

10.5 Ensure public accountability for all activities and procedures

Reporting of data must be adequate to ensure open communication of, and accountability for, the clinic's activities to the participants and the general public.

10.5.1 Clinics should make all non-identified data referred to in Section 10 available to appropriate bodies to enable subsequent collation of national statistical information about reproductive procedures, including both long-term and short-term outcomes for the embryos, the children born and the participants.

10.5.2 Reporting of data should comply with requirements of relevant privacy legislation, any state or territory legislation, NHMRC guidelines and, where necessary, be subject to the consent of the participants.

10.5.3 All data relevant to licensed activities, including both long-term and short-term outcomes for the participants, must be kept and made available to appropriate bodies to enable subsequent collation of national statistical information about these activities.

11 SEX SELECTION

11.1 Do not select sex for nonmedical purposes

Sex selection is an ethically controversial issue. The Australian Health Ethics Committee believes that admission to life should not be conditional upon a child being a particular sex. Therefore, pending further community discussion, sex selection (by whatever means) must not be undertaken except to reduce the risk of transmission of a serious genetic condition. See also paragraphs 12.1 and 12.2 on the use of preimplantation genetic diagnosis (PGD) for sex selection.

12 PREIMPLANTATION GENETIC DIAGNOSIS

12.1 Carefully evaluate any use of PGD

PGD is currently used to detect serious genetic conditions, to improve ART outcomes and, in rare circumstances, to select an embryo with compatible tissue for a sibling. These uses have profound ethical significance including:

- what counts as a serious genetic condition is controversial;
- there are different perceptions of disability;
- the practice of selecting against some forms of abnormality may threaten the status and equality of opportunity of people who have that form of abnormality;
- the procedures involve the disposal of some healthy embryos; and
- the procedures have technical limitations (such as the failure to identify the genetic abnormality of interest)

Clinics must ensure careful evaluation of these and all other relevant issues before the use of PGD (see also paragraph 12.5.1).

12.2 Restrict the use of PGD

Pending further community discussion (see Appendix C), PGD must not be used for:

- prevention of conditions that do not seriously harm the person to be born;
- selection of the sex of an embryo except to reduce the risk of transmission of a serious genetic condition; or
- selection in favour of a genetic defect or disability in the person to be born.

12.3 Seek advice before using PGD to select an embryo with compatible tissue for a sibling

Except in the case of siblings, PGD must not be used to select a child to be born with compatible tissue for use by another person.

When requested to select an embryo with tissues compatible with a sibling of a child to be born, clinics must seek advice from a clinical ethics committee (or relevant state or territory regulatory agency).

12.3.1 The ethics committee or relevant agency should ascertain that:

- the use of PGD will not adversely affect the welfare and interests of the child who may be born;
- the medical condition of the sibling to be treated is life-threatening;
- other means to manage the medical condition are not available; and
- the wish of the parents to have another child as an addition to their family and not merely as a source of tissue.

12.4 Provide access to a geneticist and genetic counsellor

It is essential that participants in ART seeking PGD testing of embryos understand the technology and how it applies to their embryos. Clinics must ensure that people seeking PGD testing have access both to clinical geneticists and to genetic counsellors.

12.5 Provide relevant information and counselling

To make informed decisions about their treatment, participants in ART seeking PGD need to understand all the procedures involved. Clinics must give up-to-date, objective, accurate information in line with the guidelines provided in paragraphs 9.1 and 9.2.

12.5.1 In dealing with a specific situation, the people seeking testing should be encouraged to consider the following factors when deciding the appropriateness of PGD:

- information about the likelihood of false positive and false negative results;
- genetic and clinical information about the specific condition;
- their previous reproductive experience;
- the distinction between the genotypic and phenotypic expression of the condition, disease or abnormality;
- the variable range of effects of the condition, disease or abnormality, including the likely rate of degeneration in the case of progressive disorders;
- the experiences of families living with the condition;
- the likely availability of effective therapy or management now and in the future; and
- the extent of social support available.

13 SURROGACY

13.1 Do not undertake or facilitate commercial surrogacy

It is ethically unacceptable to undertake or facilitate surrogate pregnancy for commercial purposes. Clinics must not undertake or facilitate commercial surrogacy arrangements.

13.2 Noncommercial surrogacy

Noncommercial surrogacy (whether partial surrogacy or full surrogacy) is a controversial subject (see Appendix C) and is prohibited in some states and territories. In other states and territories, clinics must not facilitate surrogacy arrangements unless every effort has been made to ensure that participants:

- have a clear understanding of the ethical, social and legal implications of the arrangement; and
- have undertaken counselling to consider the social and psychosocial significance for the person born as a result of the arrangements, and for themselves.

13.2.1 Clinicians should not advertise a service to provide or facilitate surrogacy arrangements, nor receive a fee for services to facilitate surrogacy arrangements.

14 INNOVATIONS, TRAINING AND QUALITY ASSURANCE

14.1 Evaluate innovations before use in clinical practice

Changes to clinical treatment methods, or introduction of innovative procedures, may have short-term or long-term consequences for the persons born and/or the participants in the treatment.

Clinics must not introduce changes in treatment methods or innovative procedures in ART into routine clinical practice without prior evaluation of safety and efficacy and consideration of legal and ethical issues.

Significant changes or innovations in procedures, practices or therapies must be considered as research and formal HREC approval obtained, even where only one person or couple is involved.

14.1.1 Innovations should be considered significant (and therefore referred to an HREC for assessment) when they have not been assessed or have been assessed and found not to comply with the following criteria.

- *Safety* — an adequate number of live births, preferably from more than one centre worldwide, with no statistically significant increase in the rates of perinatal morbidity, mortality or adverse genetic conditions.
- *Efficacy* — at least one well-designed trial published in the peer-reviewed literature demonstrating the effectiveness of the intervention.

14.1.2 If there is any doubt about whether the proposed change or innovation is significant, safe or efficacious, it should be referred to an HREC for assessment.

14.2 Obtain appropriate consent from participants and/or a licence for training activities

To ensure high standards of clinical care, ART clinics need to run an ongoing training program for clinicians and other staff involved in the ART procedures used. Clinics must inform participants about, and obtain consent for, any clinical training activities undertaken during their care.

14.2.1 Under the RIHE Act, a licence is required for any training activity that involves the use of an excess ART embryo or the fertilisation of a human egg by a human sperm up to, but not including, the first mitotic division.

14.2.2 The following ethical considerations apply to the design, licensing and conduct of training activities:

- Proper consent must be obtained before any excess ART embryo or human eggs are used for licensed training activities;
- The importance of human eggs to participants in ART programs for the purposes of achieving pregnancy must be respected; and
- The use of embryos warrants very serious moral consideration.

14.3 Conduct quality assurance activities

To ensure high standards of clinical care, ART clinics need to run regular quality assurance activities. Under the RIHE Act, a licence is required for any quality assurance activity that involves the use of an excess ART embryo, whether or not harm is likely to result to the embryo.

An embryo that is not an excess ART embryo must not be used for any quality assurance activity unless that use is for a purpose relating to the ART treatment of a woman carried out by an accredited ART centre [RIHE Act s 11].

14.3.1 As the distinction between quality assurance and research is not always clear, clinics should consult the National Statement and also refer to the advice in the NHMRC document *When Does Quality Assurance in Health Care Require Independent Ethical Review?* (NHMRC 2003), whether or not the quality assurance activity requires HREC approval.

PART C

ETHICAL GUIDELINES FOR RESEARCH

15 ETHICAL PRINCIPLES

15.1 Respect all participants

All human research must be conducted with regard to the values of research merit and integrity, justice, beneficence and respect for human beings. Researchers must therefore comply with the ethical principles provided by the NHMRC in the National Statement. Researchers using gametes and gonadal tissue must also have regard to the *Ethical guidelines on organ and tissue donation (2007).*

All research proposals must be approved by an HREC constituted and operating in accordance with the National Statement. HRECs must comply with these and other human research guidelines issued by the NHMRC.

15.2 Respect human embryos

The fact that the use of embryos warrants very serious moral considration was recognised by the Australian Parliament in the PHCR and RIHE Acts. Therefore, research on human embryos can only be performed in conformity with these guidelines and the conditions imposed by those Acts. See Section 17 for detailed guidelines on embryo research.

15.3 Do not use any unacceptable or prohibited practices

The research proposal must not include any prohibited or unacceptable practices (see Section 4).

15.4 Minimise risks

Researchers must ensure that any risks of involvement in the research are appropriate for the type of research.

15.4.1 Where clinical care is combined with research, the risks of research should be balanced by the possibility of expected benefits from the research (see the section on risk and benefit in the National Statement).

15.4.2 For research undertaken solely to develop new knowledge, any risks (particularly any long-term risks to persons born) should be minimal.

15.5 Offer separate decision-making processes

It is unethical to coerce potential research participants in any way into taking part in the research. Consent must be freely given and be explicit for the proposed research. Any concealment of the purposes of a study from the persons responsible is unethical and excludes informed and voluntary consent.

Proposals for research must include procedures to ensure that the process of providing information and obtaining consent for involvement in the research is clearly separated from clinical care.

Information sheets for research projects must be completely separate from, and capable of being read independently of, written information provided to a patient in the course of routine clinical care.

15.6 Provide information

Participants in research are often vulnerable and can easily misunderstand the purpose and nature of the research. Researchers must provide information to participants, at their level of comprehension, about the purpose, methods, demands, risks, inconveniences, discomforts and possible consequences of the research (including the likelihood and form of publication of the research results). Section 9 provides guidelines on information giving and counselling for clinical practice; the same principles must be applied for research.

15.7 Obtain consent

Participants in research involving ART processes, embryos, human gametes or human genetic material have the right to decide for themselves whether or not to take part in the proposed research. Researchers must therefore obtain the consent of all participants in any such research.

Section 9 provides guidelines on obtaining consent for clinical practice; a similar range of information must be provided for research (as identified in the sections on consent in the National Statement).

Consent for the use of excess ART embryos or human gametes or human genetic material or other embryos in research must be obtained from all responsible persons (see paragraph 17.14 for further information).

15.8 Keep detailed records

Good record keeping is an essential component of research. Researchers must keep accurate records of their research, including records of all gametes and embryos in their care, and the outcomes of the research. Section 10 provides guidelines on record keeping for clinical practice. The same principles must be applied for research.

15.9 Collect and report data on outcomes

Researchers and HRECs must, subject to appropriate requirements for privacy and confidentiality, make information about research projects involving participants, gametes or embryos available to the NHMRC on request and as part of annual reporting compliance.

Data relevant to licensed activities must be collected in accordance with paragraph 10.5.

15.10 Assess and monitor outcomes for all participants (present and future)

All clinical research requires evaluation. For research involving participants in reproductive treatment, researchers must assess, evaluate and monitor outcomes for all participants (including any persons conceived using reproductive procedures, their siblings, where relevant, and the gamete or embryo donors).

15.11 Disclose financial interests

The participants in research are entitled to know about any financial benefits that the researcher or clinic may gain from the research. Researchers must disclose in the project proposal to be submitted to the HREC, any financial interests they have in the research. The HREC must consider the extent to which disclosure of relevant financial aspects of research should be made known to the participants. For example, where researchers plan to request donation of embryos with the intention of undertaking research that may ultimately yield commercial profit, this must be made clear to the donors before consent is obtained.

15.12 Respect conscientious objections

Conscientious objectors are not obliged to be involved in the procedures or programs to which they object. If any member of staff or student expresses a conscientious objection to the research conducted by an ART clinic or a research facility they must be allowed to withdraw from involvement in the research to which he or she objects. Clinics or research facilities must also ensure that staff and students are not disadvantaged because of a conscientious objection.

16 RESEARCH INVOLVING GAMETES

This section provides guidelines for research involving gametes intended for use in the formation of embryos. See Section 17 for guidelines for research involving the formation of embryos.

16.1 Comply with National Statement

Gametes are human tissue and all research on human tissue must be conducted in accordance with the relevant sections in the National Statement.

16.2 Do not use any unacceptable or prohibited practices

The research proposal must not include any prohibited or unacceptable practices.

16.3 Use valid scientific protocols

Research must be justified in terms of its potential contribution to knowledge or technical application.

16.4 Minimise risks

Researchers must ensure that the use of gametes in research is not contrary to the best interests of any person born as a result of the use of those gametes to achieve a pregnancy.

16.5 Provide information

Researchers must give gamete providers (and their spouses or partners, if any), and any persons for whom an embryo may be created, all relevant information about the research.

16.5.1 The information provided should include a full explanation of any consequences and risks involved for any embryo created and any person born after implantation of the embryo, and how they are balanced by potential benefits.

16.6 Obtain consent

Researchers must obtain consent from the gamete providers (and their spouses or partners, if any) for research involving gametes intended for use in the formation of embryos. See Section 17 for guidelines about obtaining consent to research involving embryos.

16.7 Keep accurate records, and collect and report data about outcomes

Researchers must comply with paragraphs 15.8 to 15.10 of these guidelines.

17 RESEARCH INVOLVING EMBRYOS

INTRODUCTION

The fact that the use of embryos warrants very serious moral consideration was recognised by the Australian Parliament in the PHCR and RIHE Acts. That recognition is expressed in the special conditions imposed on human embryo research.

The RIHE Act requires that research on certain human embryos may only be conducted under a licence issued by the Licensing Committee, which must be satisfied that the research proposal has been assessed and approved by an HREC acting in compliance with the National Statement and these guidelines (See the introduction to Section 4 for a full explanation).

The RIHE Act distinguishes between embryos intended for transfer to a woman to achieve a pregnancy and embryos that have been deemed to be no longer needed in an ART program ('excess ART embryos'). The PHCR and RIHE Acts permit research on excess ART embryos, including those that are unsuitable for implantation, and embryos created by means other than by fertilisation of a human egg and human sperm.

17.1 Identify human embryo

There is a need to determine when an embryo exists and the features that distinguish an embryo from any other cell or cluster of cells.

The RIHE Act defines an embryo as an entity arising either from fertilisation or from other processes.

An embryo arising from fertilisation is "a discrete entity that has arisen from … the first mitotic division when the fertilisation of a human oocyte by a human sperm is complete". Because cleavage to yield the second cell is a verifiable event, this definition is sufficient for the purposes of proving an offence under the Act.

However, there is an ethical need to recognise that the two gametes that formed the embryo ceased to exist as gametes when they fuse almost a day earlier than the first mitotic division. To ensure that there is no hiatus in the application of ethical guidelines that apply to gametes and those that apply to human embryos as defined by the Act, all aspects of these ethical guidelines applying to human embryos also apply to this single entity formed by the combination of two gametes.

An embryo formed other than by fertilisation of a human oocyte by a human sperm, is "a discrete entity that has arisen from … any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears".

The formation of a primitive streak normally happens after, and is dependent on, implantation in the uterus of a woman. However, the Act requires that embryos formed other than by fertilisation of a human oocyte by a human sperm may not be implanted. Since it will never be known whether they have the capacity to form a primitive streak, there is an ambiguity concerning these embryos. To provide clarity in these ethical guidelines, a single cell or group of cells that is capable of reaching the stage of forming a blastocyst in vitro is considered to have the potential to develop up to, or beyond, the stage at which the primitive streak appears.

17.2 Comply with the National Statement

Research on human embryos must be conducted in accordance with the National Statement and be approved by an HREC. Researchers and HRECs are required to have regard to the values and principles of ethical conduct: research merit and integrity, justice, beneficence and respect.

17.3 Fulfil essential ethical criteria for licensable research activity

In deciding whether a research proposal meets the requirements of the National Statement and these guidelines, an HREC must be satisfied that:

- There is sufficient evidence that the likely benefits of the proposed research cannot be achieved without using human embryos;
- There is proof of concept, such as success in animal studies;
- The research is justifiable by its potential benefit in improving technologies for treatment of, or knowledge about, human diseases. This benefit must be sufficient in the light of the very serious moral consideration due to human embryos.

17.4 Restrict the number of embryos or eggs

For any licensable activity, the number of excess ART embryos, other embryos or human eggs should be restricted to that likely to be necessary to achieve the goals of the activity [RIHE Act, s 21(4)].

17.5 Do not use any prohibited practices

Research proposals involving human embryos must not include any practices prohibited by the legislation (see Section 4).

RESEARCH ON AN EMBRYO THAT WILL BE USED FOR ACHIEVING A PREGNANCY

17.6 Ensure that the research relates to reproductive treatment

The research must be for a purpose relating to the reproductive treatment of a woman, carried out by an accredited ART centre (see RIHE Act).

17.7 Respect the embryo and all persons involved

Respect for the dignity and wellbeing of the mother and the embryo must take precedence over any expected benefits. Research on embryos intended for transfer to a woman to achieve a pregnancy must not harm the embryo or make it unfit for transfer. In addition, the research may only be undertaken either to trial a new procedure that is expected to bring benefits to the embryo concerned (such as a trial to compare two culture media) or to advance knowledge without direct benefit to the embryo (such as microscopic observation of the embryo during its development before transfer to the woman).

17.8 Minimise risks

Researchers must ensure that any risks to the embryo from the research (and to the long-term health of any person born after implantation of the embryo) are appropriate for the type of research:

17.8.1 Where clinical care is combined with research, the risks of research should be balanced by the possibility of intended benefits for the embryo.

17.8.2 For research undertaken solely to develop new knowledge, any risks to the embryo should be minimal.

17.9 Provide information

Researchers must provide the persons for whom an embryo is to be used to achieve a pregnancy with all relevant information about the research, including how it relates to clinical care, which includes the clinical care of the embryo.

17.9.1 The information provided should include a full explanation of:

- whether the research has intended benefit for the embryo or will not benefit the embryo or themselves but is intended to improve scientific knowledge or technical application;
- any risks involved for the mother and/or the embryo after implantation of the embryo, and how they are balanced by any potential benefits; and
- the expected consequences for the embryo and the person born after implantation of the embryo.

17.10 Obtain separate, specific consent

Researchers must obtain consent from all participants that is separate from the consent for clinical care and specific for the proposed research procedures (see paragraph 15.7).

Researchers must also ensure that the persons for whom the embryo is to be used to achieve a pregnancy are assured that their clinical care, or the clinical care of their embryo, will not be prejudiced in any way if they do not wish to be involved.

17.11 Keep accurate records

Researchers must keep accurate records of the source, use and outcome of each embryo included in the research project.

RESEARCH INVOLVING EXCESS ART EMBRYOS

17.12 Obtain a licence

Under the terms of the RIHE Act, researchers must obtain a licence for any research involving an excess ART embryo that is not an exempt use under the RIHE Act. Researchers must conform with the requirements of the Embryo Research Licensing Committee of the NHMRC (the Licensing Committee) in making an application, as well as with all conditions of a licence. (See paragraph 17.3)

17.13 Ensure that the embryo has been declared an excess ART embryo

The decision to allow an embryo to be used for research is a difficult one for many people. Researchers must not approach the woman (and her spouse, if any) for consent to use the embryo in a specified research project until she (they) has decided, and confirmed in writing, that the embryo is no longer needed to achieve pregnancy and that it is therefore an excess ART embryo (as defined by the RIHE Act; see 'Explanation of key terms').

17.14 Identify all persons responsible for the embryo

Under the RIHE Act, the persons responsible for an embryo include the gamete providers for the embryo and their spouses, and the woman for whom the embryo was created (for the purpose of achieving her pregnancy) and her spouse or partner (if different from the gamete provider).

17.15 Apply objective criteria

The RIHE Act defines an embryo that is unsuitable for implantation as an embryo that:

- is diagnosed by preimplantation genetic diagnosis as unsuitable for implantation, in accordance with these guidelines; or
- is determined to be unsuitable for implantation in the body of a woman, in accordance with objective criteria specified in guidelines issued by the CEO of the NHMRC under the *National Health and Medical Research Council Act 1992* and prescribed by the regulations for the purposes of this paragraph [RIHE s 7(1)].

The objective criteria for determining that an embryo is unsuitable for implantation are based on whether the embryo has a low likelihood of implantation if transferred to the body of a woman. The criteria are available from the NHMRC.

17.15.1 The woman and her spouse (if any) may decide that an embryo that meets the objective criteria is not an excess ART embryo and is not available for research.

17.16 Obtain proper consent

Under the RIHE Act (s 21), before a licence can be issued for the use of an excess ART embryo in research, the Licensing Committee must be satisfied that appropriate protocols are in place to obtain proper consent from each person responsible for the embryo (as defined in the RIHE Act; see also paragraph 17.14).

Researchers must report in writing to the Licensing Committee that such consent has been obtained and must disclose any restrictions to which the consent is subject. The protocols must also enable compliance with any restrictions of the consent.

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 17.18 and 17.19 of these guidelines.

As for all other ART research (see paragraph 15.5), the process of providing information and obtaining consent for research on excess ART embryos must be clearly separated from the clinical care of the embryos or embryo donors.

If a dispute arises or a responsible person dies without leaving clearly expressed and witnessed directions, the embryos must not be used in research.

The RIHE Act permits in certain circumstances, the modification of the guidelines in relation to the giving of proper consent [s 24(8)].

17.17 Specify the purpose of the research

The consent form must be specific for the purpose, nature and scope of, and rationale for, the research. In the case of destructive embryo research, it must be made clear to the persons responsible for the embryo that it may not be possible to report the fate of individual embryos. For example, if stem cells were to be harvested from a given embryo, the persons responsible would be consulted about that use of the embryo, but, for the purpose of giving the proper consent required under the RIHE Act, would not need to be consulted about the subsequent use of those stem cells.

17.18 Provide all relevant information

Researchers must ensure that all persons responsible for the embryo are given all relevant information about the proposed research.

17.18.1 Researchers should provide an oral explanation, supported by written information in plain language and in sufficient time for it to be taken away, read and considered before consent is given.

17.18.2 The explanation should be given with sensitivity to the individual needs of the patient (including language) and include a full explanation of:

- the proposed research (including the proposed method and its scientific aims);
- why the research would represent a significant advance in knowledge or improvement in technologies for treatment;
- what will happen to each embryo, including, where applicable, that embryonic stem cells may be derived from the embryo and that any cells or cell lines so derived may be kept for some years;
- whether the results of research will have commercial potential (see paragraph 15.11) (the embryo donors should be informed that they will not receive financial or any other benefits from any such future commercial development);
- the procedures for raising concerns, obtaining further information about the research and making complaints; and
- the inspection procedures that will be conducted by the NHMRC to ensure compliance with the RIHE Act.

17.19 Allow for withdrawal of consent

A person responsible for an embryo must be free at any time to withdraw consent to further involvement in the research. In view of the fact that once an embryo has been destroyed it cannot be restored, it is recommended 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. This 'cooling-off' period before consent becomes effective must be explained to the persons responsible when consent is obtained.

17.19.1 If a modification of the guidelines relating to proper consent is made, as noted in 17.16, and the modification involves a change in the cooling-off period, any such change must provide for a period that is long enough to allow the persons responsible to consult others important to them and counsellors before making a considered decision whether or not to withdraw consent. [RIHE Act s 24(8)].

17.20 Keep accurate records whether or not to withdrawal their consent

The researchers must keep accurate records of the source, use and outcome of each embryo used in the project.

RESEARCH ON EMBRYOS CREATED BY MEANS OTHER THAN BY FERTILISATION OF A HUMAN EGG BY HUMAN SPERM

Under certain prescribed circumstances, the RIHE Act allows the creation of human embryos other than by fertilisation of a human egg by a human sperm (eg human embryo cloning), and the use of such embryos for purposes authorised by a licence.

Accordingly, women may choose to donate eggs from ART treatment to research. Further, women and men who are not involved in an ART program for the purpose of achieving a pregnancy may choose to donate gametes for purposes unrelated to reproduction, or to the treatment of infertility.

Important ethical considerations in the use of human gametes and embryos in research include:

- the empowerment of potential donors to make informed decisions on whether to participate; and
- the significance to many members of the community of the formation of an embryo for research purposes using gametes, gonadal tissue or cells.

17.21 Respect the donors of gametes or cells used to form embryos by means other than fertilisation

A person who agrees to his or her gametes or gonadal tissue, cells or genetic material being used in research is a research participant for the purposes of the National Statement.

Such tissue is human tissue and contains human genetic material. The sections on human tissue samples, human genetics and human stem cells in the National Statement particularly apply.

17.21.1 When obtaining gametes or cells from a donor involves the donor receiving treatment, there must be separation of clinical and research roles.

- The clinician treating the donor should not be an investigator in the intended research;
- Persons other than members of the research team should obtain consent to research from the potential donor. When the involvement of researchers is unavoidable, their role in the research must be made known to a donor; and
- Members of the research team should be available to discuss the involvement of the gamete or gonadal tissue donor in the research protocol. In doing so, researchers should use appropriate language and graphics to convey accurate, clear information.

17.21.2 There should be no payments or other inducements for the donation of gametes, gonadal tissue or cells for research that is subject to these guidelines. The reimbursement of reasonable out-of-pocket expenses associated with the procedures is acceptable. In research to which these guidelines apply, reimbursement does not cover compensation, including compensation for time.

17.21.3 Gametes, gonadal tissue or cells donated for research must not be used for any other purpose.

17.21.4 If genetic screening and disease testing related to gamete or cell donation is to be done, there must be an ethically defensible plan for the disclosure or withholding of such information. (See section on human genetics in the National Statement.)

17.21.5 Protocols for recruitment must ensure that donation of gametes, gonadal tissue or cells is voluntary and free from exploitation or coercion. Where participation involves non-therapeutic interventions of more than low risk, recruitment should exclude potential participants who are in dependent relationships.

Such dependent relationships include those between researchers and students or those working within the research institution, and between clinician researchers and patients. (For explanation of 'low risk' and 'dependent relationship', see the National Statement.)

17.21.6 For the purpose of consent, the potential donor should be provided with the following information in written and oral form:

- a brief description of the project in lay language and its contribution to the potential benefits of the overall research program;
- a clear statement that the provision of gametes, gonadal tissue or cells to the project is voluntary;
- a description of the intended use of the gametes, gonadal tissue or cells and any products derived from them;
- that any value from the gamete, gonadal tissue or cell donation for research, such as by the development of a cell-based treatment for a disease, may only be realised in the long term;
- a description of the retrieval process for gametes, gonadal tissue or cells, including what will be done, where the procedures will be done and by whom;
- a statement of the potential risks of retrieving and donating gametes, gonadal tissue or cells;
- a description of how to withdraw from gamete, gonadal tissue or cell donation;
- the right of a donor to refuse donation for a specific project, but agree to donation for another;
- a statement about the availability of counselling resources;
- how donor privacy will be protected;
- a statement of the potential financial and non-financial interests of researchers;
- a statement that the donor will receive no financial benefit;
- a statement that the donation will not be used for any other purpose;
- a statement of any future financial gains that the researcher may receive if the research gives rise to a commercial product; and
- any other information required by the National Statement.

17.21.7 Consent to the use of stem cells developed from donated gametes, gonadal tissue or cells must meet the requirements of the section on human stem cells, in the National Statement.

17.21.8 The donor may withdraw consent to use the donated gametes, gonadal tissue or cells up to the time of their actual use in research.

17.21.9 The donor is entitled to know the outcome of research involving donated gametes, gonadal tissue or cells.

17.21.10 Research involving procedures that carry significant risk of harm, including hormonal stimulation, anaesthesia or surgical procedures to obtain gametes, gonadal tissue or cells, must be reviewed by an HREC.

17.21.11 The risks of long-term consequences for fertility of hormonal stimulation of the ovaries and surgical collection of eggs must be disclosed to potential donors.

17.21.12 When the donation involves risks to the fertility of donors, the HREC and the Licensing Committee must have regard to whether the donors have been fully informed about the risks to fertility and have given consent.

17.21.13 In deciding whether to approve research involving donation of eggs by women who are not on an ART program to achieve pregnancy, an HREC must be satisfied that the potential benefits are sufficient to justify the risks associated with the donation process (see 17.21.11). In deciding whether there is sufficient benefit, HRECs must apply the guidelines on risk and benefit in the National Statement.

17.21.14 In deciding whether to approve research involving donation of gonadal tissue, an HREC must be satisfied that the potential benefits are sufficient to justify the risks associated with the donation process (see 17.21.11). In deciding whether there is sufficient benefit HRECs must apply the guidelines on risk and benefit in the National Statement.

17.21.15 Gamete, gonadal tissue or cell donors should be offered counselling on the risks and the psychosocial and ethical implications of donation. The counsellors must be independent of the research. Counselling should be available at any time from before the procedures for retrieval of gametes, gonadal tissue or cells are commenced to the time they are used in research.

17.21.16 The number of cycles and intensity of ovarian stimulation should be limited (see RTACT code of Practice) because it is known to be associated with harmful effects.

17.21.17 Clinicians and clinical centres engaged in gamete or gonadal tissue retrieval should encourage studies on the medical and psychological effects on the donors of the donation of gametes or gonadal tissue, with a view to achieving a more accurate evaluation of risks and benefits.

17.22 Respect persons who have died

17.22.1 Registering a consent to be a donor on the Australian Organ Donor Register does not constitute consent to the donation of gametes, gonadal tissue or cells for a licensed procedure.

17.22.2 Gametes, gonadal tissue or cells from a person who has died must not be used in a licensed activity unless that person had previously given specific consent to that use.

17.22.3 Before that consent is given, the donor must have received the information that these guidelines require for donors.

17.22.4 The needs of relatives of the deceased must be respected in accordance with *NHMRC Organ and Tissue Donation after Death for Transplantation: Guidelines for Ethical Practice for Health Professionals (2007).*

RESEARCH INVOLVING CREATION OF HUMAN EMBRYOS USING PRECURSOR CELLS FROM A HUMAN EMBRYO OR A HUMAN FOETUS [RIHE ACT S 20(1)(D)]

The RIHE and PHCR Acts permit the issue of a licence to conduct research involving the creation of human embryos using precursor cells from the human embryo or human foetus. The following guidelines are intended to inform the ethical review, approval and licensing of such research.

17.23 Respect the human foetus

17.23.1 Those conducting research involving gametes, gonadal tissue or cells obtained from the human foetus ex utero, after spontaneous miscarriage or termination of pregnancy, should have no involvement in the clinical care of the woman from whom the foetus or foetal tissue was derived, and no financial or legal relationships with those who are so involved. Such research should be conducted in a location that maintains a separation of the woman's clinical care from research.

17.23.2 Researchers should demonstrate in their proposals that there are no suitable alternatives by which the aims of research using the foetal gametes, gonadal tissue or cells can be achieved.

17.23.3 There should be no trade in human foetal gametes, gonadal tissue or cells.

17.23.4 Where research involves a separated foetus or foetal gametes, gonadal tissue or cells, researchers should ask the woman whether, in her decisions about the research, she wishes to involve others such as family members, for whom the research may have implications.

17.23.5 A foetus or foetal gametes, gonadal tissue or cells may become available for research as the result of termination. The process through which the woman is approached, informed about, and her consent sought for research on that foetus should be separate from the process under which she decides whether to terminate her pregnancy, and should not begin until a decision to terminate has been made. Consenting to the research must not compromise the woman's freedom to change that decision.

17.23.6 Where research involves her separated foetus or its gametes, gonadal tissue or cells, arrangements should be made for the woman to have access to counselling and support.

17.23.7 Research on a terminated foetus or its gametes, gonadal tissues or cells, including the timing and content of the process of seeking the woman's consent for the research, should be designed so as not to compromise the woman's decisions about the timing and method of termination.

17.23.8 Consideration of a woman's wishes and her physical, psychological and emotional welfare should inform:

- a decision whether to approach her about proposed research involving her separated foetus or its tissue; and, if she is approached,
- the way information is provided about the research and the way her consent is sought.

17.23.9 In addition to information required to be disclosed under the consent sections in the National Statement, the woman should also be informed:

- that she should consider whether to seek consent

to the proposed research from any other person;

- about the possibility of storing the foetus or foetal tissues for later use in research;
- that she is free to withdraw her consent to the research at any time, whether before or after a termination or other loss of a foetus;
- about any potential commercial application of outcomes of the research, including the development of cell lines;
- that she will not be entitled to a share in the profits of any commercial applications; and
- if foetal tissues or stem cell lines developed from them will be exported to another country.

17.23.10 A foetus delivered alive is a child, and should be treated as a child and receive the care that is due to a child.

17.23.11 Gametes, gonadal tissue and cells for use in research may not be removed from a foetus delivered dead, unless:

- the woman and any others she wishes to involve (see paragraph 17.23.4) have given consent to the removal and the research;
- the foetus is available for research only as a result of separation by natural processes or by lawful means; and
- the death of the foetus has been determined by a registered medical practitioner who has no part (or financial interest) in the research.

APPENDICES

APPENDIX A COMMITTEE MEMBERSHIP

MEMBERSHIP OF AHEC

2006–2009 NHMRC triennium

Professor Colin Thomson	Chair
Dr Rosanna Capolingua	A person who has expertise in clinical medical practice
Ms Sharon Caris	A person with understanding of health consumer issues
Mr Christopher Coyne	A person who has expertise in law
A/Professor Terry Dunbar	A person with expertise relevant to the functions of the committee
Rev Dr Gerald Gleeson	A person who has expertise in religion
Professor Paul Griffiths	A person who has expertise in philosophy
Mr Barry Maley	A person who has experience in social science research
Prof Margaret O'Connor, AM	A person who has expertise in nursing or allied health practices
Dr Gregory Pike	A person with knowledge of the ethics of medical research
A/Professor Peter Sainsbury	A person who has experience in public health research
Dr Marian Scarrabelotti	A person with knowledge of the regulation of the medical profession
Dr Nicholas Tonti-Filippini	A person with understanding of the concerns of people with a disability
Dr Nikolajs Zeps	A person who has experience in medical research
NHMRC STAFF	
Ms Jillian Barr	Project officer
Mr Matthew Sammels	Project officer
CONSULTANT	
Dr Alana Mitchell	Technical writer

APPENDIX B PROCESS REPORT

In developing and issuing guidelines, the National Health and Medical Research Council and its principal committees are obliged under the *National Health and Medical Research Council Act 1992* (sections 13 and 14A) to release draft guidelines for public consultation.

The changes made to the 2004 guidelines, as required by the new legislation, were developed by a sub-group of the Australian Health Ethics Committee and released for public consultation between 11 May 2007 and 11 April 2007. Ninety-three submissions were received.

The submissions were analysed by a sub-group of AHEC and AHEC considered a revised draft of the guidelines at a meeting on 29-30 May 2007. The Council considered the draft guidelines at a special meeting on 4 June 2007 and again on 12 June 2007.

APPENDIX C ISSUES FOR FURTHER COMMUNITY DISCUSSION

This appendix provides a brief discussion of three controversial issues in the use of assisted reproductive technology (ART), namely the use of genetic technology, sex selection and surrogate motherhood. In each instance, the Australian Health Ethics Committee (AHEC), having carefully weighed these matters, considers that they require further community debate and consideration by elected governments. Where appropriate, Part B of these guidelines contains relevant guidelines for clinics concerning these issues. The following brief discussion summarises some of the arguments around these issues. It is included to foster and assist community debate.

Further discussion of these issues can be found in the philosophical and bioethical literature, as well as in reports and guidelines developed by government agencies internationally.

In the revision of these guidelines, AHEC has not added to or altered this appendix.

C1 APPROACH TO CONTROVERSIAL ISSUES

New knowledge, scientific discoveries and technical advances frequently stimulate controversy. This is the case for the study of biology, genetics and reproduction, where techniques developed for one purpose may be used for other purposes and, in particular, where techniques developed for therapeutic purposes (that is, preventing and curing diseases, reversing disabilities and alleviating suffering associated with lack of good health) may be used for nontherapeutic, but otherwise desired, purposes (for example, for sex selection).

National, state and territory legislation reflects the variation in opinion and lack of consensus on many of these issues. In general, developments in biotechnology deserve careful consideration in order to determine whether they should be welcomed enthusiastically, tolerated within limits, met with disquiet or even prohibited by law.

Good regulation (in particular, good legislation) depends in part on a well-informed public discussion of potential benefits, possible risks, potential abuses and other areas of concern. AHEC therefore wishes to ensure that public discussion is well-informed and, in particular, is not dominated by any particular interest group.

To that end, AHEC sets out, in summary form, what it considers to be some of the more substantial considerations in favour of, and against, three relatively new and/or controversial applications of reproductive technologies:

- genetic technology associated with ART (Section C2);
- sex selection (Section C3); and
- surrogacy (Section C4).

Each of these practices affects people other than the person who has decided to use the technology. Each is properly a matter for community debate and discussion. Community regulation may be necessary, but the justification for such intervention will need to be decided for each issue based on such community debate and discussion.

C2 GENETIC TECHNOLOGY ASSOCIATED WITH ART

Introduction

Genetic technology associated with ART currently has the capacity to be put to a number of uses (eg preimplantation genetic diagnosis; see Section 12). Other, more ethically controversial applications of the technology, such as the detection of susceptibility to late-onset conditions, are on the horizon. In the future, genetic technology may also have the potential to be used to increase the chances that a child is born 'biologically advantaged'; for example, brighter, taller or more athletic.

This section outlines some ethical considerations in favour of and against these various uses.

Reasons given in support of allowing the use of genetic technologies associated with ART

- Compassion for the suffering of those afflicted with genetic diseases.
- The wish to spare families the tragedy of having, and the burden of caring for, children with deadly and devastating illnesses in the next and, in some cases, future generations.
- Sympathy for couples who might otherwise forgo having children, for fear of passing on heritable disorders.
- An interest in reducing the economic and social costs of caring for the incurable.
- Hope for progress in the overall health and fitness of human society.
- The belief that other people are not entitled to stop those who wish to use genetic technology.

Reasons given for opposing or limiting the use of genetic technologies associated with ART

- Use of genetic technology implies that admission to life is no longer unconditional.
- Use of genetic technology may foster reproductive discrimination.
- Use of genetic technology establishes the principle that parents may choose the qualities their children have.
- The handling, testing and manipulation of embryos in genetic technology procedures may expose them to significant risk of harm. (The weight of this consideration may depend on the seriousness of the outcome that the technology is being used to avert.)
- The likelihood that the social effects of general acceptance of ART (with genetic technology) as an alternative to natural reproduction will include a diminished tolerance for difference.
- Though avoidance of serious disease may be a reasonable use of genetic technology, shaping babies to parents' ideas of perfection (were this to prove possible) is not.
- Otherwise normal (so-called 'carrier') embryos that would be expected to have a normal life will be discarded.

C3 SEX SELECTION

Introduction

Selection by sex can serve medical goals (for example, to prevent the transmission of sex-linked genetic diseases; see Sections 11 and 12 of these guidelines). The focus of the discussion in this section is on the nonmedical use of selection by sex, that is to say, sex selection for the purpose of choosing the sex of a future child.

Reasons given in support of the availability of sex selection

- Sex selection permits 'family balancing'.
- Sex selection may enable parents to fulfil religious obligations or cultural expectations.
- Sex selection is properly thought of as a matter for individual autonomy.

Reasons why people are opposed to the availability of sex selection

- Sex selection is incompatible with the parent–child relationship being one that involves unconditional acceptance.
- Sex selection may be an expression of sexual prejudice, in particular against girls. As practised today around the world, it generally reflects and contributes to bias and discrimination against women.
- Sex selection harms men in some cultural groups (by contributing to the shortage of women for men to marry).

C4 SURROGACY

Introduction

Surrogacy is the arrangement by which one woman (the surrogate mother) carries and bears a child for another woman or couple (the commissioning mother, or commissioning parents) to whom she will transfer custody at or shortly after birth. The discussion in this section sets out some considerations in favour of and against the availability of noncommercial (both partial and full) surrogacy. It should be read against the background of Section 13.

Reasons given in support of allowing surrogacy arrangements

- Surrogacy enables women who would not otherwise be able to have children to do so.
- There are sometimes good reasons for transferring the burdens and risks associated with pregnancy from one woman to another. For example, the use of a surrogate mother who is also the genetic mother can prevent the transmission of serious genetic diseases by allowing a commissioning mother who is the carrier of that disease to avoid pregnancy.
- The strength of any bond between surrogate mothers and the children they carry does not outweigh the benefits to be gained by permitting surrogacy arrangements.

Reasons why people are opposed to allowing surrogacy arrangements

- The surrogate mother is reduced to the status of an incubator of another couple's child.
- Surrogacy confuses the relationship of the child to his or her parents.
- Surrogacy risks interfering with the surrogate mother's own personal relationships.

- There is often an unequal social relationship between the commissioning parents and the surrogate mother, making it unlikely that surrogacy arrangements will be fair and just.
- Surrogate mothers are sometimes reluctant to hand over the child whose birth has been commissioned.
- Surrogacy is less about the autonomous choices of the women involved than about enabling men to have children with whom they have a genetic connection.

EXPLANATION OF KEY TERMS

The following explanations show how key terms that have been used in these guidelines are to be interpreted. For consistency with national legislation, where the same terms have been used in either the *Research Involving Human Embryos Act 2002* (RIHE Act) or the *Prohibition of Human Cloning for Reproduction Act 2002* (PHCR Act), the same definitions have been used here and the relevant section of legislation is given in square brackets.

Accredited ART centre	A person or body accredited to carry out ART.
Assisted reproductive technology (ART)	The application of laboratory or clinical techniques to gametes and/or embryos for the purposes of reproduction.
Blastocyst	A 5 to 7 day-old embryo that has an outer layer of cells and a fluid-filled cavity in which there is a cluster of cells called the inner cell mass.
Clinic	Accredited ART centre.
Chimeric embryo	A human embryo into which a cell, or any component part of a cell, of an animal has been introduced. [PHCR s 8(1)] See also Hybrid embryo
Diagnostic investigation	In relation to an excess ART embryo, means any procedure undertaken on embryos for the sole purpose of diagnostic investigation for the direct benefit of the woman for whom it was created [RIHE s 10(4)]. For the purposes of these guidelines, diagnostic investigation includes preimplantation genetic diagnosis. See also Preimplantation genetic diagnosis
Donated embryo	An embryo given by either the gamete providers or the persons for whom the embryo was created to other persons for the purpose of achieving a pregnancy. The term is also used when the gamete providers for an embryo agree to their embryo being used in research or other activities that are not intended to achieve a pregnancy. See also Embryo donor, Responsible person
Donated gametes	Gametes given for use by a person other than the gamete provider or his or her spouse or partner in a reproductive procedure. The term is also used when gametes are provided for research or other activities. See also Gamete provider
Embryo	A living entity in the earliest stage of development. See also Human, Chimeric and Hybrid embryos
Embryo donor	A person who has responsibility for decisions about the use of an embryo and who donates the embryo to another person or persons for treatment, or for research or other activities. See also Responsible person
Embryonic stem cell	An undifferentiated cell that is a precursor to many different cell types, obtained from the inner cell mass of a blastocyst.
Embryonic stem cell line	A genetically identical line of cells, derived from an embryonic stem cell, which can be propagated indefinitely in culture.

Excess ART embryo	A human embryo that: (a) was created by ART, for use in the ART treatment of a woman; and (b) is excess to the needs of: (i) the woman for whom it was created; and (ii) her spouse (if any) at the time that the embryo was created. [PHCR s 8(1); RIHE s 9(1)]. For the purposes of paragraph (b), a human embryo is excess to the needs of the persons mentioned in that paragraph at a particular time if: (a) each such person has given written authority for the use of the embryo for a purpose other than a purpose relating to the ART treatment of the woman concerned, and the authority is in force at the time; or (b) each such person has determined in writing that the embryo is excess to their needs, and the determination is in force at that time. [PHCR s 8(5); RIHE s 9(2)]
Gamete	A human sperm or egg (ovum or oocyte) and includes: (a) any cell that has resulted from a process of meiosis or has a haploid chromosone complement; or (b) tissue containing such cells (also referred to as gonadal tissue) See also Gonadal tissue and Precursor cell
Gamete donor	A person who provides gametes for use: (a) by a person other than his or her spouse or partner in a reproductive procedure; or (b) for research. See also Donated gametes, Gamete provider
Gamete provider	The person who is the biological (that is, genetic) source of the gamete.
Gonadal tissue	Tissue from the ovary or testis. See also gamete.
Human egg	Human ovum or oocyte.
Human embryo	The RIHE Act defines a human embryo as: A discrete entity that has arisen from either: (a) the first mitotic division when fertilisation of a human oocyte by a human sperm is complete; or (b) any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears; and has not yet reached 8 weeks of development since the first mitotic division [PHCR s 8(1), RIHE s 7(1)] All aspects of these ethical guidelines applying to human embryos also apply to: • the single entity formed by the combination of two gametes is to be treated as an embryo for the purposes of applying these guidelines; and • a single cell or group of cells that is capable of reaching the stage of forming a blastocyst in vitro, because it is considered to have the potential to develop up to, or beyond, the stage at which the primitive streak appears. (The significance of the previous clause is discussed in paragraph 17.1) For the purposes of the definition of a human embryo, in working out the length of the period of development of a human embryo, any period when the development of the embryo is suspended is to be disregarded. [PHCR s 8]

Human embryo clone	A human embryo that is a genetic copy of another living or dead human, but does not include a human embryo created by the fertilisation of a human egg by a human sperm [PHCR s 8(1)]. For the purposes of establishing that a human embryo clone is a genetic copy of a living or dead human: (a) it is sufficient to establish that the set of genes in the nuclei of the cells of the living or dead human has been copied; and (b) it is not necessary to establish that the copy is an identical genetic copy. [PHCR s 8(2)] For the purposes of the definition of a human embryo clone, a human embryo that results from the technological process known as embryo splitting is taken not to be created by a process of fertilisation of a human egg by a human sperm. [PHCR s 8(4)]
Human sperm	Includes human spermatids. [PHCR s 8(1)]
Hybrid embryo	(a) an embryo created by the fertilisation of a human egg by animal sperm; or (b) an embryo created by the fertilisation of an animal egg by human sperm; or (c) a human egg into which the nucleus of an animal cell has been introduced; or (d) an animal egg into which the nucleus of a human cell has been introduced; or (e) a thing declared by the regulations to be a hybrid embryo. [PHCR s 8(1)] See also Chimeric embryo
Innovative procedure	A therapeutic, diagnostic or laboratory procedure that is aimed at improving reproductive outcomes beyond existing methods but has not been fully assessed for safety and/or efficacy.
Objective criteria for determining the suitability of ART embryos for implantation	Criteria for use in determining that an embryo is incapable of successful implantation if transferred to the body of a woman. The criteria are issued by the CEO of the NHMRC and obtainable from the NHMRC.
Observation	In relation to an excess ART embryo, includes taking a photograph of an embryo, or taking a recording of the embryo from which a visual image can be produced. [RIHE s 10(4)]
Participant	Any person (including a gamete or cell donor) who is the subject of (or takes part in) a reproductive procedure or research or innovative procedures involving ART or research involving the formation of an embryo. In many cases 'participant' also includes the spouse or partner of a person undertaking the ART procedure. In cases where it is essential that the spouse or partner (if any) is included (such as in giving consent for donation of gametes), this is specified.
Precursor cell	A cell that has the potential to develop into a human egg or human sperm. [PHCR s 8(1)]
Preimplantation genetic diagnosis (PGD)	Technique by which embryos fertilised in vitro are tested for genetic characteristics, particularly for specific genetic disorders (eg cystic fibrosis).

Prohibited embryo	(a) a human embryo created by a process other than the fertilisation of a human egg by a human sperm; or (b) a human embryo created outside the body of a woman, unless the intention of the person who created the embryo was to attempt to achieve pregnancy in a particular woman; or (c) a human embryo that contains genetic material provided by more than two persons; or (d) a human embryo that has been developing outside the body of a woman for a period of more than 14 days, excluding any period when development is suspended; or (e) a human embryo created using precursor cells taken from a human embryo or human foetus; or (f) a human embryo that contains a human cell (within the meaning of section 18 of the PHC) whose genome has been altered in such a way that the alteration is heritable by human descendants of the human whose cell was altered; or (g) a human embryo that was removed from the body of a woman by a person intending to collect a viable human embryo; or (h) a chimeric embryo or hybrid embryo. [PHCR s 22(4)]
Proper consent	The procedures and requirements for consent under these guidelines
Recipient	A person to whom gametes or embryos are donated.
Research	Systematic investigation with the aim of increasing knowledge.
Responsible person	(a) In relation to an excess ART embryo: (i) each person who provided the egg or sperm from which the embryo was created; and (ii) the woman for whom the embryo was created, for the purpose of achieving her pregnancy; and (iii) any person who was the spouse of a person mentioned in paragraph (a) at the time the egg or sperm mentioned in that paragraph was provided; and (iv) any person who was the spouse of the woman mentioned in paragraph (b) at the time that the embryo was created; or [RIHE s 8] (b) in relation to an embryo other than an excess ART embryo—each person whose reproductive material, genetic material or cell was used, or is proposed to be used, in the creation or use of the embryo; or (c) in relation to a human egg—the person who was the biological donor of the egg.
Spouse or partner	In relation to a person, includes a person who is legally married to the person (spouse), as well as a person who, although not legally married to the person, is living with the person on a bona fide domestic basis (partner). [Defined as 'spouse' in RIHE s 7]
Treatment cycle	A series of treatments for the purposes of in vitro fertilisation, gamete intrafallopian tube transfer or similar procedures. It is defined as beginning either on the day on which treatment by superovulatory drugs is commenced or on the first day of the patient's menstrual cycle, and ending not more than 30 days later.

Unsuitable for implantation	A human embryo that: (a) is diagnosed by preimplantation genetic diagnosis as unsuitable for implantation, in accordance with these guidelines, issued by the CEO of the NHMRC; or (b) is determined to be unsuitable for implantation in the body of a woman, in accordance with objective criteria specified in guidelines issued by the CEO of the NHMRC under the *National Health and Medical Research Council Act 1992* and prescribed by the regulations for the purposes of this paragraph. [RIHE s 7(1)]

ABBREVIATIONS

AHEC	Australian Health Ethics Committee
ART	assisted reproductive technology
COAG	Council of Australian Governments
CREGART	Committee to Review the Ethical Guidelines on Assisted Reproductive Technology
HREC	human research ethics committee
IVF	in vitro fertilisation
Licensing Committee	Embryo Research Licensing Committee (NHMRC)
National Statement	*National Statement on Ethical Conduct in Research Involving Humans*
NHMRC	National Health and Medical Research Council
NHMRC Act	*National Health and Medical Research Council Act 1992*
PGD	preimplantation genetic diagnosis
PHC Act	*Prohibition of Human Cloning Act 2002*
PHCR Act	*Prohibition of Human Cloning for Reproduction Act 2002*
RIHE Act	*Research Involving Human Embryos Act 2002*

KEY INFORMATION SOURCES

NHMRC GUIDELINES

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House of Representatives Standing Committee on Legal and Constitutional Affairs (2001). *Human Cloning: Scientific, Ethical and Regulatory Aspects of Human Cloning and Stem Cell Research.* Parliament of the Commonwealth of Australia, Canberra (Andrews Report).

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NHMRC (2003b). *When Does Quality Assurance in Health Care Require Independent Ethical Review? Advice to Institutions, Human Research Ethics Committees and Health Care Professionals.* NHMRC, Canberra. http://www.nhmrc.gov.au/publications/synopses/e46syn.htm (Accessed 14 June 2007)

NHMRC/AVCC (Australian Vice-Chancellors' Committee) (2007). *Australian Code for the Responsible Conduct of Research*.

LEGISLATION

Australian Government legislation

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http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/0/23029FDD3FCC3FD7CA25719C008331D3/$file/NatHeaMedResCou1992WD02.pdf (Accessed 14 June 2007)

Privacy Act 1988
http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/0/B471AB909A18D172CA25725C0083858A/$file/Privacy1988_WD02HYP.pdf (Accessed 14 June 2007)

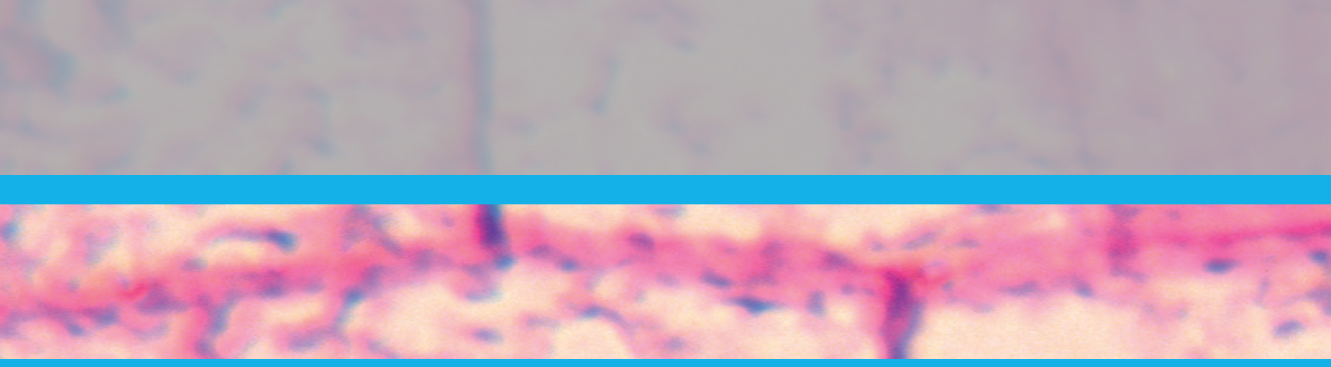
Prohibition of Human Cloning for Reproduction Act 2002
http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/0/647EBC139FB39FDDCA2572F7007B272E/$file/ProhibHumanCloningforRep2002_WD02.pdf (Accessed 14 June 2007)

Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006
http://www.comlaw.gov.au/ComLaw/Legislation/Act1.nsf/0/71AC9EAE45677788CA2572440012F18A/$file/1722006.pdf (Accessed 14 June 2007).

Research Involving Human Embryos Act 2002
http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/0/03F95E485D04231DCA2572F80003B1C3/$file/ResearchInvolvingHumanEmbryosAct2002_WD02.pdf (Accessed 14 June 2007)

State and territory government legislation

Information about relevant state and territory legislation is available on state/territory government websites.



Code of Practice for the use of Human Stem Cell Lines

Foreword

The UK Stem Cell Bank has been established in response to Government recommendations to facilitate the sharing of quality controlled human stem cell lines by the clinical and research communities and thus to support research that will help improve understanding of human development and disease and aid the generation of strategies to treat serious disease. The Bank is overseen by an independent Steering Committee (the Steering Committee for the Stem Cell Bank and for the Use of Stem Cell Lines – hereafter called the Stem Cell Steering Committee), which has developed this Code of Practice to explain the role of the Steering Committee and to provide guidance and assistance on best practice to those working with stem cell lines.

In the UK, research involving human embryos, including the generation of human embryonic stem cell lines is under statutory control by the Human Fertilisation and Embryology Authority (HFEA). Embryonic stem cell lines once established are not embryos and the Government decided that research involving established stem cell lines does not need the same level of regulation to which embryo research is subject to by the HFEA. However, as the generation of embryonic stem cell lines involves the destruction of human embryos oversight in form of a Steering Committee was recommended to ensure that research is conducted within an ethical framework that is transparent to the public and is keeping with HFEA Regulations. The oversight mechanisms governing research involving established embryonic stem cell lines and this Code of Practice are voluntary. However, they are a condition of the statutory regulation in the UK and there is an expectation by Government that there are adhered to.

This Code of Practice for the Use of Human Stem Cell Lines should be regarded as an evolving interim document which will be revised and updated in line with practice, and requirements arising from the Human Tissue Act and the EU Tissue Directive.

Comments on this document are welcomed and should be forwarded to:
stemcellsecretary@headoffice.mrc.ac.uk.

Contents

1. Purpose of the Code of Practice

This Code was drawn up by the Stem Cell Steering Committee and benefited from input by a wide range of stakeholders, including consumers. It provides guidance on best practice for those working with stem cell lines and specifies oversight mechanisms for research involving human embryonic stem cell lines. The Code should provide confidence and reassurance to professionals and the public alike that stem cell research in the UK is performed to best practice and is conducted within a transparent and ethical framework. The main emphasis of the Code is on human embryonic stem cell lines but references to stem cell lines derived from other human tissues are included as the UK Stem Cell Bank will curate and distribute human cell lines from all sources. For ease of reference text referring specifically to embryonic stem cells has been italicised.

2. Definition of stem cells

2.1 Stem cells

Stem cells have the capacity to divide to generate "daughter" cells that retain the properties of the stem cell, or to produce daughters that begin to "differentiate" into a more specialised cell type, or to produce one daughter cell of each type. Stem cells are thus central to normal human growth and development, and are also a potential source of new cells for the regeneration of diseased or damaged tissue. Stem cells are present at all stages of development, and in many (possibly most) tissues of the adult. At present, stem cells are impossible to identify by their physical characteristics alone although they can be enriched in a population of cells. Stem cells from different tissues, and from different stages of development, vary in terms of the number and types of cells to which they normally give rise. For the purposes of this Code of Practice the Steering Committee has defined three classes of stem cells: embryonic stem cells, somatic stem cells and embryonic germ cells (see below).

Until it is known which stem cells have the greatest potential in terms of developing human therapies, it is vital that research be conducted on all types.

2.1.1 Embryonic Stem Cells

At the earliest stages after fertilisation (up to about the eight cell stage) all the cells of the embryo are "totipotent" (i.e. they have the capacity to develop into every type of cell needed for full development, including extra-embryonic tissues such as the placenta and umbilical cord). After about five days the blastocyst stage is reached. Within this ball of 50 to 100 cells lies the inner cell mass which will develop into the embryo proper. The inner cell mass comprises about a quarter of the cells at this stage of development and a unique class of stem cells, referred to as embryonic stem cells, can be derived from it. Embryonic stem cells derived from the mouse have the innate capacity ("potential") to differentiate into each of the 200 or so cell types which make up the body, and are described as "pluripotent" (see also glossary of terms). The capacity of human embryonic stem cells to contribute to all tissue types in development has not yet been fully established. Both human and mouse embryonic stem cells can to the best of our knowledge be grown over long periods of time in culture and expanded in number without changing their cellular phenotypes or genotypes. In the case of mouse stem cells they are also known to maintain their pluripotent state under these culture conditions.

2.1.2 Embryonic Germ Cells

Embryonic germ cells are another special class of stem cells derived from primordial germ cells; such cells have been shown in the mouse to be pluripotent. The situation for human cells is not yet clear.

2.1.3 Somatic Stem Cells

As development proceeds beyond the blastocyst, stem cells comprise a progressively decreasing proportion of cells in the embryo, fetus and body after birth. However, many, if not most tissues in the fetus and human body contain stem cells which, in their normal location, have the potential to differentiate into a limited number of specific cell types in order to regenerate the tissue in which they normally reside. These stem cells are described as “pluripotent” or "multipotent". In the latter case they may have a more restricted potential than embryonic stem cells in that they normally give rise to some but not all of the cell types present in the human body. Extra-embryonic tissues such as the placenta and umbilical cord also contain multipotent stem cells with the same genetic makeup as the cells of the embryo.

It has been reported that rare mesenchymal stem cells present in human bone marrow can be cultured and expanded for more than 80 population doublings. Such cells have also been shown to differentiate into a variety of different cell types in culture (Jiang et al. 2002). Parallel studies using mesenchymal cells from rodents have shown that similar cells (called multipotent adult progenitor cells), when injected into an early blastocyst, may contribute to most if not all somatic cell types (Jiang et al. 2002). This work is still at an early stage, but such cells, derived at any stage of development, could potentially provide Bankable cell lines.

2.1.4 The relationship between embryonic stem cells and other stem cells

Embryonic stem cells are a very specific class of stem cell which can be derived from the blastocyst and, in mice, are known to be pluripotent. Confusingly, stem cells derived from the early embryo after the blastocyst stage and from the fetus are sometimes also referred to as embryonic stem cells in the literature; however, such cells are not known to be pluripotent and (along with extra-embryonic stem cells) are more akin to adult stem cells. They are therefore referred to in this Code of Practice as "somatic” stem cells.

2.2 Stem cell lines

A stem cell line comprises cells that can be expanded for prolonged periods in appropriate culture conditions without any change in genotype or phenotype. A "normal" cell line would not include cells which have been immortalised following any acquired or induced alteration in genotype. Importantly, phenotypically indistinguishable stem cell lines might have different differentiation capacities. Ideally cell lines should be clonal, that is derived from a single cell. In practice, however, this criterion cannot always be satisfied.

3. Legislation governing the establishment of human stem cell lines

3.1. The Human Tissue Act (2004) – (See Page 26 for Full Web Link)

The removal, storage and use of human material (organs, tissues and cells) will be governed by the Human Tissue Act (2004).
The Act makes donor consent a fundamental principle underpinning the lawful storage and use of human material and makes it an offence to carry out regulated activities without appropriate consent. It also provides for the establishment of the Human Tissue Authority,

which will draw up the regulations, hold the responsibility for licensing regulated activities within its remit, and issue Codes of Practice giving practical guidance on the conduct of these activities. The Act will come into force by April 2006. Until then Department of Health interim guidance continues to apply. In parallel with the English Human Tissue Act, a Human Tissue Bill is currently being drafted in Scotland. The expectation is that this will also be enacted by April 2006.

The Human Tissue Act applies to any material from a human body consisting of, or including human cells, with exception of hair and nail of a living person, and gametes and embryos, which are separately regulated by the Human Fertilisation and Embryology Act 1990). Established cell lines as well as any other human material created outside the human body are excluded from the Act.

3.2. The Human Fertilisation and Embryology (HFE) Act (1990) - (See Page 26 for Full Web Link)

The special regulations which govern the creation and use of human embryonic stem cells reflect the fact that the human embryo has a special moral status. The position taken by many (perhaps most) is that the embryo, unlike an infant, does not have the full rights of a person; however, its human potential gives it an intrinsic value which implies that neither its creation nor its destruction are to be treated casually, as reflected in law. Regulation of research on human embryos in the UK is governed by the Human Fertilisation and Embryology Act (1990). The HFEA is the regulatory authority empowered to issue licences for research using human embryos. It is an offence to carry out such research without a licence from the HFEA. A research licence will not be granted unless the HFEA is satisfied that any proposed use of embryos is necessary for the research and that the research is necessary or desirable for the purposes specified in the Act, namely:

- *promoting advances in the treatment of infertility*
- *increasing knowledge about the causes of congenital disease*
- *increasing knowledge about the causes of miscarriages*
- *developing more effective techniques for contraception*
- *developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation*
- *for such other purposes as may be specified in regulations*

The Human Fertilisation and Embryology (Research Purposes) Regulations (2001) specify three further purposes for which research may be authorised[*]*:*

- *increasing knowledge about the development of embryos*
- *increasing knowledge about serious disease, or*
- *enabling any such knowledge to be applied in developing treatments for serious disease*

Licences issued by the HFEA are subject to conditions. Importantly, HFEA licences for projects involving the derivation of human embryonic stem cell lines require licensees to deposit a sample of each cell line generated in the UK Stem Cell Bank. Licensees are not

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* The regulations were brought forward following the Report of the Chief Medical Officer's Expert Group Reviewing the Potential of Developments in Stem Cell Research and Cell Nuclear Replacement to Benefit Human Health "Stem Cell Research: Medical Progress with Responsibility (2000)".

permitted to carry out secondary research projects on ES cells or to transfer ES cell lines to third parties without the approval of the Steering Committee.

The HFEA's regulatory responsibility is for research using human embryos. Stem cells taken from an embryo are no longer the subject of regulation by HFEA with the exception of the requirement to fulfil conditions of the licence as described above. The conservation and use of human embryonic stem cells and stem cell lines is the responsibility of the Steering Committee (see Chapter 6).

The Human Reproductive Cloning Bill, 2001 makes it an offence, punishable by up to 10 years imprisonment and an unlimited fine on conviction, to implant into a woman an embryo created other than by fertilisation.

4. The House of Lords Select Committee report on stem cell research (2002) - (See Page 26 for Full Web Link)

In March 2001, the House of Lords appointed a Select Committee to consider and report on issues connected with human cloning and stem cell research arising from the HFE (Research Purposes) Regulations. The report (2002) concluded *inter alia* that stem cells appear to have great therapeutic potential for the treatment of many disorders and for the repair of damaged tissue, and that for maximum medical benefit it is necessary to conduct research on both adult somatic and embryonic stem cells. *The Select Committee recommended that an embryonic stem cell Bank should be established that would provide scientists with ready access to human embryonic stem cell lines of guaranteed purity and provenance and from sources which operate ethically-approved standards. Also, that the Bank should be overseen by a Steering Committee that would establish codes of conduct for the use of embryonic stem cells, whether obtained from the Bank or imported from elsewhere, and monitor their use.* The Select Committee noted that it would be desirable for adult somatic stem cell lines to be Banked, but agreed that no special consideration needed to be given to regulations for adult somatic stem cells above and beyond those of informed consent. Given that it is not yet clear which stem cell source will prove the most useful in terms of developing human therapies, the funders of the UK Stem Cell Bank decided that adult and fetal somatic stem cell lines as well as embryonic stem cells should be curated there.

The Government response to the House of Lords Select Committee Report, published in June (2003), welcomed and endorsed these conclusions and recommendations which therefore form the basis of Government policy on stem cell research.

5. The UK Stem Cell Bank – (See Page 26 for Full Web Link)

Stem cell lines can be stored frozen for long periods of time in a stem cell Bank. The frozen cells can then be thawed as required and cultured again.

The UK Stem Cell Bank was established at the National Institute for Biological Standards and Control (NIBSC) in January 2003, with funding from the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC), to curate ethically sourced, quality controlled human stem cell lines from all sources (adult, fetal and embryonic) on a single site.
The Bank facilitates the sharing of quality controlled stem cell lines by the clinical and research communities and thus supports research that will help to better understand human development and disease and aid the development of strategies to treat serious diseases.

The UK Stem Cell Bank will reduce the need for individual research teams to generate their own stem cell lines, minimise the use of human tissues, and enable different researchers to work on identical material so that direct comparisons may be made between studies. The Bank has been located in an independent national Institution to avoid potential conflict of interest. It will not receive or store human embryos and will not conduct discovery research on the Banked stem cell lines; the staff may however, pursue research aimed at improving Banking processes and procedures.

Significant progress in stem cell research can only be made through International collaboration and it has therefore been agreed that the UK Stem Cell Bank can be accessed by researchers from academia and Industry in the UK and abroad. Overseas researchers have to undergo the same review procedures as researchers in the UK (see Section 8).

The UK Stem Cell Bank will curate and distribute stem cell lines but ownership of any Intellectual Property embodied in the these lines will remain with the originator. Therefore, stem cell lines can only be released from the Bank if a Material Use Licence with the originator is in place (see terms and conditions for deposition and access of human stem cell lines, Annex 6).

The Bank is expected to establish separately: a) areas for processing research grade stem cell lines and b) areas for processing clinical grade stem cell lines that are destined for human therapy. All facilities must meet appropriate quality systems requirements, depending on the intended use of the cells for research or for use in humans.

5.1 Inventory of Banked stem cell lines

Once a cell line has been processed by the UK Stem Cell Bank and approved for release to researchers, it will be listed on the UK Stem Cell Bank web site along with a scientific description and data available on the cells, as approved by Management Committee and the Steering Committee.

5.2 Charges levied by the UK Stem Cell Bank

The contract between the funders and the UK Stem Cell Bank makes provision for a schedule of charges to be developed by the UK Stem Cell Bank Management Committee for the curation, supply and transportation of Banked stem cell lines to users. It is expected that academic researchers cover marginal costs for accessing stem cell lines from the Bank and where necessary, seek funds for this on grant applications to funding agencies. Commercial users are expected to cover full economic costs. The charging for services provided by the UK Stem Cell Bank is in line with general principles applied by funding bodies for Banks and resources and will allow recovering some of the operating costs for the Bank over time.

In order to facilitate uptake by the scientific community in the early phase of Banking and to allow the Bank to determine realistic costs for quality control, curation and distribution of cell lines, no charges over and above handling fees will be levied for research grade lines until December 2005. Afterwards the situation will be kept under review. Charges will be publicised on the web page of the UK Stem Cell Bank.

5.3. Liability

NIBSC is responsible for all aspects of operation of the UK Stem Cell Bank and for any breaches in Bank operating standards, procedures or quality control arrangements.

Stem cell lines stored in the UK Stem Cell Bank will be supplied to users without warranty of merchantability or fitness for a particular purpose or any other warranty, express or implied, and without any representation or warranty that they are not free of extraneous agents or that the use or supply of the cell lines will not infringe any patent, copyright, trademark or other right of any third party.

Researchers accessing Banked stem cell lines will be required to agree via a Materials Access Agreement (at Annex 8), to indemnify and hold harmless NIBSC against any claim or liability arising from the use, handling or storage of the cell lines or any products that might arise from the results of research, including any claim or liability arising from alleged infringement of third party rights or use in clinical trials by the researcher or any customer, licensee, partner or agent of the researcher.

6. Governance of research involving established human embryonic stem cell lines

Unlike human embryos, embryonic stem cells do not have the potential to become a human person; so they do not have the moral status of human embryos and therefore the Government decided that research involving established stem cell lines does not need the same regulation to which embryo research is subject to by the HFEA. However, as the generation of embryonic stem cell lines involves the destruction of human embryos oversight in form of a Steering Committee was recommended to ensure that research performed is in keeping with HFEA Regulations. The oversight mechanisms governing research involving established embryonic stem cell lines are voluntary. However, they are a condition of the statutory regulation in the UK and there is an expectation by Government that these are adhered to.

6.1. Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines

The Steering Committee was established in December 2002 as an independent national Committee overseeing the UK Stem Cell Bank and research involving established human embryonic stem cell lines whether these have been obtained from the Bank or from elsewhere. The Steering Committee is a non- statutory body that reports annually to the MRC, works closely with the DH, the HFEA and the MHRA and briefs Ministers. It is the role of the Steering Committee to support stem cell research and to ensure that this is conducted within an ethical framework that is transparent to the public. The membership of the Committee includes expertise in science, medicine, ethics and theology as well as lay members and representatives from regulatory and funding agencies. The membership and terms of reference and summaries of issues discussed at Steering Committee meetings are posted on the MRC web site. (Steering Committee)–(See Page 26 for Full Web Link)

6.2. User and Clinical Liaison Committees

The User and Clinical Liaison Committees include stem cell researchers and clinicians from academia and Industry; They provide fora for discussion and consultation on issues relating to the UK Stem Cell Bank and oversight of stem cell research and therapy development in the UK; they do not report formally to the Steering Committee, but the two chairs are charged with bringing relevant issues to the Steering Committee's attention.
The memberships and terms of reference of the User and Clinical Liaison Committees are published on the MRC web site along with summaries of issues discussed at meetings.
(User and Clinical Liaison Committees) – (See Page 26 for Full Web Link)

6.3. Bank Management Committee

A Management Committee for the UK Stem Cell Bank (see Section 5) has been established by NIBSC to deal with operational issues; its terms of reference and membership, which includes in house and external experts, professionals, lay members and representatives from the funding agencies are published on the MRC and NIBSC web sites along with summaries of issues discussed (Bank Management Committee)–(See Page 26 for Full Web Link). The Management Committee reports formally to the Steering Committee and provides to it a full written report on an annual basis.

7. Depositing stem cell lines in the UK Stem Cell Bank

The UK Stem Cell Bank curates and makes available human embryonic and somatic stem cell lines (see section 2). The Bank does not curate heterogenous pools of stem cells that contain or are merely enriched for stem cells (e.g. bone marrow, peripheral blood or cord blood). The UK Stem Cell Bank is overseen by the Stem Cell Steering Committee. Before accepting stem cell lines for deposition in the Bank the Steering Committee has to satisfy itself that these have been ethically sourced, with fully informed donor consent, and that the cell lines present a valuable resource for the biomedical research community. *It is a condition of an HFEA licence that a sample of all human embryonic stem cell lines derived in the UK must be deposited in the UK Stem Cell Bank. Consent procedures for these cell lines are audited by the HFEA. The Steering Committee encourages the deposition of human embryonic stem cell lines derived outside the UK as well as somatic stem cell lines derived in the UK or abroad as long as these fulfil the criteria of informed consent and value to the research community.* A route map outlining the steps from stem cell derivation to deposition in the UK Stem Cell Bank is at Annex 1. In order to provide the Steering Committee with the information needed to make an informed decision about the deposition of cell lines in the Bank researchers are requested to complete an application form. A template form is at Annex 3 and guidance on the application procedure is provided in Section 9.

7.1. Examples of stem cell lines that can be deposited in the Bank

- *human embryonic stem cell lines*
- human stem cell lines from extra-embryonic tissues (trophoblast and yolk sac endoderm)
- human embryonic germ cell lines
- human mesenchymal stem cell lines other somatic stem cell lines from any stage of development, if available
- human fetal progenitor/stem cell lines (N.B. fetal neural stem cells are neither clonal nor immortal)
- haematopoietic stem cell lines from cord blood or bone marrow (N.B. These might be propagated using genetic manipulations, new culture conditions, or growth factors)
- stable, human somatic stem cell lines derived from embryonic stem cells
- conditionally immortalised human progenitor/stem cell lines (N.B. these can only be deposited in the Bank if depositors can make a persuasive case to the

Steering Committee that the lines are of outstanding research value to the scientific community).

In addition the Bank will curate cells used to facilitate the growth of embryonic stem cell lines in culture (e.g. standardised feeder cells).

Following approval for Banking by the Steering Committee UK Stem Cell Bank personnel will normally visit research teams to discuss the arrangements and procedures for the establishment of stem cell lines in the Bank. Before stem cell lines can be transferred a Material Deposition Agreement has to be signed between the owner of the cell lines (normally the employer of the researcher who has derived the stem cell line) and the Bank, agreeing to make the stem cell line available to requestors, on the terms of access to be negotiated between the depositor and the requestor in the Materials Use Licence (MUL). A Material Deposition Agreement can be obtained from the UK Stem Cell Bank (please see page 26 for full web link). This will be negotiated between the owner of the stem cell lines and the Bank on a case by case basis. It is recommended that technology transfer staff is alerted to the Material Deposition Agreement at an early stage to avoid unnecessary delays.

8. Accessing stem cell lines from the UK Stem Cell Bank and using human embryonic stem cell lines from sources other than the Bank

8.1. General principles

8.1.1. Research projects in which human embryonic stem cell lines may be used

The use of embryonic stem cells in research was debated at length in both Houses of Parliament during the passage of the Human Fertilisation and Embryology (Research Purposes) Regulations 2001. Parliament made clear that human embryonic stem cell lines should not be used for trivial purposes.

The Steering Committee expects that human embryonic stem cell lines are only used by bona fide research groups for justified and valuable purposes that reflect the requirements of the HFEA Regulations. This is:

(a) research which increases the knowledge about the development of embryos or has the long term goal of helping to increase knowledge about serious diseases and their treatment (as in the 2001 HFEA Regulations)*
(b) basic cell research which underpins these aims (as recommended in the House of Lords Report 2002)
(c) development of cell based therapies for clinical trials in respect of serious human diseases

The Steering Committee recognises the importance of training of staff using human embryonic stem cell lines and therefore the requirement to use stem cell lines for training purposes.

8.1.2. Peer Review

It is normally expected that the research projects for which human embryonic stem cell lines are used have been subjected to scientific peer review. However, peer review is not a pre-condition for Steering Committee approval. For instance researchers should have the opportunity to access human embryonic stem cell lines in order to generate preliminary data for grant applications.

8.1.3. Research Ethics Committee approval

Research Ethics Committees are concerned that patient care and diagnostic needs are not compromised by the diversion of material for research purposes and protect the dignity, rights, safety and well being of all research participants. Research Ethics Committee approval must be obtained:

(i) *as part of the application procedure for an HFEA research licence*
(iii) for research involving human tissues
(ii) for clinical trials of all stem cell derived therapeutic products

The Steering Committee has agreed that Research Ethics Committee approval is not required for research involving established human embryonic stem cell lines.

8.2. Accessing stem cell lines from the UK Stem Cell Bank

A route map outlining the steps for the accession of stem cell lines from the UK Stem Cell Bank is at Annex 2. In order to provide the Steering Committee with the information needed to oversee research involving stem lines researchers are requested to complete the relevant application form following the guidance in Section 9. The Bank will curate separately research grade stem cell lines that cannot be used in human application and clinical grade lines which have been derived an curated in facilities approved by the MHRA and could eventually be used in human therapy. Subsets of clinical grade lines will be processed by the Bank in research grade facilities in order to be accessed by users for basic research. It will be important to specify in the application form whether research or clinical grade stem cell lines are requested. All stem cell lines available from the Bank in the early phase will be research grade only.

The ownership of any Intellectual Property embodied in stem cell lines curated by the Bank will remain with the originator. Therefore stem cell lines can only be released by the Bank if a Material Use Licence between the depositor and accessor is in place setting out the rights of exploitation and ownership of any intellectual property arising from the research conducted by the user. This can be negotiated before or after Steering Committee approval has been given. Once the UK Stem Cell Bank receives confirmation of the Steering Committee's approval to access a Banked cell line and a signed copy of the MUL, it will negotiate a Materials Access Agreement (MAA) (see Annex 8) with the requestor and release the cell line.

The Bank can be accessed by researchers from academia and Industry in the UK and abroad. UK and overseas applications must be approved by the host Institution (academia or companies) and the same review procedures by the Steering Committee apply. Researchers accessing stem cell lines from the Bank must comply with legislation in the UK and the country where the research is performed and are expected to comply with this Code of Practice.

*including research for disease diagnosis, toxicology studies and the understanding of drug interactions

The Steering Committee will be responsible for assuring parity of standards, procedures and obligations in respect of applications from overseas researchers.

Researchers should notify the UK Stem Cell Bank if cell lines accessed from the Bank fail to exhibit expected properties. Complaints will be documented and investigated by a designated person within the UK Stem Cell Bank and notified to the Management Committee for further action.

Stem cell lines accessed from the UK Stem Cell Bank will be given a unique Bank accession number; this should be quoted by the primary accessor in all publications.

8.3. Using human embryonic stem cell lines from sources other than the Bank

The Steering Committee oversees research involving human embryonic stem cell lines in the UK whether these are accessed from the UK Stem Cell Bank or from elsewhere.

It is expected that the UK Stem Cell Bank will become the first port of call for researchers wishing to work with human embryonic stem cell lines. The Bank will make available standardised, quality controlled aliquots of stem cell lines and will allow researchers to work with well defined material so that direct comparisons can be made between studies.

Although the Steering Committee expects the UK Stem Cell Bank to be the preferred source of stem cell lines it is not a requirement that lines are exclusively accessed from the Bank. It is expected that there will be occasions when researchers wish to access human embryonic stem cell lines from other sources (e.g. International cell lines not deposited in the Bank or cell lines not yet ready for distribution by the Bank). However, all researchers wishing to work with human embryonic stem cell lines (whether accessed from the Bank, from other sources in the UK or oversees) should inform the Steering Committee through the application procedure detailed in Section 9.

The Steering Committee needs to satisfy itself that the research fulfils the criteria in section 8.1.1. and that the human embryonic stem cell lines have been ethically sourced with fully informed and free donor consent. Information in relation to the ethical sourcing of human embryonic stem cell lines does not need to be provided for human embryonic stem cell lines that a) were created in the UK (as consent procedures have been approved by the HFEA), b) are listed on the National Institute of Health (NIH) registry (as ethical sourcing has been confirmed by NIH) or c) have previously been approved by the Steering Committee for import or Banking. A register of Steering Committee approved human stem cell is available on the MRC web site. (SC Lines Register) – (See Page 26 for Full Web Link)

UK researchers wishing to transfer human embryonic stem cell lines to collaborators for a project that has been approved by the HFEA as part of the licence for the derivation of human ES cell lines do not need to apply to the Steering Committee.

8.4. Export of stem cell lines

Researchers wishing to wishing to export human embryonic stem cell lines should apply to the Steering Committee as outlined in Section 9. Research performed oversees should fulfil the criteria in Section 8.1.1 and must comply with legislation in the UK and in the country where the research is performed and is expected to comply with this Code of Practice.

9. Application Procedure

The Steering Committee meets three times per year. Applications that do not raise any issues can be approved between meetings through circulation, if necessary.

Template application forms for a) the deposition of stem cell lines in the Bank, b) for access to stem cell lines from the Bank and c) to import, export and use human embryonic stem cell lines from other sources than the Bank are at Annexes 3, 4, & 5 respectively, for information. These are subject to minor changes and applicants should always contact the secretary to the Steering Committee in order to request an up to date application form, to obtain details of deadlines and alert the secretary that an application is forthcoming thereby

permitting the timely scheduling for the attention of the Steering Committee. Applications forms can be requested or submitted by e-mail to stemcellsecretary@headoffice.mrc.ac.uk.

10. Donor Consent

Donor Consent

Free and informed consent are key principles of the Human Tissue Act (2004) and the HFE Act (1990). Comprehensive information must be given in a form that is readily accessible and allows a free and informed decision to be made by potential donors. All written information provided and consent forms have to be approved by Local Ethics Committees and for research involving embryos also by the HFEA. The HFEA requires that the donor couple must have given in principle consent for the use of embryos in research. In addition, the Steering Committee has in collaboration with the HFEA drawn up a list of criteria that must be addressed in information leaflets and consent forms provided by IVF clinics for the donation of embryos for stem cell research. Donors should be approached as early as possible, usually before ovary stimulation, to allow sufficient time to think issues over.

INFORMATION LEAFLET:

Before patients give consent to donation of their embryos for use in research projects to derive stem cell lines, they must be given oral information supported by relevant written material which confirms:

- the research project directed towards the creation of stem cell lines, including any tests that may be performed as part of the licensed research project on embryos or cells derived from the embryos;
- that in only a few cases stem cell lines will be successfully derived from donated embryos
- that any stem cells lines created may continue indefinitely and may be used in many different research projects; donors cannot restrict the subsequent research conducted with stem cell lines derived
- that any cell lines derived from their donated embryos may eventually be used for treatment purposes in the future *
- that stem cell lines derived in this project will be deposited in the UK Stem Cell Bank and the implications of this including that they may be used for other projects within the UK and/or overseas**
- that the Bank is overseen by an independent Steering Committee to ensure that the research performed on stem cell lines is in keeping with the HFEA regulations
- that research and their treatment are separated and that the decision whether to donate is voluntary and will not affect their treatment in any way;
- that the embryos will be anonymised***
- whether any information emerging from tests done on the genetic material will be fed back to donors****
- that the donors can vary or withdraw the terms of their consent until the point that the embryos are used for research; Gametes and / or embryos will be regarded as so used after they are under the control of the researchers and they are being cultured / grown for use in research
- that the research will not lead to any direct medical benefit to the donor
- that cell lines or discoveries made using them may be patented and used for commercial purposes, but that the donor will not benefit financially from this;
- how the research is funded, including any benefit which will accrue to researchers and/or their departments.

CONSENT FORM:

Each gamete provider must consent in writing to the following:

- to the use of embryos created using their gametes in the research project for the derivation of stem cell lines
- that they understand that a sample of any stem cell line will be deposited in the UK Stem Cell Bank and that the derived stem cell lines may be used in other research projects
- that they are under no obligation to take part in the study and that a decision not to participate will not alter the treatment that they would normally receive
- that they understand that they have a right to withdraw their consent without giving any reason, at any stage until the gametes and / or embryos have been used for research.
- that they understand that any cell line derived from their donated gametes/ embryos may eventually be used for treatment purposes (including cell replacement therapies) in the future *
- that they understand that cell lines or discoveries made using them may be patented and used for commercial purposes, but that the donor will not benefit financially from this
- whether they agree to be contacted in the future in the unlikely event that that the Stem Cell Steering Committee considers that they should be contacted in relation to confirmed test results performed on stem cell lines that are of direct relevance to their own, their family's or public health.

Explanatory notes

* This may not always be appropriate and may be omitted (e.g. stem cell lines with known genetic defects may be valuable for research purposes only) or some donors may decide to donate for research purposes only. However, it is recommended that consent for potential use in human therapy is obtained at the outset as it may not always be desirable or possible to contact donors at a later stage to obtain additional consent for clinical use. For hES cell lines derived in research grade facilities clinical use is unlikely. However, should such cell lines have unparalleled therapeutic potential, regulatory approval for clinical use may exceptionally be considered after detailed risk/benefit analysis.

** The UK Stem Cell Bank has been established by the Research Councils as a national resource for doctors and scientists. The Bank is overseen by an independent Steering Committee to ensure that the research performed on stem cell lines is in keeping with the HFEA Regulations. For instance researchers will wish to access stem cell lines from the Bank to learn more about how stem cell lines grow in a dish in the laboratory and how they develop into the different cell types found in the body.

This research may lead to the improvement of IVF treatment, can yield new information about how the human embryo develops and how this sometimes goes wrong during early pregnancy, or may contribute to the development of treatments for serious diseases. Stem cell lines may be grown in culture to investigate the effects of drugs or they may be grown to provide healthy replacement cells for transplantation, similar to bone marrow transplants.

*** The HFE Act imposes strict requirements on patient confidentiality. Donors must be informed that embryos will be coded and researchers accessing embryos or stem cell lines will not have access to any identifying information. The EU Tissue Directive requires that stem cell lines for human application can be traced from the donor to

recipient and vice versa. Traceability should also be best practice for research grade stem cell lines.

**** Donors receive feedback on tests performed by the IVF clinic as part of their IVF treatment. Donors should be advised that their identity is anonymous to the UK Stem Cell Bank and to researchers accessing stem cell lines for subsequent studies. It is recommended that donors are informed that no individual feedback will be given on tests performed by the UK Stem Cell Bank or research results of subsequent studies unless in the very unlikely event that the Stem Cell Steering Committee considers that the donor should be contacted in relation to confirmed test results of direct relevance to the donor's or the donor's family health or public health. General information on the UK stem cell initiative, including results of research using embryonic stem cell lines will be published on the web site of the UK Stem Cell Bank –(See Page 26 for Full Web Link).

11. Derivation and use of Stem Cell Lines

11.1. Quality and safety standards in fundamental stem cell research

Careful recording of procedures and results is essential for the verification of quality and integrity of research and can prove invaluable in resolving problems.

Those working with stem cell lines are expected to follow the general principles of Good Research Practice – (See Page 26 for Full Web Link) (Medical Research Council, 2000) as well as best practice for cell culture procedures (UK Co-ordinating Committee on Cancer Research,1999) –(See Page 26 for Full Web Link)

11.2 Regulation governing the derivation and processing of clinical grade stem cell lines

All tissues and cells intended for human application will be governed by the EU Directive on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Storage and Distribution of Human Tissues and Cells –(See Page 26 for Full Web Link) (adopted in March 2004 with a 2 year implementation period). The Directive covers haematopoietic, umbilical cord and bone marrow stem cells, reproductive cells (eggs, sperm), foetal tissues and cells and adult and embryonic stem cells. The Directive does not cover research for purposes other than application to the human body, e.g. in vitro research or in animal models. The aim of the Directive is to lay down standards of quality in order to ensure a high level of protection of human health.

A key principle of the EU Tissue Directive is the requirement of traceability of human tissues and cells from donor to recipient and vice versa in order to make it possible to verify the compliance with quality and safety standards. A cell line developed de novo should be given a unique and unambiguous identifying number that must preserve donor anonymity and be used in all procedures and publications.
Researchers must ensure that it is possible to trace cryopreserved stem cell lines to the primary cells and the donated human tissue, and must ensure that an anonymised link can be put in place with the UK Stem Cell Bank for the purposes of traceability

The technical Annexes for the EU Tissue Directive are under development at the time of writing and will address:

a) requirements for the accreditation, designation, authorisation or licensing of tissue
b) requirements for the procurement of human tissues and cells
c) quality systems, including training

d) selection criteria for the donor of tissues and/or cells
e) laboratory tests required for donors
f) cell and/or tissue procurement procedures and reception at the tissue establishment
g) requirements for the tissue and cell preparation process
h) tissue and cell processing, storage and distribution
i) requirements for the direct distribution to the recipient of specific tissues and cells

It is likely that these will build on current UK guidance, including the Code of Practice for Tissue Banks (DH, 2001) – (See Page 26 for Full Web Link),
Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation (DH, 2000) – (See Page 26 for Full Web Link), and the
Code of Practice for the Production of Human-derived Therapeutic Products –(2002)- (See Page 26 for Full Web Link) issued by the UK Medical Devices Agency (now part of the Medicines and Healthcare products Regulatory Agency [MHRA])

A further Directive is currently under negotiation in relation to Tissue Engineering.

Stem cells and stem cell lines intended for human use must be derived and processed in clinical grade facilities that meet the requirements set out in the Code of Practice for Tissue Banks (DH, 2001) and have been inspected by the MHRA and other appropriate accreditation agencies.

12. Intellectual property

12.1 Patentability of stem cells

A notice setting out the Patent Office's general practice on the patentability of inventions involving human stem cells, was issued in May 2003 and may be found at www.patent.gov.uk/patent/notices/practice/stemcells.htm; this states that each case will be treated on its own merits in the light of all relevant circumstances, and stresses that the Office's practice is subject to any future guidance from the UK courts. In summary, the Patent Office:

- will not grant patents for processes of obtaining stem cells from human embryos
- will not grant patents for human totipotent stem cells
- will grant patents for inventions involving human pluripotent stem cells provided they satisfy the normal requirements for patentability

12.2 Intellectual property generated by the UK Stem Cell Bank

Subject to the approval of the Steering Committee, the staff of the UK Stem Cell Bank will perform validation and other tests on newly deposited cell lines, as well as research aimed at improving Banking processes and procedures (e.g. relating to storage, reproducibility and quality). Bank staff must not however, conduct discovery research on Banked cell lines.

During the initial period of MRC/BBSRC funding, any intellectual property arising from research and development activities carried out pursuant to the UK Stem Cell Bank's operation will be assigned to MRC for the purposes of protection and exploitation. Net revenues generated from exploitation of such intellectual property will be used solely for supporting the operation of the UK Stem Cell Bank. Owners of any Banked stem cell lines used by the UK Stem Cell Bank in generating such intellectual property shall have the royalty-free, non-exclusive right, without the right to sub-license, to such intellectual property for use only with the specific cell line(s) involved in generating such intellectual

property. In the event the depositor wishes to use the intellectual other than solely with the specific stem cell line then a further licence or permission will be required from MRC.

Other than as set out above, the UK Stem Cell Bank will not take any direct interest in intellectual property embodied in deposited cell lines, or become involved in the negotiations between depositors and users.

13. Glossary of terms

Accessor
A researcher who withdraws a stem cell line from the UK Stem Cell Bank for use in an approved research project.
(Note: applications to the Steering Committee to access a stem cell line from the UK Stem Cell Bank must be made by the host institution rather than the researcher)

Anonymisation
The process of removing personal names and data from documents that would reveal the identity of a person.

Archived
Data or samples that have been preserved against future need.

Auditing
A systematic, independent and documented process for obtaining evidence to determine the extent to which the Quality Management System requirements are fulfilled.
(Note:Guidance on auditing quality and environmental management systems is provided in ISO 19011)

Blastocyst
A hollow ball of 50-100 cells reached after about five days' embryonic development just prior to implantation in the uterus.

Cells
The basic structural and functional unit of all organisms.

Cell culture
Cells maintained by repeated passage in a sterile container.

Cell line
A well characterised culture that has been demonstrated to be phenotypically and genotypically consistent over a specified number of population doublings.

Cell nuclear replacement (CNR)
The transfer of an adult cell nucleus into an egg that has had its nucleus removed to asexually create an embryonic clone without the fusion of sperm and egg**.**

Clinical trial
A rigorously controlled test on human subjects of a new drug, or other treatment, or a new invasive medical device.

Clonal
Derived from a single cell.

Confidentiality
Prevention of disclosure, other than to authorised individuals, of a participant's identity.

Consent
The voluntary consent given by a patient (or their next of kin) to participate in a study (which may include donating tissue) after being informed of its purpose, method of treatment, procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedule.

Consumers
Those who use products or services.

Curation
Long term preservation of material or data, sometimes in an archive.

Depositor
A researcher who deposits a stem cell line in the UK Stem Cell Bank
(Note: applications to the Steering Committee to deposit a stem cell line in the UK Stem Cell Bank must be made by the host institution rather than the researcher).

DNA
Deoxyribonucleic acid; the genetic material.

Documented procedures
Procedures that have been tested and optimised and written up in an operating manual for others to use.

Donor
A person who gifts embryos, cells or tissues.

Embryo
The first stage in the development of a human being, usually the result of fertilising an egg with a sperm; from the eighth week of fertilisation the embryo is referred to as a fetus.

Embryonic germ cells
Stem cells derived from primordial germ cells.

Exploitation
The process of turning a patented invention into a commercial success.

Fetus
A developing human from eight weeks after conception to birth.

Full economic costs
The all inclusive cost of producing a finished cell line.

Gamete
A male sperm or female egg.

Gene
A functional unit of heredity that is a segment of DNA located in a specific site on a chromosome. A gene directs the formation of an enzyme or other protein

Genotype
The genetic constitution of an organism. This information is used as a "blueprint" or set of instructions for building and maintaining the organism. The instructions are located within cells and are written in a coded language (the genetic code); they are copied at the time of cell division or reproduction and are passed from one generation to the next.

Informed consent
The voluntary consent given by a patient to participate in a study after being informed of its purpose, method of treatment, procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedule.

Intellectual Property
Intellectual Property is any product of the human intellect that is unique, novel and unobvious and has some value in the market place.
(Note: the employer of a researcher who derives a stem cell line is normally the owner of any intellectual property relating to that cell line)

IVF
In vitro fertilisation; the fertilisation of an egg by a sperm outside of the human body.

Liability
The state of being legally obliged and responsible.

Marginal costs
The amount by which production costs are increased as a result of generating one additional unit of output.

Mesenchymal stem cells
Rare stem cells present in human bone marrow that have been shown to differentiate into a variety of different cell types in culture

Multipotent stem cells
Stem cells that have the potential to differentiate into a limited number of specific cell types in order to regenerate the tissue in which they normally reside.

Passage
Transfer of cells from one culture environment to another.

Patent
A patent for an invention is granted by government to the inventor, giving the inventor the right for a limited period to stop others from making, using or selling the invention without the permission of the inventor. When a patent is granted, the invention becomes the property of the inventor, which - like any other form of property or business asset - can be bought, sold, rented or hired.

Phenotype
The "outward, physical manifestation" of the organism; i.e. the sum of the atoms, molecules, macromolecules, cells, structures, metabolism, energy utilization, tissues, organs, reflexes and behaviours. The phenotype is the product of the genotype.

Pluripotent stem cell
A single pluripotent stem cell has the ability to give rise to types of cells that develop from the three germ layers (mesoderm, endoderm and ectoderm) from which all the cells in the body arise. Pluripotent cells thus have the potential to develop into every cell type in the human body, but cannot develop into an embryo on their own.

Population doubling
A measured doubling of cell numbers.

Primary cells
Cells derived from an in vivo or ex vivo source.

Processing
All operations involved in the preparation of the stem cell line, from receipt through preparation and packaging to its completion as a finished therapy.

Quality management systems
The set of interrelated or interacting elements that is implemented by an organisation to direct and control its activities in order to fulfil stated, implied or obligatory needs or expectations.
(Note: fundamental principles of Quality Management Systems are described in ISO 9000)

Recipient
The patient for whom a particular treatment is intended.

Reproductive cloning
The implantation of an embryo produced by therapeutic cloning (cell nuclear replacement) into the womb of a woman.
(Note: this procedure is illegal in the UK)

Requestor
A researcher seeking approval from the Steering Committee to withdraw a stem cell line from the UK Stem Cell Bank for use in an approved research project.
(Note: applications to the Steering Committee to access a stem cell line from the UK Stem Cell Bank must be made by the host institution rather than the researcher)

Risk
Combination of the probability of occurrence of harm and the severity of that harm.

Risk/benefit assessment
Weighing of the potential benefits of a treatment against the harm that the recipient might experience.

Safety
Freedom from unacceptable risk.

Somatic stem cells
Stem cells derived from the early embryo (beyond the blastocyst stage), fetus and adult body that are multipotent rather than pluripotent.

Stakeholders
Parties or individuals with an interest in an issue or question.

Stem cells
Cells capable of self replication, proliferation and differentiation.

Stem cell Bank
A facility that is responsible for accessioning, processing, packaging, labelling, storage and delivery of a finished stem cell line issued under its name.

Sterile
Condition of a product that is free from contaminating organisms.

Therapeutic cloning (cell nuclear replacement)
The transfer of an adult cell nucleus into an egg that has had its nucleus removed to asexually create an embryonic clone without the fusion of sperm and egg.

Tissue engineering

The application of principles and methods of engineering and life sciences to the design, specification and fabrication of cells, biomaterials or biomolecules to restore or modify the biological functions of tissues.

Third party
Someone other than the principals who are involved in a transaction

Totipotent stem cell
At two to three days after fertilisation an embryo consists of identical cells which are totipotent; that is to say, each could give rise to an embryo on its own. Such cells are totally unspecialised and have the capacity to differentiate into any of the cells which constitute the fetus including the placenta and membranes around the fetus.

Toxicology
Study of the potential of materials to give rise to harm to health by virtue of their effect on biological systems.

Traceability
Tracking an individual through their medical history.

Trademark
A formally registered symbol identifying the manufacturer or distributor of a product.

Validation
Establishment of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes.

Verification
Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

14. Annexes

ANNEX 1 Route map showing the licences, approvals and accreditations needed to deposit stem cell lines in the UK Stem Cell Bank

ANNEX 2 Route map showing the licences, approvals and accreditations needed to access stem cell lines from the UK Stem Cell Bank

ANNEX 3 Application form to Deposit stem cell lines in the UK Stem Cell Bank

ANNEX 4 Application form to Access stem cell lines from the UK Stem Cell Bank

ANNEX 5 Application form to Import stem cell lines accessed from sources other than the UK Stem Cell Bank

ANNEX 6 Application form to Export stem cell lines accessed from sources other than the UK Stem Cell Bank

ANNEX 7 Application form to Use on stem cell lines accessed from sources other than the UK Stem Cell Bank

ANNEX 8 The UK Stem Cell Bank: Terms and Conditions for deposition and access of human stem cell lines

ANNEX 9 Materials Access Agreement

ANNEX 10 Relevant National and European Guidance

15. Full Website Links:

3.1 **The Human Tissue Act (2004):**
http://www.legislation.hmso.gov.uk/acts/acts2004/20040030.htm

Interim Guidance:
http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Tissue/TissueGeneralInformation/TissueGeneralArticle/fs/en?CONTENT_ID=4102169&chk=7yP5JQ

3.2 **The Human Fertilisation and Embryology (HFEA) Act (1990):**
http://www.hmso.gov.uk/acts/acts1990/Ukpga_19900037_en_1.htm

4. **The House of Lords Select Committee report on stem cell research (2002):**
http://www.parliament.the-stationery-ffice.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm

5. **The UK Stem Cell Bank:**
http://www.ukstemcellbank.co.uk/

6.1 **Steering Committee:**
http://www.mrc.ac.uk/index/strategy-strategy/strategy-science_strategy/strategy-strategy_implementation/strategy-government_spending_review_initiatives/strategy-stem_cells/strategy-stem_cell_governance.htm

6.2 **User and Clinical Liaison Committees:**
http://www.mrc.ac.uk/index/strategy-strategy/strategy-science_strategy/strategy-strategy_implementation/strategy-government_spending_review_initiatives/strategy-stem_cells/strategy-stem_cell_governance/strategy-user_and_clinical_liaison_committees.htm

6.3 **Bank Management Committee:**
http://www.mrc.ac.uk/index/strategy-strategy/strategy-science_strategy/strategy-strategy_implementation/strategy-government_spending_review_initiatives/strategy-stem_cells/strategy-stem_cell_governance/strategy-management_committee.htm

8.3 **SC Lines Register:**
http://www.mrc.ac.uk/index/strategy-strategy/strategy-science_strategy/strategy-strategy_implementation/strategy-government_spending_review_initiatives/strategy-stem_cells/strategy-stem_cell_governance/strategy-registry_of_stem_cell_lines.htm

11.1 **Good Research Practice:**
http://www.mrc.ac.uk/pdf-good_research_practice.pdf

UK Co-ordinating Committee on Cancer Research, 1999:
http://cellBank.nihs.go.jp/information/guidelines/ukcccr/cell_lines_guides.html.

11.2 **Directive on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, processing, Storage and Distribution of Human Tissues and Cells**
http://europa.eu.int/comm/health/ph_threats/human_substance/tissues_en.htm.

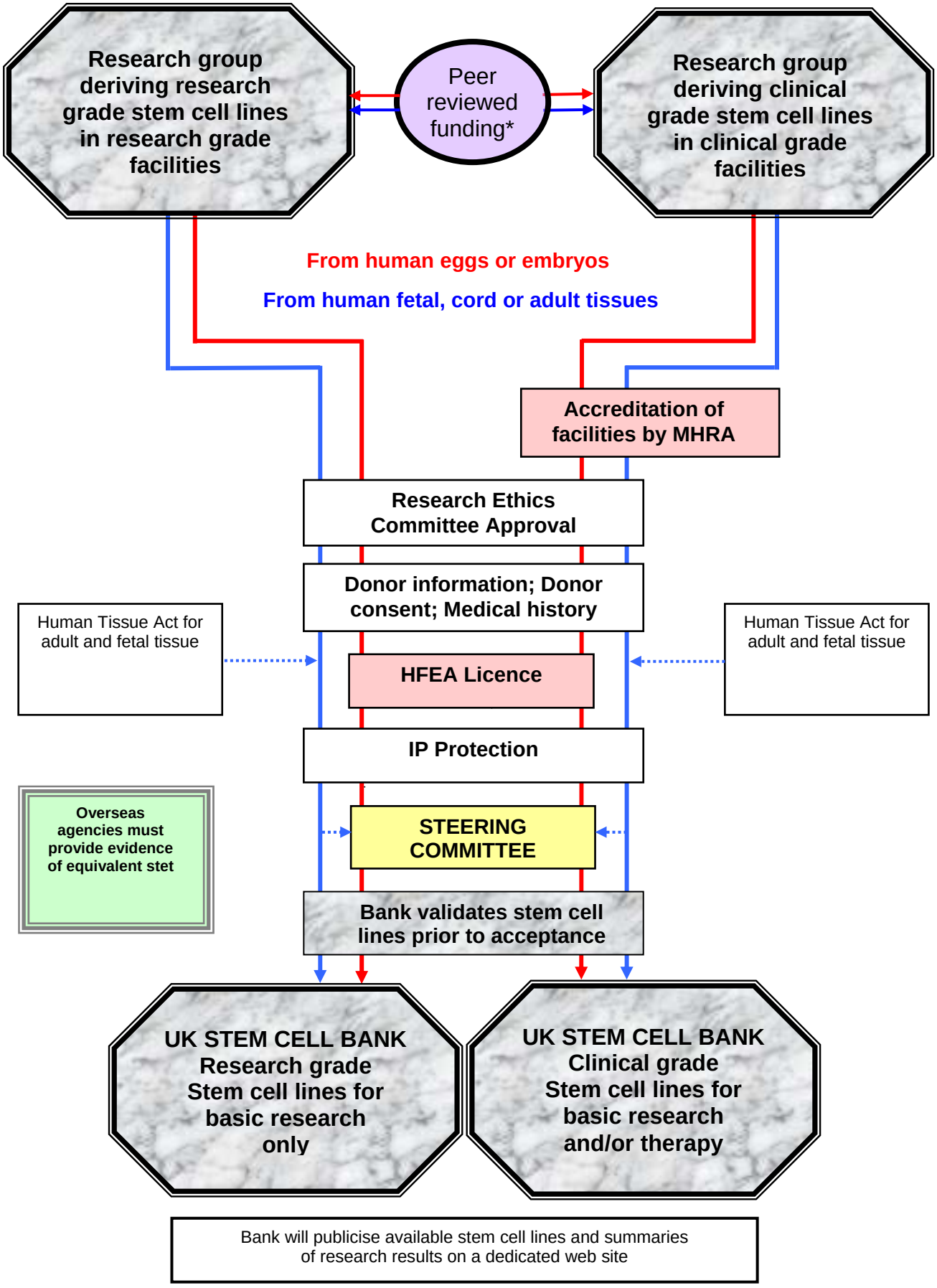
Code of Practice for Tissue Banks (DH, 2001):
http://www.dh.gov.uk/assetRoot/04/03/42/63/04034263.pdf

Guidance on the Microbiological Safety of human Organs, Tissues and Cells used in Transplantation (DH, 2000):

http://www.dh.gov.uk/assetRoot/04/07/90/53/04079053.pdf

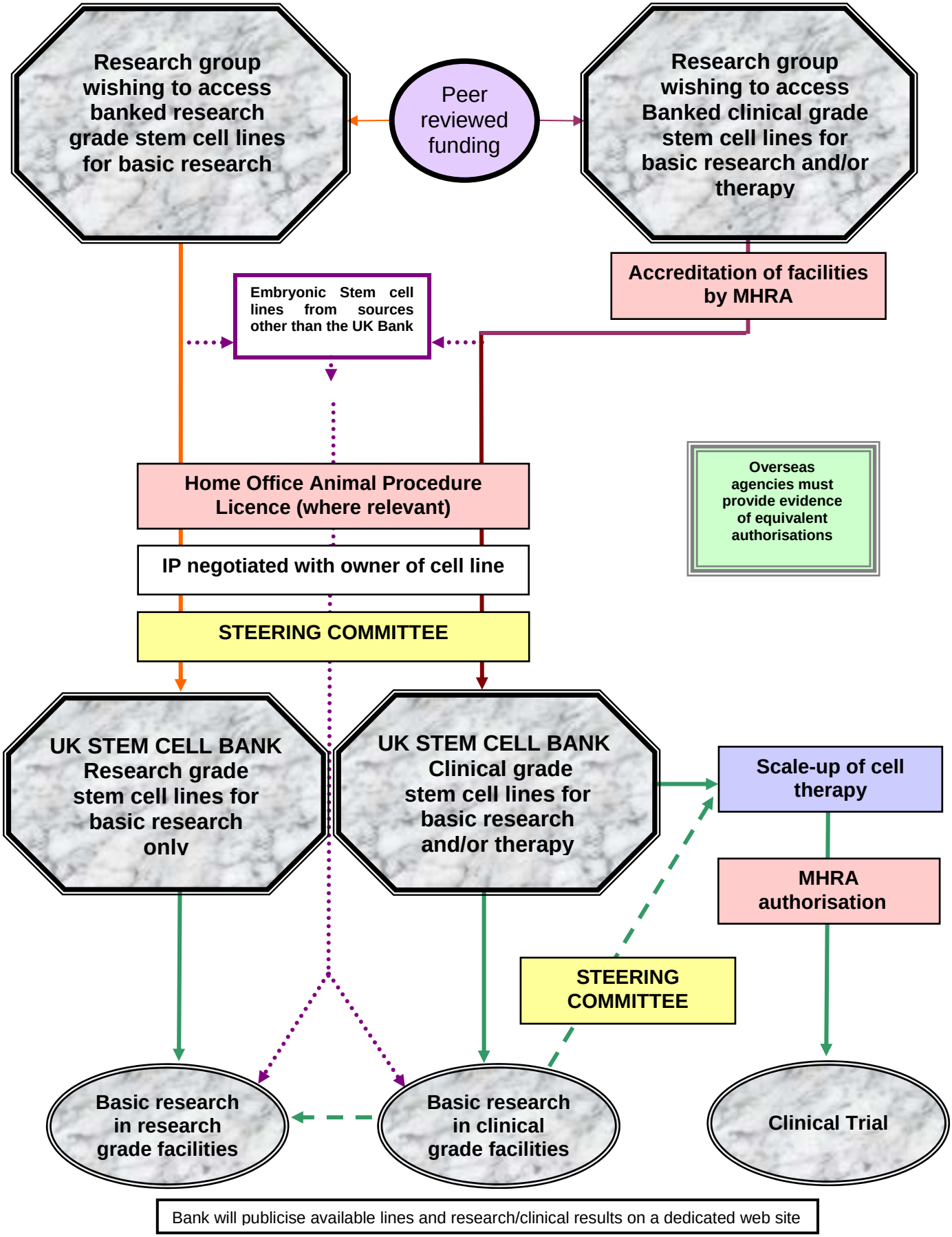
Code of Practice for the Production of Human-derived Therapeutic Products:
http://devices.mhra.gov.uk/mda/mdawebsitev2.nsf/72a26a46ed28515400256a7600410653/a488213b589ae99280256be4003bc2f0/$FILE/Code_of_Practice_for_HTP's.pdf

ROUTE MAP FOR UK GROUPS WISHING TO DERIVE AND BANK RESEARCH GRADE AND CLINICAL GRADE STEM CELL LINES



*** Companies, and academics funded by companies, must secure equivalent independent approval**
HFEA = Human Fertilisation and Embryology Authority; MHRA = Medicines and Healthcare products Regulatory Agency; IP = Intellectual Property. Steering Committee = Steering Committee for the UK Stem Cell Bank and for the use of Stem Cell Lines

ROUTE MAP FOR UK GROUPS WISHING TO ACCESS RESEARCH GRADE OR CLINICAL GRADE BANKED STEM CELL LINES FOR BASIC RESEARCH AND/OR THERAPY



HFEA = Human Fertilisation and Embryology Authority; IP = Intellectual Property; MHRA = Medicines and Healthcare products Regulatory Agency; Steering Committee = Steering Committee for the UK Stem Cell Bank and for the use of Stem Cell Lines

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STEERING COMMITTEE FOR THE UK STEM CELL BANK AND FOR THE USE OF STEM CELL LINES

APPLICATION FORM TO DEPOSIT A HUMAN STEM CELL LINE IN THE UK STEM CELL BANK

Notes to Depositors

(Please read these notes before completing the application form)

Submit your completed application form by email to the Secretary of the Stem Cell Steering Committee:

stemcellsecretary@headoffice.mrc.ac.uk

For general information contact:

The Secretary to the Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines,
20, Park Crescent,
London.
W1B 1AL *Tel: +44 (0) 207 670 5440*
UK *Fax: +44 (0) 207 436 5229*

For scientific information contact:

Dr Robin Buckle: **Robin.Buckle@headoffice.mrc.ac.uk**

The following documents must accompany your application:

- A copy of the donor consent form (see below)
- A copy of ethics committee approval (or equivalent)
- A copy of any published scientific papers related to the derivation and/or characterization of the stem cell line
- A one page CV for the Principle Investigator

If submitting electronically, PDF files of WORD documents are acceptable. Paper copies may be submitted to the Secretary, but must be accompanied by a completed copy of the application form.

If you are including a copy of the signed donor consent form with the application, you must contact the Secretary to the Stem Cell Steering Committee to request a pre-addressed envelope for submission of this document.

It is important that this application is understandable by lay members and all abbreviations explained.

Notes to Sections

Note 1: Stem cell lines suitable for clinical/therapeutic will have been derived under conditions that make them suitable for use in humans. This includes facilities, growth media and any associated feeder cell layers and the conditions under which these were grown. Cell lines suitable for clinical/therapeutic application may also be used for research

Note 2: Any restrictions made by the donor(s) on the utilisation of the cell line must be detailed in section 5.

Note 3: The Register of Steering Committee approved stem cell lines can be viewed on the UK Stem Cell Bank website at www.ukstemcellbank.org.uk . If the line is on the approved list please provide the application number assigned by the UK Steering Committee. The National Institutes of Health Registry is available at http://stemcells.nih.gov/research/registry

Note 4: For the purpose of traceability, HFEA licence holders are requested to provide both their licence number and the name and centre number of the unit providing the embryo(s) from which the hES cell line(s) were derived.

Note 5: The Steering Committee considers all applications on a case by case basis and appreciates that in the area of consent that there may be occasions when not all the criteria listed in Section 3 are fulfilled. The Steering Committee reserves the right to ask for original documentation if considered necessary.

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SCSC Application No. _____	UKSCB Accession No. _____

APPLICATION FORM TO DEPOSIT A HUMAN STEM CELL LINE IN THE UK STEM CELL BANK

SECTION 1 General Information

Complete all boxes

Name(s) of cell line(s):	**Number of cell lines for which application is made:**
Name and title of Principle Investigator:	**Name of owner of the cell line(s)**
Country of origin of the cell line(s):	**Origin of the cell line(s):** **Embryonic** ☐ **Fetal** ☐ **Adult** ☐
Grade of cell line (*see note1*)**:** **Clinical/therapeutic** ☐ **Research** ☐	**Have any restrictions been placed on the use of the cell line by the donor?** *(see note 2)*: **Yes** ☐ **No** ☐
Is the cell line listed on the Register of Steering Committee Approved Stem Cell Lines *(see note 3)*: **Yes** ☐ **No** ☐ *If Yes provide original SCSC Application number* **SCSC application number:**	**Is the cell line listed on the NIH Registry** *(see note 3)* **Yes** ☐ **No** ☐

Please continue on page 2.

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Date application received:	
1. Copy of signed consent form attached:	**Yes** ☐ **No** ☐ *(if No complete 5 below)*
2. Copy of ethics committee approval received:	**Yes** ☐ **No** ☐
3. Principal Investigator's CV received:	**Yes** ☐ **No** ☐
4. Cell line publication(s) received:	**Yes** ☐ **No** ☐
5. Record details of method used to ascertain appropriate consent was provided by the donor (include donor number/reference number to donation). **Donor/Ref. No.:**	
Print Name:	**Signature:**
Date application considered by SC:	
Date application approved:	**Date UK Stem Cell Bank notified:**

FOR OFFICE USE ONLY	
SCSC Application No. _____	UKSCB Accession No. _____

SECTION 2 — Applicant Details

2.3 Name and title of Principle Investigator:	**Post held:**
Address:	**Telephone:** **Fax:** **E-mail:**

2.2 ***(Complete only if different from 2.1 above)*****:**	
Name and title of the provider of the cell line	**Post held:**
Address:	**Telephone:** **Fax:** **E-mail:**

2.3 Name of person with authority to sign Materials Transfer Agreements	**Name of owner of the cell line** *(if different from 2.1 -2.2 above)***:**
Address:	**Telephone:** **Fax:** **E-mail:**

2.4 ***Complete only if different from 2.1 above*** *(applies only to UK centres deriving embryonic stem cell lines)***.**	
Name and title of HFEA license holder:	**Post held:**
Address:	**Telephone:** **Fax:** **E-mail:**

2.5 ***This section applies only to UK centres deriving embryonic stem cell lines*** *(see note 4)***:**	
HFEA license number for derivation	
Centre from which embryo(s) were obtained	**HFEA centre number** *(see note 4)*

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SCSC Application No. _____ UKSCB Accession No. _____

SECTION 3 Details of Consent

DO NOT complete this section if the cell line is of embryonic origin and derived in the UK.
Complete this section ONLY IF the cell line(s):

- were derived outside the UK;
- are non-hES cell line(s) derived in the UK;

AND

- are not listed on the Register of Steering Committee Approved Stem Cell Lines;
- are not listed on the NIH Registry.

Complete ALL boxes in this section *(see note 5)*.

3.1 Was the study to approve the derivation of the cell lines(s) approved by an ethics committee *(or equivalent if application is from outside the UK)*:

Yes ☐ **No** ☐

The following criteria constitute best practice in the UK for informed consent.

3.2 At the time of consenting, was the donor(s) informed:

i about the specific research project, including any tests that may be performed as part of the licensed research project on embryos or cells derived from the embryos

Yes ☐ **No** ☐

ii that any stem cell lines created may continue indefinitely and may be used in many different research projects

Yes ☐ **No** ☐

iii that the decision whether to donate would not affect their treatment in any way

Yes ☐ **No** ☐

iv about whether the embryos/cells would be reversibly or irreversibly anonymised and the implications of this

Yes ☐ **No** ☐

v whether any information will be fed back to the donor(s)

Yes ☐ **No** ☐

vi that the donors may vary or withdraw their consent until the point the embryos/cells are used in the project

Yes ☐ **No** ☐

vii that once the embryo/cells has been used in the project, the donor(s) have no control over any use of the cells or any stem cell lines derived

Yes ☐ **No** ☐

viii that stem cell lines derived in this project will be deposited in the UK Stem Cell Bank and the implications of this including long term storage and use in other research projects and potential therapeutic applications

Yes ☐ **No** ☐

ix that stem cell lines may not be generated where the consent places a constraint on future use

Yes ☐ **No** ☐

x that cell lines may be used for commercial purposes, but that donor(s) will not benefit financially from this

Yes ☐ **No** ☐

xi that cell lines derived or discoveries made from them may be patented but donor(s) will not financially benefit

Yes ☐ **No** ☐

xii regarding how the research was funded, including any benefit which may accrue to researchers and/or their departments/companies

Yes ☐ **No** ☐

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SCSC Application No. _____	UKSCB Accession No. _____

SECTION 3 (continued) Details of Consent

3.3 Name of licensing authority or body accrediting the derivation centre *(in the country of origin)*:	
Address:	**Telephone:** **Fax:** **E-mail:**
Licensing or Accreditation number for the licence holder / derivation centre*(in the country of origin)*:	

3.4 Name of licensing authority or body accrediting the donation centre *(the centre, in the country of origin, from which the embryo(s) were obtained – if different from 3.3 above)*:	
Address:	**Telephone:** **Fax:** **E-mail:**
Licensing or Accreditation number for the donation centre *(in the country of origin)*:	
Address:	**Telephone:** **Fax:** **E-mail:**

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SCSC Application No. _____ UKSCB Accession No. _____

SECTION 4 Details of Cell Line(s)

Complete all boxes in this section *(failure to do so in sufficient detail may delay the application)*

4.1 Description and characterisation of the tissue of origin

4.2 Was the tissue of origin fresh or cryopreserved?

Fresh ☐ Cryopreserved ☐

4.3 Date of donation

4.4 Date used or thawed *(if frozen)*

4.5 Was the stem cell line derived in facilities accredited by the host country under EU cGMP or the EU Directive for Cells and Tissues *(or similar recognized standard if derived outside the EU)*

Yes ☐ **No** ☐

4.6 Was the stem cell line derived within a quality system accredited by the host country under EU cGMP or the EU Directive for Cells and Tissues *(or similar recognized standard if derived outside the EU)*

Yes ☐ **No** ☐

4.7 Is the cell line intended for basic research?

Yes ☐ **No** ☐

4.8 Is the cell line suitable for use in animals

Yes ☐ **No** ☐

4.9 Could the cell line be used for human therapy? *(Only answer Yes if you ticked Yes in 4.5 and 4.6 above)*

Yes ☐ **No** ☐

4.10 Has the cell line been genetically modified?

Yes ☐ **No** ☐

4.11 Details of the morphological characteristics in culture of the cell line *(If this is covered in an accompanying peer reviewed publication only cite reference)*

4.12 Details of differentiation characteristics and functional analysis of the cell line *(If this is covered in an accompanying peer reviewed publication only cite reference)*

4.13 Details of the determination of pluripotency *(If this is covered in an accompanying peer reviewed publication only cite reference)*

4.14 Markers used to characterise cell line and result *(Indicate passage level at which marker studies were carried out)*

4.15 Was clonal analysis performed

Yes ☐ **No** ☐

4.16 If **Yes** indicate how it was conducted and outcome

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SCSC Application No. _____	UKSCB Accession No. _____

SECTION 5 Restrictions

The stem cell line will be listed on the Bank Website. It is possible for the depositor to request that release of the cell lines to accessors, for research in a restricted field, is embargoed for 12 months. In exceptional cases, the Stem Cell Steering Committee may be prepared to consider embargo periods for up to 5 years. *(E.g. it would be possible to seek to embargo for 12 months the use of a cell line to generate dopamine producing cells for Parkinson's Disease, but it would not be acceptable to try to embargo for 12 months the use of the cell line for any research into neuroscience).*

5.1 If you wish to request and embargo, please specify the restricted field and fully justify the request
(the case and restricted field must be approved by the steering committee)

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Yes ☐ **No** ☐

Date:

5.2 In certain circumstances the donor(s) of the original material may have placed restrictions on the use of that material. Do you know of any such restriction?

Yes ☐ **No** ☐

5.3 If the answer to 5.2 was YES please specify restrictions

SECTION 6 Declaration

By submitting this application to the secretary to the Stem Cell Steering Committee, I confirm that the information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

Signed on behalf on Host Institution *(Person responsible e.g. Head of Department/Dean)* Date:	**Signed by Principal Investigator** Date:
6.3 Name and title of Signatory for Host Institution:	
Address:	**Telephone:** **Fax:** **E-mail:**

Date received:

STEERING COMMITTEE FOR THE UK STEM CELL BANK AND FOR THE USE OF STEM CELL LINES

APPLICATION FORM TO:

Access a human stem cell line(s) from the UK Stem Cell Bank

Name and title of Principal Investigator

Title of project

Name/number of cell line given by originator (as shown on Bank website - http://www.ukstemcellbank.org.uk)

UK Stem Cell Bank Accession Number

Is the cell line of fetal, adult or embryonic origin?

Is the cell line Clinical or Research grade?

INSTRUCTIONS:

- **Availability of stem cell lines should first be confirmed by checking the UK Stem Cell Bank web page at http://www.ukstemcellbank.org.uk**
- **It is important that this application is understandable by lay members and abbreviations explained.**
- **Please submit this application form plus a one page C.V of the Principal Investigator by email to the Stem Cell Steering Committee: stemcellsecretary@headoffice.mrc.ac.uk**
- **For further information please contact the Secretary to the Steering Committee at: stemcellsecretary@headoffice.mrc.ac.uk**

  Or for scientific queries please contact Dr Robin Buckle at: Robin.Buckle@headoffice.mrc.ac.uk

Key to abbreviations:
hES = Human Embryonic Stem (cell line)
HFEA = Human Fertilisation and Embryology Authority
MHRA = Medicines and Healthcare products Regulatory Agency

SECTION 1 - CONTACT DETAILS

1.1 Principal investigator (*attach a one page C.V.)*

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

1.2 Contact person if different from person listed at 1.1

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

1.3 Collaborators (Name and institution of Principal Investigators who wish to have access to hES cell lines as part of this application)

SECTION 2 – DETAILS OF THE RESEARCH PROJECT FOR WHICH THE LINE IS BEING REQUESTED

2.1 Title of the project:

2.2 Has a study previously approved by the Stem Cell Steering Committee?

Yes ☐ **No** ☐

2.3 Abstract of research project including aims and objectives *(Approx. 300 words):*
(The Stem Cell Steering Committee needs to satisfy itself that hES cell lines are not used for trivial purposes and their uses are within the remit of HFEA regulations. The Stem Cell Steering Committee will not conduct a scientific review of experimental detail or repeat the peer review.)

2.4 Has the research project been subjected to peer review?

Yes ☐ **No** ☐

If yes, please provide details (Funding Body, etc.)

If no, please explain why not (e.g generation of preliminary data) and state how the research will be supported

2.5 Does the research project include experiments in animals?

Yes ☐ **No** ☐

If yes, please provide details

2.6 Do you intend to perform experiments creating hES cell/animal embryo aggregation chimaeras?

Yes ☐ **No** ☐

If yes, please provide details

2.7 Are all experiments involving animals covered by appropriate Home Office Animal Procedures Licences (or its equivalent if the cell line is to be used outside of the UK)?

Yes ☐ **No** ☐

2.8 If you have requested a clinical grade cell line, do you:

(i) have access to clinical grade facilities accredited by the UK MHRA (or its equivalent where the application is from overseas)?

Yes ☐ **No** ☐

(ii) intend to use the line for human therapy?

Yes ☐ **No** ☐

SECTION 3 - DECLARATION

DECLARATION

By submitting this application to the Secretary to the Stem Cell Steering Committee, I confirm that;

3.1 **The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.**

3.2 **I have read and understood the Code of Practice for the Use of Stem Cell Lines* including the Authorisations required for Third Party Transfers of Human Embryonic Stem Cell Lines. Also the IPR Terms and Conditions for the deposition and access of human stem cell lines I agree to abide by all of these documents (Code of Practice for the Use of Human Stem Cell Lines).**

3.3 **The research is consistent with UK legislation**

On behalf of Host Institution
(Person Responsible [e.g. Head of Department/Dean])

Principal Investigator

Date

Date

Name and title of host institution Signatory:

Post held:

Institution:

Postal Address:

Country :
Tel:
Fax:
Email:

Date received:

STEERING COMMITTEE FOR THE UK STEM CELL BANK AND FOR THE USE OF STEM CELL LINES

APPLICATION FORM TO:

Export human embryonic stem cell line(s) from the UK to another country

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Name and title of Recipient

Title of project

Provider of cell line(s)

Name/number of cell line(s) designated by originator

Is the cell line Clinical or Research grade?

Is the cell line listed on the Register of Steering Committee approved Stem Cell Lines? (http://www.mrc.ac.uk/index/strategy-strategy/strategy-science_strategy/strategy-strategy_implementation/strategy-government_spending_review_initiatives/strategy-stem_cells/strategy-stem_cell_governance/strategy-registry_of_stem_cell_lines.htm)

Is the cell line listed on the NIH Registry? (http://stemcells.nih.gov/research/registry/)

INSTRUCTIONS:

- **It is important that this application is understandable by lay members and abbreviations explained.**
- **Please submit this application form plus a one page C.V of the Recipient by email to the Stem Cell Steering Committee: stemcellsecretary@headoffice.mrc.ac.uk**
- **For further information please contact the Secretary to the Steering Committee at: stemcellsecretary@headoffice.mrc.ac.uk**

  Or for scientific queries please contact Dr Robin Buckle at: Robin.Buckle@headoffice.mrc.ac.uk

Key to abbreviations:

hES	**=**	**Human Embryonic Stem (cell line)**	**HFEA**	**=**	**Human Fertilisation and Embryology Authority**
MHRA	**=**	**Medicines and Healthcare products Regulatory Agency**	**NIH**	**=**	**National Institutes of Health**

SECTION 1 – CONTACT DETAILS

1.1 Recipient (***attach a <u>one page</u> C.V.)***

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

1.2 Provider of the cell line(s)

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

1.3 Collaborators (Name and institution of Investigators who wish to have access to hES cell lines as part of this application)
(You must inform the Stem Cell Steering Committee if collaborators join the project subsequent to this application)

SECTION 2 – DETAILS OF CELL LINE(S)

2.1 For hES cell lines derived in the UK, please provide the HFEA Licence number

2.3 For hES cell lines derived abroad that are not listed on the Register of Steering Committee approved Stem Cell Lines or the NIH Registry, please complete the following:

a) Was the study to derive the cell line(s) approved by an ethics committee (or its equivalent if the application is from overseas)?

Yes ☐ **No** ☐

b) Have you clarified with the consenting clinician that informed consent in line with UK guidelines has been given?

(The following criteria constitute best practice in the UK. Please tick as appropriate)

At the time of consenting, the Donor was informed*:

i. about the specific research project, including any tests may be performed as part of the licensed research project on embryos or cells derived from the embryos

Yes ☐ **No** ☐

ii. that any stem cells lines created may continue indefinitely and be used in many different research projects

Yes ☐ **No** ☐

iii that the decision whether to donate will not affect their treatment in any way;

Yes ☐ **No** ☐

iv. about whether the embryos will be reversibly or irreversibly anonymised, and the implications of this

Yes ☐ **No** ☐

v. whether any information will be fed back to the donors

Yes ☐ **No** ☐

vi. that the donors can vary or withdraw the terms of their consent until the point the embryos are used in the project of research

Yes ☐ **No** ☐

vii. that once an embryo has been used in the project of research the donors have no control over any future use of the embryonic cells and any stem cell lines derived

Yes ☐ **No** ☐

viii. that stem cell lines derived in this project will be deposited in the UK Stem Cell Bank and the implications of this including they may be used for other projects

Yes ☐ **No** ☐

ix. that stem cell lines must not be generated from donated embryos where the consent from the relevant donors, or one of them, places a constraint on future use

Yes ☐ **No** ☐

x. that cell lines may be used for commercial purposes, but that the donor will not benefit financially from this

Yes ☐ **No** ☐

xi. that any cell lines derived, or discoveries made using them, could be patented, but that the donor will not benefit financially from this

Yes ☐ **No** ☐

xii. about how the research is funded, including any benefit which will accrue to researchers and/or their departments

Yes ☐ **No** ☐

*__The Steering Committee considers all applications on a case by case basis and appreciates that there may be occasions where not all criteria are fulfilled. The Steering Committee reserves the right to ask for original documentation if considered necessary.__

SECTION 3 – DETAILS OF THE RESEARCH PROJECT FOR WHICH THE CELL LINE(S) IS BEING EXPORTED

3.1 Title of the project:

3.2 Has a study previously approved by the Stem Cell Steering Committee?

Yes ☐ **No** ☐

3.3 Abstract of research project including aims and objectives *(Approx. 300 words):*
(The Stem Cell Steering Committee needs to satisfy itself that hES cell lines are not used for trivial purposes and their uses are within the remit of HFEA regulations. The Stem Cell Steering Committee will not conduct a scientific review of experimental detail or repeat the peer review.)

3.4 Has the research project been subjected to peer review?

Yes ☐ **No** ☐

If yes, please provide details (Funding Body, etc)

If no, please explain why not (e.g generation of preliminary data) and state how the research will be supported

3.5 Does the research project include experiments in animals?

Yes ☐ **No** ☐

If yes, please provide details

3.6 Do you intend to perform experiments creating hES cell/animal embryo aggregation chimaeras?

Yes ☐ **No** ☐

If yes, please provide details

3.7 Are all experiments involving animals covered by an equivalent to the UK Home Office Animal Procedures Licences?

Yes ☐ **No** ☐

3.8 Was the stem cell line derived in clinical grade facilities accredited by the UK MHRA?

Yes ☐ **No** ☐

If yes, do you have access to clinical grade facilities accredited by an equivalent to the UK MHRA?

Yes ☐ **No** ☐

SECTION 4 – DECLARATION FOR THE EXPORT OF HUMAN EMBRYONIC STEM CELL LINES FROM THE UK TO ANOTHER COUNTRY

4.1 By submitting this application form, the person responsible (e.g. Head of Department at the host institution) of the recipient of the exported stem cell line(s) confirms that:

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. The cell line(s) will only be used for the following purposes:

   i) Research that is consistent with UK legislation (as specified in the Code of Practice for the Use of Stem Cell Lines and the recipient hereby agrees to abide by this Code.
   ii) Research which has the long term goal of helping to increase knowledge about serious diseases and their treatment
   iii) Basic cell research which underpins these aims
   iv) Development of cell based therapies for clinical trials in respect of serious human diseases

3. Research that does not contravene UK legislation such as human reproductive cloning.

4. Research that is consistent with and does not contravene legislation in the country in which the recipient is working.

On behalf of Host Institution
(Person Responsible [e.g. Head of Department])
Signature:

Date

Recipient of the exported stem cell line(s)
Signature:

Date

Name and title of host institution Signatory:

Post held:

Institution:

Postal Address:

Tel:
Fax:
Email:

Date received:

STEERING COMMITTEE FOR THE UK STEM CELL BANK AND FOR THE USE OF STEM CELL LINES

APPLICATION FORM TO:

Import human embryonic stem cell line(s) into the UK

Name and title of Principal Investigator:

Title of project

Provider of cell line(s)

Country of origin of cell line(s)

Name/number of cell line(s) designated by originator

Is the cell line Clinical or Research grade?

Is the cell line listed on the Register of Steering Committee approved Stem Cell Lines? (http://www.mrc.ac.uk/index/strategy-strategy/strategy-science_strategy/strategy-strategy_implementation/strategy-government_spending_review_initiatives/strategy-stem_cells/strategy-stem_cell_governance/strategy-registry_of_stem_cell_lines.htm)

Is the cell line listed on the NIH Registry? (http://stemcells.nih.gov/research/registry/)

INSTRUCTIONS:

- **It is important that this application is understandable by lay members and abbreviations explained.**
- **Please submit this application form and a one page C.V of the Principal Investigator by email to the Stem Cell Steering Committee: stemcellsecretary@headoffice.mrc.ac.uk**
- **For further information please contact the Secretary to the Steering at: stemcellsecretary@headoffice.mrc.ac.uk**

  Or for scientific queries please contact Dr Robin Buckle at: Robin.Buckle@headoffice.mrc.ac.uk

Key to abbreviations:

hES	**=**	**Human Embryonic Stem (cell line)**	**HFEA**	**=**	**Human Fertilisation and Embryology Authority**
MHRA	**=**	**Medicines and Healthcare products Regulatory Agency**	**NIH**	**=**	**National Institutes of Health**

SECTION 1 – CONTACT DETAILS

1.1 Principal investigator (*attach a one page C.V.)*

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

1.2 Contact person if different from person listed at 1.1

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

1.3 Collaborators (Name and institution of Principal Investigators who wish to have access to hES cell lines as part of this application)
(You must inform the Stem Cell Steering Committee if collaborators join the project subsequent to this application)

SECTION 2 - DETAILS OF CELL LINE(S)

2.1 Provider of cell line(s) and contact details

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

2.2 For hES cell that are not listed on the Register of Steering Committee approved Stem Cell Lines or the NIH Registry, please complete the following:

a) Was the study to derive the cell line(s) approved by an ethics?

Yes ☐ **No** ☐

b) Have you clarified with the consenting clinician that informed consent in line with UK guidelines has been given?
(The following criteria constitute best practice in the UK. Please tick as appropriate)

At the time of consenting, the Donor was informed*:

i. about the specific research project, including any tests may be performed as part of the licensed research project on embryos or cells derived from the embryos

Yes ☐ **No** ☐

ii. that any stem cells lines created may continue indefinitely and be used in many different research projects

Yes ☐ **No** ☐

iii that the decision whether to donate will not affect their treatment in any way;

Yes ☐ **No** ☐

iv. about whether the embryos will be reversibly or irreversibly anonymised, and the implications of this

Yes ☐ **No** ☐

v. whether any information will be fed back to the donors

Yes ☐ **No** ☐

vi. that the donors can vary or withdraw the terms of their consent until the point the embryos are used in the project of research

Yes ☐ **No** ☐

vii. that once an embryo has been used in the project of research the donors have no control over any future use of the embryonic cells and any stem cell lines derived

Yes ☐ **No** ☐

viii. that stem cell lines derived in this project will be deposited in the UK Stem Cell Bank and the implications of this including they may be used for other projects

Yes ☐ **No** ☐

ix. **that stem cell lines must not be generated from donated embryos where the consent from the relevant donors, or one of them, places a constraint on future use**

Yes ☐ **No** ☐

x. **that cell lines may be used for commercial purposes, but that the donor will not benefit financially from this**

Yes ☐ **No** ☐

xi. **that any cell lines derived, or discoveries made using them, could be patented, but that the donor will not benefit financially from this**

Yes ☐ **No** ☐

xii. **about how the research is funded, including any benefit which will accrue to researchers and/or their departments**

Yes ☐ **No** ☐

***The Steering Committee considers all applications on a case by case basis and appreciates that there may be occasions where not all criteria are fulfilled. The Steering Committee reserves the right to ask for original documentation if considered necessary.**

SECTION 3 – DETAILS OF THE RESEARCH PROJECT FOR WHICH THE CELL LINE(S) IS BEING IMPORTED

3.1 Title of the project:

3.2 Has a study previously approved by the Stem Cell Steering Committee?

Yes ☐ **No** ☐

3.3 Abstract of research project including aims and objectives *(Approx. 300 words):*
(The Stem Cell Steering Committee needs to satisfy itself that hES cell lines are not used for trivial purposes and their uses are within the remit of HFEA regulations. The Stem Cell Steering Committee will not conduct a scientific review of experimental detail or repeat the peer review.)

3.4 Has the research project been subjected to peer review?

Yes ☐ **No** ☐

If yes, please provide details (Funding Body, etc):

If no, please explain why not (e.g generation of preliminary data) and state how the research will be supported:

3.5 Does the research project include experiments in animals?

Yes ☐ **No** ☐

If yes, please provide details:

3.6 Do you intend to perform experiments creating hES cell/animal embryo aggregation chimaeras?

Yes ☐ **No** ☐

If yes, please provide details:

3.7 Are all experiments involving animals covered by appropriate Home Office Animal Procedures Licences?

Yes ☐ **No** ☐

3.8 Was the stem cell line derived in clinical grade facilities accredited by an equivalent to the UK MHRA?

Yes ☐ **No** ☐

If yes, do you have access to clinical grade facilities accredited by the UK MHRA?

Yes ☐ **No** ☐

SECTION 4 – DECLARATION FOR THE IMPORT OF HUAMN EMBRYONIC STEM CELL LINES INTO THE UK

4.1 By submitting this application form, the person responsible (e.g. Head of Department at the host institution) of the recipient of the exported stem cell line(s) confirms that;

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. The cell line(s) will only be used for the following purposes:

   i) Research that is consistent with UK legislation (as specified in the Code of Practice for the Use of Stem Cell Lines and the recipient hereby agrees to abide by this Code.
   ii) Research which has the long term goal of helping to increase knowledge about serious diseases and their treatment
   iii) Basic cell research which underpins these aims
   iv) Development of cell based therapies for clinical trials in respect of serious human diseases

3. Research that does not contravene UK legislation such as human reproductive cloning.

On behalf of Host Institution
(Person Responsible [e.g. Head of Department/Dean])
Signature:

Date

Principal Investigator

Signature:

Date

Name and title of host institution Signatory:

Post held:

Institution:

Postal Address:

Country :
Tel:
Fax:
Email:

STEERING COMMITTEE FOR THE UK STEM CELL BANK AND FOR THE USE OF STEM CELL LINES

APPLICATION FORM TO:

Use stem cell lines from sources within the UK other than the UK Stem Cell Bank

---

Name and title of Principal Investigator:

Title of project

Provider of cell line(s)

Name/number of cell line(s) designated by originator

Is the cell line Clinical or Research grade?

Is the cell line listed on the Register of Steering Committee approved Stem Cell Lines? (http://www.mrc.ac.uk/index/strategy-strategy/strategy-science_strategy/strategy-strategy_implementation/strategy-government_spending_review_initiatives/strategy-stem_cells/strategy-stem_cell_governance/strategy-registry_of_stem_cell_lines.htm)

Is the cell line listed on the NIH Registry? (http://stemcells.nih.gov/research/registry/)

INSTRUCTIONS:

- **It is important that this application is understandable by lay members and abbreviations explained.**
- **Please submit this application form and a <u>one page</u> C.V of the Principal Investigator by email to the Stem Cell Steering Committee: stemcellsecretary@headoffice.mrc.ac.uk**
- **For further information please contact the secretary for the Steering Committee at: stemcellsecretary@headoffice.mrc.ac.uk**
- **Or for scientific queries please contact Dr Robin Buckle at: Robin.Buckle@headoffice.mrc.ac.uk**

Key to abbreviations:

hES = Human Embryonic Stem (cell line)
MHRA = Medicines and Healthcare products Regulatory Agency
HFEA = Human Fertilisation and Embryology Authority
NIH = National Institutes of Health

SECTION 1 – CONTACT DETAILS

1.1 Principal investigator (***attach a one page C.V.***)

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

1.2 Contact person if different from person listed at 1.1

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

1.3 Collaborators (Name and institution of Principal Investigators who wish to have access to hES cell lines as part of this application)
(You must inform the Stem Cell Steering Committee if collaborators join the project subsequent to this application)

SECTION 2 – DETAILS OF CELL LINE(S)

2.1 Provider of cell line(s) and contact details

Name and title:

Post held:

Address:

Tel:
Fax:
Email:

2.2 For hES cell lines derived in the UK, please provide the HFEA Licence number

2.3 For hES cell lines derived abroad that are not listed on the Register of Steering Committee approved Stem Cell Lines or the NIH Registry, please complete the following:

a) Was the study to derive the cell line(s) approved by an ethics committee (or its equivalent if the application is from overseas)?

Yes ☐ **No** ☐

b) Have you clarified with the consenting clinician that informed consent in line with UK guidelines has been given?
(The following criteria constitute best practice in the UK. Please tick as appropriate)

At the time of consenting, the Donor was informed*:

i. about the specific research project, including any tests may be performed as part of the licensed research project on embryos or cells derived from the embryos

Yes ☐ **No** ☐

ii. that any stem cells lines created may continue indefinitely and be used in many different research projects

Yes ☐ **No** ☐

iii that the decision whether to donate will not affect their treatment in any way;

Yes ☐ **No** ☐

iv. about whether the embryos will be reversibly or irreversibly anonymised, and the implications of this

Yes ☐ **No** ☐

v. whether any information will be fed back to the donors

Yes ☐ **No** ☐

vi. that the donors can vary or withdraw the terms of their consent until the point the embryos are used in the project of research

Yes ☐ **No** ☐

vii. that once an embryo has been used in the project of research the donors have no control over any future use of the embryonic cells and any stem cell lines derived

Yes ☐ **No** ☐

viii. that stem cell lines derived in this project will be deposited in the UK Stem Cell Bank and the implications of this including they may be used for other projects

Yes ☐ **No** ☐

ix. that stem cell lines must not be generated from donated embryos where the consent from the relevant donors, or one of them, places a constraint on future use

Yes ☐ **No** ☐

x. that cell lines may be used for commercial purposes, but that the donor will not benefit financially from this

Yes ☐ **No** ☐

xi. that any cell lines derived, or discoveries made using them, could be patented, but that the donor will not benefit financially from this

Yes ☐ **No** ☐

xii. about how the research is funded, including any benefit which will accrue to researchers and/or their departments

Yes ☐ **No** ☐

*__The Steering Committee considers all applications on a case by case basis and appreciates that there may be occasions where not all criteria are fulfilled. The Steering Committee reserves the right to ask for original documentation if considered necessary.__

SECTION 3 - DETAILS OF THE RESEARCH PROJECT FOR WHICH THE CELL LINE(S) IS BEING USED

3.1 Title of the project:

3.2 Has a study previously approved by the Stem Cell Steering Committee?

Yes ☐ **No** ☐

3.3 Abstract of research project including aims and objectives *(Approx. 300 words):*
(The Stem Cell Steering Committee needs to satisfy itself that hES cell lines are not used for trivial purposes and their uses are within the remit of HFEA regulations. The Stem Cell Steering Committee will not conduct a scientific review of experimental detail or repeat the peer review.)

3.4 Has the research project been subjected to peer review?

Yes ☐ **No** ☐

If yes, please provide details (Funding Body, etc)

If no, please explain why not (e.g generation of preliminary data) and state how the research will be supported

3.5 Does the research project include experiments in animals?

Yes ☐ **No** ☐

If yes, please provide details

3.6 Do you intend to perform experiments creating hES cell/animal embryo aggregation chimaeras?

Yes ☐ **No** ☐

If yes, please provide details

3.7 Are all experiments involving animals covered by appropriate Home Office Animal Procedures Licences?

Yes ☐ **No** ☐

3.8 Was the stem cell line derived in clinical grade facilities accredited by the UK MHRA?

Yes ☐ **No** ☐

If yes, do you have access to clinical grade facilities accredited by the UK MHRA (?

Yes ☐ **No** ☐

SECTION 4 - DECLARATION TO USE HUMAN EMBRYONIC STEM CELL LINES FROM SOURCES OTHER THAN THE UK STEM CELL BANK

4.1 By submitting this application form, the person responsible (e.g. Head of Department at the host institution) of the recipient of the exported stem cell line(s) confirms that;

the cell line(s) (insert name/no) will only be used for the following purposes:

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. Research that is consistent with UK legislation (as specified in the Code of Practice for the Use of Stem Cell Lines* and the recipient hereby agrees to abide by this Code.

   (a) research which has the long term goal of helping to increase knowledge about serious diseases and their treatment
   (b) basic cell research which underpins these aims
   (c) development of cell based therapies for clinical trials in respect of serious human diseases

3. Research that does not contravene UK legislation such as human reproductive cloning.

On behalf of Host Institution
(Person Responsible [e.g. Head of Department/Dean])
Signature:

Date

Principal Investigator

Signature:

Date

Name and title of host institution Signatory:

Post held:

Institution:

Postal Address:

Country :
Tel:
Fax:
Email:

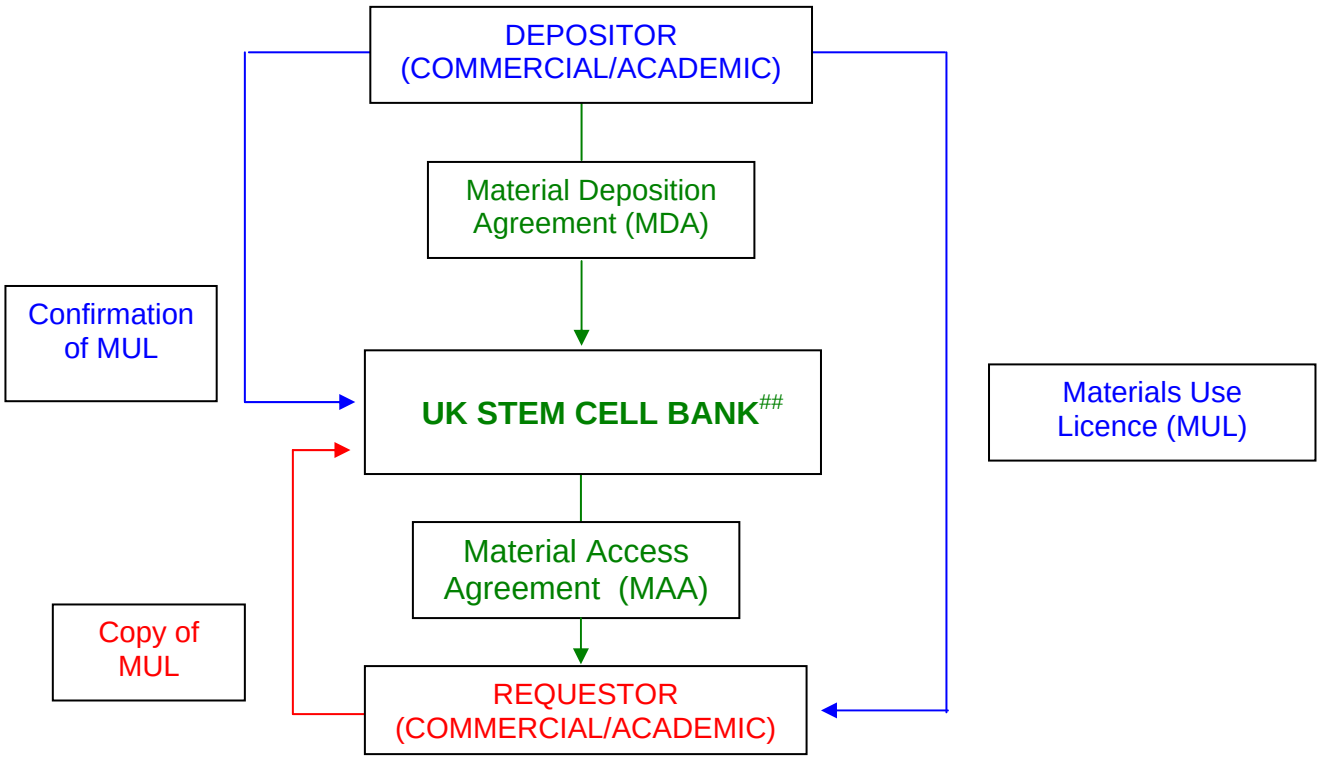
TERMS AND CONDITIONS FOR DEPOSITION AND ACCESS OF HUMAN STEM CELL LINES

Background

The UK Stem Cell Bank (Bank) will provide access to new and existing ethically approved, quality controlled stem cell lines. The Bank has been located in an independent national institution rather than an academic laboratory to avoid possible conflicts of interests. Depositors and users of the Bank will include academics and industrialists from the UK and overseas and depositions will be sought worldwide.

Transferring biological material to any national Bank accessed by a multiplicity of users is a complex matter, no more so than in the field of stem cell research. Depositors of stem cell lines may have interests in the materials (e.g. intellectual property, confidential know-how) which they will wish to see protected and, in donating their cell lines, may wish to impose certain terms and conditions for distribution and subsequent use. The Bank will release cell lines to users provided they have obtained the "freedom to use" directly from the originator of the cell line and have also secured approval for the intended research from the Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines (Steering Committee).

It is not the intention that the Bank will take any direct interest in IP embodied in deposited cell lines or become involved in the negotiations between depositor and user. It is the intention that material transfer agreements will be required between depositor and Bank and user and Bank (respectively Material Deposition Agreement and Material Access Agreement) and that a use licence will be required by the user from the depositor (owner) of the cell line. The following scenario is envisaged for deposition of and access to materials:



Use of the Bank for both deposition and access requires Steering Committee approval

Deposition

Depositors (i.e. the Institution or Company owning the cell line in question) shall sign a Materials Deposition Agreement (MDA) with the Bank agreeing to make the cell lines available to requestors, on terms of access to be agreed between depositor and requestor. Approval to deposit the line must first be secured from the Steering Committee.

Access

Requestors (i.e. the host Institution of the Principal Investigator wishing to access the banked stem cell line) approaching the Bank for access to a cell line will be advised to contact the depositor with whom a Materials Use Licence (MUL) must be signed. Once agreement has been reached, the depositor confirms to the Bank that the cell line may be released. The requestor must then sign a Material Access Agreement (MAA) with the Bank (the MUL must be attached) and the cell line will be released. Approval for research using the cell line must first be secured from the Steering Committee. Where negotiations on the MUL are protracted, the Steering Committee may decide to give "in principle" approval to access the banked cell line subject to the signed MUL being provided prior to access.

Terms and Conditions for deposition in and access to stem cell lines in the Bank

The following Terms and Conditions will be applied both to depositors and accessors of cell lines, provided they have first secured approval from the Steering Committee. A standard MDA and MAA will available from the Bank for signature by depositors and accessors.

Deposition of cell lines in the UK Bank

Cell lines will be deposited under an MDA with the Bank. This will specify that the depositor agrees to the following:

- The cell line is available for distribution
- Research grade cell lines will be made available for research purposes only
- Clinical grade cell lines will be made available for research leading to the development of therapies and/or use in clinical studies
- In the case of human embryonic stem cell lines, Steering Committee approval must be obtained if stem cell lines are passed on to third parties.
- Cell lines must not be sold for financial gain
- The cell line will be made available to requestors who have agreed and signed an MUL with the depositor (see below). Where the requestors are academics who have no pre-existing commercial obligations this procedure is expected to be straight forward with minimum delay to supplying the cell line
- Where the depositor is a company, the company may exercise a first option to negotiate a licence to any Intellectual Property (IP) arising from use of the cell line by the academic group
-

- Where the depositor is an academic body, it would be more usual to seek a revenue share on any products developed

Interface with Depositor

The cell line will be listed on the Bank website after verification by the Bank .
It may be possible to embargo release of cell lines for 12 months after acceptance into the Bank in a restricted field upon approval by the Steering Committee of a justified case. In exceptional circumstances requests for longer embargo periods may be considered by the Steering Committee. The restricted field is expected to reflect the research (academics) or business (companies) interest of the depositor and must be specific to cell type (e.g. a restricted field of generating dopamine producing cells for Parkinson's Disease would be acceptable, whereas use of the cell line for any research into neuroscience would be unacceptable).

- Distribution by the Bank will be subject to a Materials Use Licence (MUL) being signed between depositor and accessor
- The terms of such an MUL must:
  - require that any clinical studies carried out using stem cell lines from the Bank will be carried out in clinical grade facilities accredited by the Medicines and Healthcare products Regulatory Agency if conducted in the UK, or in equivalent facilities accredited by an equivalent national authority if conducted elsewhere
  - address development of therapies and ensure there are no terms that could prevent development of therapies (except in the case of research-only studies on non-GMP lines)
- The terms of such an MUL may include the following:
  - reasonable financial terms for the licence
  - no upfront fee should be expected from academics
  - a reasonable upfront fee may be applied to commercial users
  - revenue share on products developed may be acceptable and these should conform to industry standard
  - the MUL may relate to a specific project or use

Access to banked cell lines

- Academics accessing cell lines will be expected to contribute towards the marginal costs of running the Bank
- Commercial users will be expected to pay full economic costs for accessing cell lines
- Academics engaged in contract research on behalf of companies will be expected to pay full economic costs
- The MAA will specify that:
  - NIBSC cannot warrant that the cell lines are free of extraneous agents, or biologically active contaminants (e.g. TSE's) which may have been present in donor samples and for which there are currently no effective screening tests. Or that the use or supply of the cell lines will not infringe any patent, copyright, trademark or other right of any third party.
    It will be for the recipient to decide whether he/she needs or wishes to take further third party licences, other than the MUL available from the depositor
  - Users of banked cell lines must deposit any further cell lines developed through use of the material back with the Bank
  - In the case of human embryonic stem cell lines, Steering Committee approval must be obtained if stem cell lines are passed on to third parties.

- Cell lines must not be sold for financial gain
- Research grade cell lines will be made available for research purposes only, and clinical grade cell lines for research leading to the development of therapies and/or use in clinical studies
- The cell lines must not be used for reproductive cloning (which is illegal in the UK)
- The user may protect and commercialise any intellectual property arising from use of the cell lines (subject to the agreement they have in place with the depositor, MUL)
- The user will acknowledge the Bank, the cell line and the depositor in publications and a copy of each publication must be lodged with the Secretariat of the Steering Committee; the Secretariat is located at MRC Head Office
- the Steering Committee will have the right to seek independent audit of the research carried out using the accessed stem cells to ensure compliance with appropriate regulations and permissions

MATERIALS ACCESS AGREEMENT

This Agreement is made on the …….. day of …….. , 200…

BETWEEN

(1) NIBSC ……..

and

(2) [*REQUESTOR*] whose principal place of business is situated at [*address*] (hereinafter called "the REQUESTOR").

In respect of the following material:

(3) [Name/Number of Cell Line designated by the DEPOSITOR] …….

WHEREAS

(A) NIBSC is responsible for managing the UK Stem Cell Bank (the "BANK" as hereinafter defined) funded by Medical Research Council (hereinafter referred to as "MRC") and the Biotechnology and Biological Sciences Research Council.

(B) The DEPOSITOR has developed the stem cell line described hereunder as MATERIAL and has deposited it in the BANK.

(C) REQUESTOR wishes to obtain the MATERIAL to use in its research and has (i) obtained the necessary permission from the STEERING COMMITTEE to undertake the work and (ii) has entered into an appropriate agreement with DEPOSITOR to allow access to DEPOSITOR's MATERIAL.

(D) This Agreement sets out the terms and conditions under which NIBSC will supply the deposited MATERIAL to REQUESTOR.

NOW IT IS HEREBY AGREED AS FOLLOWS

1. DEFINITIONS AND INTERPRETATION

1.1 In this agreement the following words and phrases shall have the following meanings unless the context requires otherwise:

(a) "The Effective Date" shall mean the date of last signature of this Agreement.

(b) "The MATERIAL" shall mean the stem cell line requested by the REQUESTOR. Any derivatives thereof generated by the REQUESTOR shall be deposited in the BANK through a separate application.

(c) "DEPOSITOR" shall mean the Institution or Company owning the cell line that deposited sample(s) of the MATERIAL(S) in the BANK.

(d) "STEERING COMMITTEE" shall mean the Stem Cell Steering Committee established by MRC to oversee the BANK and the use of stem cell lines. The membership and terms of reference of the STEERING COMMITTEE can be found on the MRC website (**www.mrc.ac.uk**)

(e) "RESEARCH" means the programme of work to be undertaken by the REQUESTOR and approved by the STEERING COMMITTEE. [A copy of the approval letter/notification is attached at Schedule 1].

(f) "DOCUMENTS" means written evidence of both STEERING COMMITTEE approval pursuant to Clause 2.1 and agreement between DEPOSITOR and REQUESTOR for RESEARCH involving MATERIAL, copies of which are attached at Schedule 1.

(g) "PRINCIPAL INVESTIGATOR" means the UK HFEA licence holder in the case where MATERIAL is an embryonic stem cell line.

(h) "REQUESTOR" means the host Institution of the Principal Investigator wishing to access the banked stem cell line.

2. ACCESS TO AND USE OF MATERIALS

2.1 REQUESTOR will submit an application to the STEERING COMMITTEE for approval to access the MATERIAL for use in the research project and/or clinical trials specified in the application.

2.2 The REQUESTOR shall agree appropriate terms with the DEPOSITOR in a Material Use Licence (MUL) for access to and use of the MATERIAL provided that:

(i) the MUL will conform to the guidelines: The UK Stem Cell Bank: Terms and Conditions for deposition and access of human stem cell lines (MRC, 2004) a copy of which is attached at Schedule 2; and

(ii) where the MATERIAL is used in a clinical trial then the MUL must address procurement of the appropriate permission from regulatory bodies and the liability and indemnity issues arising from such use to the satisfaction of both NIBSC and the STEERING COMMITTEE; and

(iii) where the REQUESTOR is an academic body or scientist access shall be free of consideration, though the BANK will make a charge to cover marginal costs; and

(iv) where the REQUESTOR is a company or a for-profit organisation then the BANK will charge full economic costs for the supply of cell lines. This charge shall be separate from any consideration that the REQUESTOR may seek under the terms of the MUL.

(v) where the DEPOSITOR is a company and the REQUESTOR is an academic body or scientist the DEPOSITOR may seek an option to negotiate a licence to any intellectual property arising from the REQUESTOR's research and/or clinical trials.

(vi) Where negotiations on the MUL are protracted, the Steering Committee may decide to give "in principle" approval to access the banked cell line subject to the signed MUL being provided prior to access.

2.3 Upon execution of this Agreement and supply of the DOCUMENTS to NIBSC, then NIBSC agrees to supply REQUESTOR with the MATERIAL for academic or in-house research and/or clinical trials purposes only in accordance with the RESEARCH approved by the STEERING COMMITTEE.

To avoid doubt use of the MATERIAL will be subject to the provisions of the MUL and shall not under any circumstances be used for reproductive cloning.

2.4 The REQUESTOR recognises that the MATERIAL may be embargoed for a period of time in a specified field and may therefore be unavailable until such embargo terminates. The period of the embargo could be up to twelve months from the deposit date, or longer in exceptional circumstances as agreed by the STEERING COMMITTEE.

2.5 Notwithstanding anything to the contrary in this Agreement, the terms and conditions set out herein are supplemental to any legal or regulatory requirements governing research and/or clinical trials involving material derived from stem cells that may be in force from time to time, which legal or regulatory requirements will take precedence over any term of this Agreement.

2.6 Where the MATERIAL is a human embryonic stem cell line, any third party transfers must be approved by the Steering Committee.

2.7 Where the MATERIAL comprises a non-embryonic human stem cell line a REQUESTOR who intends to pass the MATERIAL to a third party must first remove the unique BANK accession number. Similarly, the third party recipient must not under any circumstances refer to such a cell line, either orally or in writing, as having been accessioned from the BANK.

2.8 In the event that the results of the RESEARCH lead to clinical trials of any products then REQUESTOR shall procure that such trials and products, whether conducted or produced by REQUESTOR or a partner or licensee of REQUESTOR, shall be carried out in clinical grade facilities accredited by the Medicines and Healthcare products Regulatory Agency in the UK, or in equivalent facilities accredited by an equivalent national authority if conducted elsewhere.

2.9 The REQUESTOR must put mechanisms in place to i) identify all adverse events resulting from use of the MATERIAL and ii) report such adverse events immediately to the BANK.

3. CONFIDENTIALITY

3.1 Each party agrees not to use or refer to this Agreement in any promotional activity, or use the names or marks of the other without express written permission.

3.2 The obligations of confidence referred to in this Clause 3 shall not extend to any information which:

(a) is or becomes generally available to the public otherwise than by reason of a breach by the recipient party of any provision of this Clause 3; or

(b) is known to the recipient party and is at its free disposal prior to its receipt from the other; or

(c) is subsequently disclosed to the recipient party without obligations of confidence by a third party owing no such obligations to the disclosing party in respect thereof; or