CALIFORNIA CODE OF REGULATIONS
TITLE 17, DIVISION 4
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

CHAPTER 1. HUMAN EMBRYONIC STEM CELL RESEARCH

Section 100000 Scope of Chapter

(a) All CIRM grantees shall be required to adhere to this Chapter for CIRM-sponsored research. This Chapter covers all research funded by the California Institute for Regenerative Medicine ("CIRM") that involves the derivation of human embryonic ("hES") cell lines or the use of hES cells derived from:

(1) Blastocysts originally created for reproductive purposes which are no longer required for such purpose and later obtained for research from in vitro fertilization ("IVF") clinics.

(2) Blastocysts made specifically for research using IVF.

(3) Somatic cell nuclear transfer ("NT") into oocytes.

(4) Any other source or by any other procedure.

(b) This chapter does not apply to:

(1) Research that uses nonhuman stem cells.

(2) Reproductive uses of nuclear transfer, which are prohibited by article XXXV, section 3 of the California Constitution.

Section 100001 Categories of hES Cell Research

This chapter specifies categories of CIRM-sponsored research that:

(a) Are permissible after currently mandated reviews and proper notification of the relevant research institution.

(b) Are permissible after additional review by an Embryonic Stem Cell Research Oversight ("ESCRO") committee, as described in Section 100006.

(c) Are prohibited at this time.

Section 100002 hES Cell Research Eligible for CIRM Funding After Currently Mandated Reviews

(a) 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, as described in Section 100006, receives documentation of: (i) the provenance of the cell lines; (ii) appropriate informed consent in their derivation; and (iii) evidence of compliance with any required review of the proposed research by an Institutional Review Board (IRB), Institutional Animal Care and Use Committee (IACUC), or Institutional Biosafety Committee (IBC), or other mandated review.

(b) hES cell lines approved by the National Institutes of Health, deposited in the United Kingdom Stem Cell Bank, or derived by, or approved for use by, a licensee of the Human Fertilisation and Embryology Authority shall be deemed to have complied with the requirements for informed consent and donor compensation and therefore do not require documentation by the ESCRO committee or equivalent body designated by the investigator's institution. hES cell lines derived under equivalent standards to the United Kingdom Stem Cell Bank or such other benchmark organizations, as recommended by the Standards Working Group and approved by the Independent Citizens' Oversight Committee, would also qualify for this exception for documentation for informed consent and donor compensation. The ESCRO committee, the Standards Working Group, or a committee established by the Standards Working Group and approved by the Independent Citizens' Oversight Committee, shall determine whether the standards are equivalent to the United Kingdom Stem Cell Bank.

Section 100003 hES Cell Research Eligible for CIRM Funding Only After Additional Review and Approval

The following research is permissible after additional review and written approval by an Embryonic Stem Cell Research Oversight (ESCRO) committee, as described in Section 100006:

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

(b) Research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development; provided that investigators evaluate the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues.

(c) 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.

Section 100004 hES Cell Research That is Prohibited

The following activities are prohibited:

(a) The culture in vitro of any intact human embryo, regardless of derivation method, after the appearance of the primitive streak or after 12 days whichever is earlier. The 12 day prohibition does not count any time during which the blastocysts and/or cells have been stored frozen.

(b) The introduction of hES cells into nonhuman primate blastocysts and the introduction of any embryonic stem cells into human blastocysts.

(c) The breeding of an animal into which hES cells have been introduced at any stage of development.

Section 100005 Obligations of Investigators and Institutions

All scientific investigators and their institutions, regardless of their field, shall be responsible for ensuring that they conduct themselves in accordance with professional standards and with integrity. In particular, investigators whose research involves hES cells shall 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.

Section 100006 Establishment of an Institutional Embryonic Stem Cell Research Oversight Committee

(a) To provide oversight of all issues related to the procurement and use of hES cell lines and to facilitate education of investigators involved in hES cell research, each institution involved in hES cell research funded by the CIRM shall establish an Embryonic Stem Cell Research Oversight ("ESCRO") committee. The committee shall include representatives of the public and persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hES cell research, and shall be capable of conducting its own review, including, where necessary, management of various other reviews required for a particular protocol. This provision does not preclude the establishment of a joint ESCRO committee that would assume oversight responsibilities for two or more research institutions, provided the ESCRO has oversight authority for each institution consistent with the requirements of this chapter.

(b) A pre-existing committee may serve the functions of the ESCRO committee provided that it has the recommended expertise and representation to meet the

requirements of this section. An institution may constitute an ESCRO committee from among members or staff of an existing IRB. The ESCRO committee, however, shall not be a subcommittee of the IRB

(c) The ESCRO committee shall:

(1) Provide oversight over all issues related to the procurement and use of hES cell lines.

(2) Review and approve in writing the scientific merit of research protocols, as required by Section 100008.

(3) Review compliance of all in-house hES cell research with all relevant regulations and these guidelines.

(4) Maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators.

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

(6) Maintain, at a minimum, a registry of stem cell lines, including information regarding all of the following, unless the requirement for documentation has been waived pursuant to subdivision (b) of section 100002: (1) whether the cells were obtained ethically and with informed consent in a manner consistent with Section 100007; (2) whether they are well-characterized and screened for safety; (3) the conditions under which they are maintained and stored.

Section 100007 Procurement of Gametes, Blastocysts or Cells for hES Generation

(a) An IRB that meets the membership requirements established by section 46.107 of title 45 of the Code of Federal Regulations shall review the procurement of all gametes, blastocysts, or somatic cells for the purpose of generating new hES cell lines, including 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.

(b) Consent for donation shall be obtained from each donor, including individuals who have given prior indication of their intent to donate to research any blastocysts that remain after clinical care, at the time of donation. Donors shall be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

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

(d) (1) 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 shall not be reimbursed for the costs of storage prior to the decision to donate.

(2) Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for NT) shall be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an IRB. No payments, cash or in-kind, shall be provided for donating oocytes for research purposes. Similarly, no payments shall be made for donations of sperm for research purposes or for donations of somatic cells for use in NT.

(e) To facilitate autonomous choice, decisions related to the creation of embryos for infertility treatment shall 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 shall not be the same person.

(f) (1) In the context of donation of gametes or blastocysts for hES cell research, the informed consent process, shall, at a minimum, provide the following information:

(A) A statement that the blastocysts or gametes will be used to derive hES 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 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; provided, however, that traceable information shall be secured to ensure confidentiality.

(F) A statement that derived hES cells and/or cell lines might be kept for many years.

(G) A statement that the hES and/or cell lines might be used in research involving magnetic 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 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.

(2) Donors could be offered the option of agreeing to some forms of hES cell research but not others. The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored.

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

(h) Researchers shall be prohibited from asking 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 shall not pay, or be paid, for the material obtained, except for cost-based reimbursements and payments for professional services.

Section 100008 Derivation of hES Cell Lines

(a) Requests to the ESCRO committee for permission to attempt derivation of new hES cell lines from donated embryos or blastocysts or from any other source or by any other procedure shall include evidence of written approval by an IRB of the procurement process as required by section 100007.

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

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

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

(e) Blastocysts made using NT (whether produced with human or nonhuman oocytes) and parthenogenetic or androgenetic human embryos shall not be transferred to a human or nonhuman uterus and shall not be cultured as intact embryos *in vitro* after the appearance of the primitive streak or 12 days after cell division begins, whichever is earlier. The 12-day prohibition does not count any time during which the blastocysts and/or cell have been stored frozen.

(f) Investigators shall 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.

Section 100009 Banking and Distribution of hES Cell Lines

(a) Institutions engaged in CIRM-Funded hES derivation or research shall be encouraged at present and possibly mandated in the future to create or participate in central repositories for hES cell lines, including through partnerships or augmentation of existing quality research cell lines repositories, and shall adhere to high ethical, legal, and scientific standards consistent with Section 100009(a) and Section 100007.

(b) Cell lines derived or modified in any way with CIRM-funds are required to be shared through a well recognized stem cell bank that will make the lines widely available to investigators. Cell lines derived or modified in any way with CIRM-funds are required to be deposited in a bank in a timely manner.

(c) CIRM encourages but does not require the following:

(1) Institutions that are banking or plan to bank hES cell lines should establish: (A) uniform guidelines to ensure that donors of material give informed consent through a process approved by an IRB and that records are maintained about all aspects of cell culture and (B) uniform tracking systems and common guidelines for distribution of cells.

(2) Any facility engaged in obtaining and storing hES cell lines should:

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

(B) Establish documentation requirements for investigators and sites that deposit cell lines, including:

(i) A copy of the donor consent form.

(ii) Proof written approval by an Institutional Review Board 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 lines 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) Establish 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) Establish 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 Website 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, including 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) Establish clear criteria for distribution of cell lines, including but not limited to evidence of written approval of the research by an embryonic stem cell research oversight committee or equivalent body at the recipient institution.

Section 100010. Research Use of hES Cell Lines

(a) 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) shall monitor their use in research.

(b) Institutions shall require documentation of the provenance of all hES cell lines, whether the cells were imported into the institution or generated locally, unless the requirement for such documentation has been waived pursuant to subdivision (b) of Section 100002. Notice to the institution shall include evidence of written IRB-approval of the procurement process, evidence of and adherence to basic ethical and legal principles of procurement. In the case of lines imported from another institution, documentation that these criteria were met at the time of derivation will suffice.

(c) *In vitro* experiments involving the use of already derived and coded hES cell lines shall not require review beyond the notification required in Section 6.1.

(d) Each institution shall 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.

(e) All protocols involving the combination of hES cells with nonhuman embryos, fetuses, or adult animals shall 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.

(f) Experiments in which hES cells, their derivatives, or other pluripotent cells are introduced into nonhuman fetuses and allowed to develop into adult chimeras shall be carefully reviewed, including consideration of any major functional contributions to the brain

(g) Introduction of hES cells into nonhuman mammalian blastocysts shall be considered only under circumstances in which no other experiment can provide the information needed.

(h) 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 identify of the donors of the blastocysts, gametes, or somatic cells is readily ascertainable or might become known to the investigator.

Section 100011. 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.