As part of its commitment to public participation in the development of scientific, medical and ethical standards; the Scientific and Medical Accountability Standards Working Group of the California Institute of Regenerative Medicine is providing Draft CIRM Regulations to all interested parties. Additional supporting document may be found at: http://www.cirm.ca.gov/working_group/standards.asp. The Scientific and Medical Accountability Standards Working Group is committed to an open, inclusive and deliberative process. This working group invites participation at all of its open meetings. CIRM and its working groups' commitment to public participation goes beyond that required by California law. Pursuant to the California Administrative Procedure Act, additional public participation will be invited once the rulemaking record is open.

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

CHAPTER 1. STEM CELL RESEARCH

Section 100000 Scope of Chapter & Intent

Under the authority of the California Health and Safety Code Section 125290.35 the Independent Citizens Oversight Committee (ICOC) establishes medical and scientific accountability standards for the conduct of stem cell research as authorized by Article 35 of the California Constitution. It is the intent of the ICOC in the enacting this chapter to assure that CIRM-funded research is conducted safely, in accordance with the highest ethical standards, and in compliance with state and national policies that protect patient safety, patient rights and patient privacy.

The standards set forth in this chapter apply to all *institutions* (as defined by CFR 46.102) performing *research* (as defined in 45 CFR Part 46.102) funded by the California Institute of Medicine (CIRM) as authorized by Article 35 of the California Constitution.

The policy is intended to govern the oversight of CIRM-funded research.[1] It is the intent of the ICOC, in the enacting this chapter, to require each funded institution to be responsible for providing assurance satisfactory to CIRM that research complies with the requirements set forth in this policy.

Section 100001 Definitions

As used in this chapter the following terms have the following meaning:

(a) *Covered stem cell line*: A culture-derived, self renewing human cell population that thought to be capable of tri-lineage differentiation potential into tissues of the endoderm, ectoderm and mesoderm. This definition includes both embryonic and non embryonic human stem cell lines regardless of the original tissue of origin.

[1] Previous draft focused on *research involving derivation and use of human stem cells*. This scoping is more consistent with Proposition 71 mandate. See section 125290.55.

or

Covered stem cell line: A culture-derived, human stem cell population which is capable of: 1) sustained propagation in culture, 2) differentiation along multiple cell lineages, and 3) self-renewing to produce daughter cells with equivalent developmental potential. This definition includes both embryonic and non-embryonic human stem cell lines regardless of the tissue of origin.

(b) *Ethically derived:* Stem cells derived in accordance with the requirements of section 100007.

(c) *Expenses:* necessary and reasonable costs directly incurred or expended as a result of donation or participation in research activities.[2]

(d) *Funded research:* research as defined by CFR 46.102 supported in whole or part by funds authorized by article XXXV of the California Constitution. For the purpose of this chapter, training activities supported by such funds shall be considered funded research.[3]

(e) *Human subjects*: as defined by 45 CFR 46.102.[4] [i]

(f) *Institution:* as defined by 45 CFR 46.102.[ii]

(g) *Research:* as defined by 45 CFR 46.102.[iii]

(h) *Stem Cell Research Oversight Committee (SCRO committee):* a committee established in accord with Section 100005 for the purpose expressed in this chapter.[5]

(i) *Somatic Cell Nuclear Transfer (SCNT):* The transfer of a cell nucleus from a somatic cell into an egg (oocyte) ~~or another cell~~ from which the nucleus has been removed.

(j) *Stem Cells:* undifferentiated (i.e., nonspecialized) cells that have the capacity to self-renew (i.e., one or both progeny retain the undifferentiated state) and, to differentiate into mature cells with specialized functions.[6]

Section 100002 Activities Not Eligible for CIRM Funding

The following activities are not eligible for CIRM funding:

(a) Reproductive uses of SCNT (human reproductive cloning) prohibited by article XXXV section 3 of the California Constitution.

(b) 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.

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[2] See Reimbursement Working Notes 11.
[3] Received comments requesting clarification whether training activities constitute *research*.
[4] This definition is consistent with federal regulations regarding informed consent.
[5] SCRO committee is more consistent with the function described in these regulations. See public comment #32.
[6] This definition is identical to the definition used in the CIRM Grants Administration Policy.

(c) The introduction of covered stem cells human stem cells into nonhuman primate[7] blastocysts.

(d) The introduction of covered stem cells, whether human or nonhuman, into human blastocysts.[8]

(e) Research leading to or resulting in the breeding of any animal into which covered stem cells have been introduced.

Section 100003 Institutional Assurances of Compliance

All research institutions shall be responsible for providing written assurance satisfactory to CIRM that CIRM-funded research complies with the requirements set forth in this chapter.[9]

Each institution shall at a minimum:

(a) Designate an institutional official responsible for oversight and documentation of compliance for CIRM-funded research.

(b) Designate one or more SCRO committee established in accordance with the requirements of section 100005.[10]

(c) Designate one or more IRB established in accordance with 45 CFR Part 46.

(d) Ensure that clinical personnel who have a conscientious objection to stem cell research 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.

Section 100004 Compliance

All conditions set forth in this chapter will be complied with as a condition of releasing research funds. Failure to comply with requirements set forth in this chapter constitutes ground for [repayment?] non-continuation of existing, or disqualification for future, CIRM funding.

Section 100005 SCRO Committee Membership and Function

An institution, a group of institutions, the CIRM or other state agency may convene an SCRO committee. An SCRO committee may provide oversight for two or more funded research institutions, provided the SCRO committee has oversight authority consistent with the requirements of this chapter.

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[7] Consistent with NA Guidelines; in previous "primate" was accidentally omitted.
[8] (c) and (d) were previously in one subsection; they have been separated for clarity.
[9] Written assurance will be provided pursuant to the CIRM Grants Administration Policy; this policy has not yet become regulation, so it cannot be cited in this draft.
[10] The regulations allow for joint or shared SCRO committee see 100005. *Designating a* SCRO committee as opposed to *creating* a SCRO committee is intend to be clear that each institution does not need to create a unique committee. Final language may be modified to confirm with OAL requirements.

(a) Membership: An SCRO committee shall be comprised of persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical ~~and legal~~[11] issues in stem cell research with at least one representative of the public[12] who is not affiliated with the research institution.

(b) Function and operation: The designated SCRO committee shall provide expertise to support the scientific and ethical review of CIRM-funded research consistent with the requirements of Section 100006, and other applicable CIRM requirements. The SCRO committee shall facilitate education of investigators with applicable requirements of this chapter.

Section 100006 SCROC Review & Notification

(a) The designated SCRO committee shall review and approve in writing all CIRM-funded research attempting to derive covered stem cell lines or research which otherwise involves the use of human oocytes or blastocysts. This requirement includes, but is not limited to, attempted derivation of new stem cell lines from donated blastocysts, oocytes, sperm, somatic cells or by SCNT.[13] CIRM-funded research involving derivation of covered stem cell lines or use of human oocytes or blastocysts cannot commence without SCRO committee approval. The designated SCRO committee can require that modification be made to proposed research or documentation of compliance with the requirements of 100006(a)(3) as a condition of granting its approval.[14] At a minimum, the SCRO committee shall require the investigator to:

(1) Provide a clearly presented scientific rationale for the need to derive human stem cell lines. When such research involves the use of oocytes and blastocysts, a justification for the number needed for derivation shall be provided. If SCNT is proposed as a route to generating human stem cell lines, justification for SCNT shall be provided.

(2) Demonstrate ~~appropriate~~ experience, expertise or training in derivation or culture of human or nonhuman stem cell lines before approval is given.

(3) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.[15]

(4) Document how stem cell lines will be characterized, validated, stored, and distributed to ensure that the confidentiality of the donor(s) is protected.[16]

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[11] Modification base on comment from workshop, institutions have legal expertise available and such expertise should not mandate on the SCRO committee.
[12] The NA guidelines specify a "member of the public." One commenter indicated that "public" is vague. Another commenter suggested "lay-member of the public."
[13] This requirement is substantially from existing NA Guidelines requirements.
[14] see comment #33, reviewer suggests that regulations should be clear that research cannot commence without approval, but allows for conditional approval. Preserves the policy that order of ESCRO/IRB review is not prescribed in regulation.
[15] 1-3 are from the National Academy Guidelines.
[16] This is intended to capture the intent of recommendation 12 in the NA Guidelines.

(b) The designated SCRO committee shall review and approve in writing all CIRM-funded research attempting to introduce covered stem cell lines into human or non-human animals at any state of embryonic, fetal, or postnatal development. CIRM-funded research involving the introduction of covered stem cell lines cannot commence without SCRO committee approval. The designated SCRO committee can require that modification be made to proposed research or documentation of compliance with the requirements of 100006(b)(3) as a condition of granting its approval. At a minimum, the SCRO Committee shall require the investigator to:

(1) Provide assurance[17] that all covered stem cell lines have been ethically derived.

(2) Evaluate the probable pattern and effects of differentiation and integration of the human cells into the human[18] or nonhuman animal tissues.

(3) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, ICB, or other mandated review.

(c) The investigator shall provide written notification to the designated SCRO Committee for all purely in vitro CIRM-funded research utilizing covered stem cell lines. At a minimum, the notification shall:

(1) Provide assurance that all covered stem cell lines have been ethically derived.

(2) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, ICB, or other mandated review prior to commencing research.

Section 100007 Acceptable Research Materials

All human covered stem cell lines obtained from human subjects or through the procurement of gametes or blastocysts for use in CIRM-funded research must be ethically derived.[19]

(a) For human covered stem cell lines derived with CIRM funding after the effective date of this chapter to be considered ethically derived, the SCRO committee must determine all of the following requirements are satisfied:.

(1) Informed consent has been has been obtained from all gamete, somatic cell or tissue donors in accordance with section 100008.

(2) No payments have been provided for donating gametes, blastocysts, somatic cells or tissue for research purposes.[20] Individuals may be reimbursed for expenses, as determined by an IRB, directly incurred or expended as a result of participation in

[17] Commentators were concerned that terms like “evidence” or “documentation” implied that research would need to collect consent forms and other written documentation related to the cell lines.
[18] In previous draft, review for introduction to humans was not explicit.
[19] This language says a standard of ethical derivation is intended to apply to the materials used in all funded research. a-c define what constitutes ethical derivation based on funding source and date of derivation.
[20] We would need an opinion on this, but by stating *no payment …. for research purposes* is intended to prevent the sale of these materials for research but not interfere with existing practices at IVF clinics.

research activities.[21] Individuals who consent to donate stored gametes, embryos or somatic cells may not be reimbursed for the cost of storage prior to the decision to donate. Any infertility clinic or third party responsible for obtaining consent or collecting gametes or embryos shall conform with this section.

(3) If oocytes are required for derivation and obtained from a woman providing oocytes for research and clinical infertility treatment (either for herself or another woman), CIRM-funded research shall not compromise the optimal reproductive success of the woman in infertility treatment.

(4) If gametes are required for derivation, the physician attending to any donor involved in oocyte retrieval procedures and the funded researcher shall not be same person unless an IRB has approved an exemption from this requirement.

(b) For covered stem cell lines that are to be used in CIRM-funded research, obtained from human subjects or through the procurement of gametes or blastocysts, without CIRM funding after the effective date of this chapter to be considered ethically derived, the SCRO committee must determine all of the following requirements are satisfied.

(1) Derivation of human covered stem cell lines from human subjects or through the procurement of gametes or blastocysts occurred under the oversight of an IRB (or, in the case of foreign sources, an IRB-equivalent).

(2) Voluntary and informed consent was obtained from all donors of gametes, blastocysts or somatic cells.

(3) The donation of gametes, blastocysts, somatic cells or tissue occurred without payment beyond reasonable compensation for participation. A determination of reasonable compensation shall be performed in accordance with the policies governing the institution involved in derivation activities.[22]

(c) For human stem cell lines that are to be used in CIRM-funded research that were derived before the effective date of this chapter to be considered ethically derived, the SCRO committee must determine either of the following requirements are satisfied:

(1) The human cell lines have been 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.
(2) The cell lines have been derived in accordance with the requirements of Section 100007(b).

[21] We can also define expenses. For example, necessary and reasonable costs directly incurred or expended as a result of his or her donation or participation in research activities.

[22] At the 12/1 SWG meeting a distinction was made between “expenses” in CIRM-funded research and compensation practices in outside research. The term “expenses” is not used here to allow for differences in that may exist in outside (non-CIRM funded) institutions.

Section 100008 Informed Consent Requirements

All funded human subjects research shall be performed in accordance with 45 CFR 46 Protection of Human Subjects and California Health and Safety Code Section 24173. In accordance with existing law, California Health and Safety Code Section 24173 shall not apply to a person who is conducting research as an investigator within an institution that holds an assurance with the United States Department of Health and Human Services pursuant to Part 46 of Title 45 of the Code of Federal Regulations and who obtains informed consent in the method and manner required by those regulations.[23]

(a) CIRM-funded research shall be conducted with the intent of not violating the preferences of prospective donors with regard to the use of donated materials. To ensure donors are fully informed of the potential uses of donated materials, researchers shall disclose, in addition to the general requirements for informed consent, the following. Specific items may be omitted from disclosure if the SCRO committee or IRB has made the determination that the specific item is not applicable to the CIRM-funded research or potential future use.[24]

(1) Derived cells or cell products may be kept for many years.
(2) Whether the identity(ies) of the donor(s) will be ascertainable to those who work with the resulting cells or cell products. If the identities of the donor(s) are retained (even coded), CIRM-funded researchers must discuss any plans for recontact of donors of materials used to derive cell lines and obtain consent for recontact. This requirement includes both recontacting donors to provide information about research findings and recontacting donors to ask for additional health information. Donors may be recontacted in the future only if they consent to contact at the time of donation.
(3) Researchers may use cell lines for future studies, which cannot be described at this time.
(4) Derived cells or cell products may be used in research involving genetic manipulation.
(5) Derived cells or cell products may be transplanted into humans or animals.
(6) Derived cells or cell products are not intended to provide direct medical benefit to the donor(s), except in the case of autologous donation.
(7) The donation is being made without restriction regarding who may be the recipient of transplanted cells, except in the case of autologous donations.
(8) A statement that neither consenting or refusing to donate materials for research will affect the quality of any future care provided to potential donors.
(9) Disclosure of the possibility that the results of research may have commercial potential and a statement that the donor will not receive financial or any other benefits from future commercial development.

[23] This exemption already exists in CA law.
[24] As written, the informed consent requirements of the NA Guidelines would be applied to all materials used to derived cell lines.

(b) For funded research involving the donation of oocytes, the description of foreseeable risk shall include but not be limited to information regarding the risks of ovarian hyperstimulation syndrome, bleeding, infection, and anesthesia.

(c) For funded research involving the donation of blastocysts for stem cell research, the informed consent process, should, include a statement that blastocysts will be destroyed in the process of deriving embryonic stem cells.

(d) For funded research involving the donation of the umbilical cord, cord blood or the placenta, consent shall be obtained from each [known biological parent]. Informed consent should include a statement as to whether the donated calls may be available for autologous treatment in the future.

(e) For funded research involving the donation of somatic cells for SCNT, informed consent ~~should~~ shall include a statement as to whether the donated calls may be available for autologous treatment in the future.

(f) Researchers may limit participation to those donors who agree to all future uses that are approved by appropriate scientific and ethics review panels.

(g) All researchers obtaining informed consent for the donation of oocytes for funded research shall ascertain that the donor has understood the essential aspects of the research. Researchers may meet this requirement by following a process that is approved by the designated Institutional Review Board or SCRO committee. When considering approval, the IRB or SCRO committee shall determine the process satisfactorily ascertains whether the subject has understood, at a minimum, the following points:

(1) Eggs donated for stem cell research will not be used for reproductive purposes.
(2) There are medical risks in oocyte donation, including the risks of ovarian hyperstimulation syndrome, bleeding, infection, and anesthesia..
(3) The research will not benefit them or any other individuals directly at this time.
(4) Explanation of whether stem cell lines will be derived from their oocytes through fertilization, SCNT, parthenogenesis, or some other method.
(5) Stem cell lines developed from their oocytes will be grown in the lab and shared with other researchers for studies in the future.
(6) If stem cells are to be transplanted into patients, researchers ~~may~~ might contact you to get additional information about your health.
(7) Donors receive no payment beyond reimbursement for [*expenses*].
(8) Stem cell lines derived as a result of their oocyte donation may be patented, but donors will not share in any revenue from the patents.
(9) Potential donors may decline to donate oocytes for research without any adverse impact on their clinical care.

(h) Researchers obtaining consent for gamete donation for derivation of hSC lines need to take steps to enhance the informed consent process. Measures to do so shall include, but are not limited to, adequate period of time to deliberate about the decision to donate. After such deliberation, potential donors shall initiate contact with the researchers to continue the consent and donation process.

Section 100009 Fairness and Diversity in Research

It is the intent of CIRM to ensure that women and members of minority groups are appropriately included as subjects of health research projects carried out by CIRM-funded institutions. CIRM endorses the objectives of California Health Research Fairness Act (Health and Safety Code, Sections 439.900-439.906) and Inclusions of Women and Minorities in Clinical Research Act (Health and Safety Code, Sections 100237-100239). All CIRM-funded research shall conform to the reporting requirements in the CIRM Grants Administration Policy pursuant to the objectives of these policies.

Section 100010 Research Tracking

CIRM-funded research shall be tracked, in accordance with this section.

(a) Each institution shall track CIRM-funded research activities. At a minimum, the institution shall maintain a research registry that includes, but is not limited to, documentation of:
(1) stem cell research conducted by the intuition;
(2) covered stem cells lines derived or used by institutional investigators;
(3) any required review or notification requirement as described in Section 100006,
(4) the methods utilized to characterize and screen the materials for safety;
(5) the conditions under which the materials have been maintained and stored.
(6) any additional requirements set forth in CIRM grants policy (cite regulations).

Section 100011 Materials Sharing

Stem cell lines and biomedical materials developed with CIRM funding at academic, commercial research and development organizations should be broadly disseminated. CIRM-funded research institutions shall comply with the CIRM-IP policy intended to ensure data and materials sharing.

Definitions:

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[i] *Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains*

[ii] *Institution means any public or private entity or agency (including federal, state, and other agencies).*

[iii] *Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.*