CALIFORNIA'S STEM CELL AGENCY

TO: Members of the ICOC

FROM: C. Scott Tocher, Deputy General Counsel

DATE: September 15, 2016

RE: Final Adoption of Amendments to MES Regulations

Executive Summary

In 2015, the Scientific and Medical Accountability Standards Working Group convened to consider new amendments to the MES regulations. A major policy driver of these amendments are changes brought about by is CIRM 2.0 and associated revisions to the Grants Administration Policy already approved by the ICOC. The Board authorized CIRM to initiate the rulemaking process to accomplish the proposed amendments. The rulemaking process is nearly complete and the amendments are now finalized for the ICOC's approval.

CIRM received no public comment on the proposed amendments and no changes have been proposed since the language was reviewed and approved by the Standards Working Group and the ICOC. ***Board approval is sought to close out the amendment process.***

Regulation Amendments

A following amendments (see Attachment A) were considered at a public meeting of the Standards Working Group in April 2015. The proposed amendments are grouped into three categories.

(1) Amendments intended to align MES Regulations with CIRM 2.0 & GAP revisions.

These amendments primarily involve incorporating terms such as "awardee" that are in the revised GAP. In addition, the term "human subjects research" is defined to align the MES regulations with Federal policies for protection of research subjects.

(2) Amendments intended to make the regulations clearer and easier to implement.

These amendments primarily involve section 100050 Compliance. Section 100050 contains provisions identical to those in CIRM's Grants Administration Policy. Rather that restate the requirements here, CIRM proposes referring to the applicable section of the GAP.

(3) Amendments to regulatory review and oversight.

Two policy changes relating to animal studies are proposed. The first change to section 100030 would allow the breeding of animals where covered stem cell lines have been introduced provided human genetic material does not contributed to the germ line. This policy is consistent with the 2010 National Academies' Guidelines for Human Embryonic Stem Cell Research and is designed to allow multi-generational safety studies of stem cell therapies in animal models.

The second change proposes to exempt pre-clinical animal studies, where human neural progenitor cells are transplanted to the brains of mature animals, from review by a stem cell research oversight committee provide the study is being performed pursuant to an FDA IND or IDE. The rationale for this change is twofold. First, institutional animal care and use committees (IACUCs) provide oversight for animal studies. Second, a major goal of the CIRM 2.0's Late Stage Preclinical Projects is to speed the introduction of therapies into the clinic. Organizations applying under CIRM 2.0 may not have access to a stem cell research oversight committee thus creating a potential barrier to entry.

Requested Action: CIRM requests the ICOC adopt the proposed amendments to the Standards Working Group regulations.

Amend 17 Cal. Code of Regs. section 100010 to read:

§ 100010. Scope of Chapter 2 – Stem Cell Research.

The standards set forth in this chapter apply to ~~all institutions~~Awardees, as defined ~~by~~ in Title 17, California Code of Regulations, section 100020, ~~subdivision (f),~~ performing research, as defined in Title 17, California Code of Regulations, section 100020, ~~subdivision (d),~~ funded by the California Institute for Regenerative Medicine (CIRM) as authorized by Article XXXV of the California Constitution.

Note: Authority cited: Article XXXV, California Constitution; and Section 125290.40(j). Reference: Sections 125290.35, 125290.40, 125290.55, Health and Safety Code.

Amend 17 Cal. Code of Regs. section 100020 to read:

§ 100020. Definitions.

As used in this chapter:

(a) ~~(a)~~ "Acceptably derived" means derived in accordance with the requirements of Code of California Regulations, Title 17, sections 100080 and 100090.

(b) "Awardee" means an organization that is the recipient of an award from CIRM and that is legally responsible and accountable for their use of the funds provided and for the performance of the CIRM-funded project or activity. The Awardee is the entire legal entity even if a particular component is designated in the notice of award. Campuses of the University of California shall be considered as separate and individual Awardees.

(c~~b~~) "CIRM" means the California Institute for Regenerative Medicine.

(d~~c~~) "Covered stem cell line" means a culture-derived, human pluripotent stem cell population that is capable of: 1) sustained propagation in culture; and (2) self-renewal 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. "Pluripotent" means capable of differentiation into mesoderm, ectoderm, and endoderm.

(e~~d~~) "Funded research" means research 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.

(f~~e~~) "Human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains:

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(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

~~(f) "Institution" means any public or private entity or agency (including federal, state, local or other agencies).~~

(g) "Human Subjects Research" is research defined by Title 45, Code of Federal Regulations, Part 46 (Protection of Human Subjects), revised June 23, 2005.

(hg) "Institutional Review Board" ("IRB") is an entity established in accordance with Title 45, Code of Federal Regulations, section 46.107, revised June 23, 2005.

(i~~h~~) "Permissible Expenses" means necessary and reasonable costs directly incurred as a result of donation or participation in research activities. Permissible expenses may include but are not limited to costs associated with travel, housing, child care, medical care, health insurance and actual lost wages.

(ji) "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 these regulations, whether or not they are conducted or supported under a program which is considered research for other purposes.

(k~~j~~) "Somatic Cell Nuclear Transfer" ("SCNT") means the transfer of a somatic cell nucleus into an oocyte.

(l~~k~~) "Stem Cell Research Oversight Committee" ("SCRO" committee) means a committee established in accordance with Code of California Regulations, Title 17, section 100060.

Note: Authority cited: Article XXXV, California Constitution; Section 125290.40(j), Health and Safety Code. Reference: Sections 125290.35, 125290.40, 125290.55, 125292.10, subds. (p)(q), Health and Safety Code.

Amend 17 Cal. Code of Regs. section 100030 to read:

§ 100030. Activities Not Eligible for CIRM Funding.

The following activities are not eligible for CIRM funding:

(a) Human reproductive cloning, as defined in California Health and Safety Code Section 125292.10. subdivision (k), or reproductive uses of SCNT prohibited by article XXXV, section 3, of the California Constitution.

(b) The culture in vitro of (i) any intact human embryo or (ii) any product of SCNT, parthenogenesis or androgenesis, 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 embryos and/or cells have been stored frozen.

(c) The introduction of stem cells from a covered stem cell line into nonhuman primate embryos.

(d) The introduction of any stem cells, whether human or nonhuman, into human embryos.

(e) Breeding any animal into which covered stem cells ~~from a covered stem cell line~~ have been introduced such that they could contribute to the germ line.

(f) The transfer to a uterus of a genetically modified human embryo.

Note: Authority cited: Article XXXV, California Constitution; Section 125290.40(j), Health and Safety Code. Reference: Sections 125290.35, 125290.40, 125290.55, 125292.10, Health and Safety Code.

Amend 17 Cal. Code of Regs. section 100040 to read:

§ 100040. Institutional Assurance of Compliance.

(a) ~~All research institutions~~Awardees shall be responsible for providing written assurance satisfactory to CIRM that CIRM-funded research complies with the requirements set forth in this chapter.

~~(b)~~ Each ~~institution~~ Awardee shall~~:~~

~~(1)~~ Ensure that the chancellor, chief executive officer or person with plenary authority designates an institutional official responsible for oversight of and documentation of compliance ~~for CIRM-funded research.;~~

(b) Awardees conducting human subjects research or research requiring SCRO committee review and approval under Title 17, California Code of Regulations section 100070, shall:

(1~~2~~) Designate one or more SCRO committee(s) established in accordance with the requirements of Code of California Regulations, title 17, section 100060; and

(2~~3~~) Designate one or more IRB(s).~~;~~

(c) ~~(4) Ensure~~ Awardees shall ensure that that clinical personnel conducting human subjects research who have a conscientious objection not be required to participate in providing donor information or securing donor consent for research use of gametes or embryos. That privilege shall not extend to the care of a donor or recipient.

Note: Authority cited: Article XXXV, California Constitution; Section 125290.40(j), Health and Safety Code. Reference: Sections 125290.35, 125290.40, 125290.55, Health and Safety Code.

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Amend 17 Cal. Code of Regs. section 100050 to read:

§ 100050. Compliance.

Grantees must report promptly to CIRM any failure to comply with the terms and conditions of an award. ~~Depending on the severity and duration of the non-compliance, CIRM actions may include, but are not limited to, the following~~Failure to comply with the provisions of this chapter, as well as any other conditions of the award, are set for the in the Grants Administration Policy that govern the award.~~:~~

~~(a) Temporary withholding of payment;~~

~~(b) Placing special conditions on awards;~~

~~(c) Conversion to a reimbursement payment method;~~

~~(d) Precluding the grantee (principal investigator (PI) or grantee organization, as appropriate) from obtaining future awards for a specified period;~~

~~(e) Debarment from receipt of further CIRM funds;~~

~~(f) Recovery of previously awarded funds;~~

~~(g) Civil action, including referring the matter to the Office of the Attorney General of the State of California for investigation and enforcement;~~

~~(h) Other available legal remedies.~~

Note: Authority cited: Article XXXV, California Constitution; Section 125290.40(j), Health and Safety Code. Reference: Sections 125290.35, 125290.40, 125290.55, Health and Safety Code.

Amend 17 Cal. Code of Regs. section 100070 to read:

§ 100070. SCRO Committee Review and Notification.

(a) ~~CIRM-funded~~ R~~r~~esearch involving the procurement or use of human oocytes or the creation of human gametes may not commence without SCRO committee review and approval in writing. If ~~CIRM-funded~~ research involves the procurement of human oocytes from a living donor, a member of the committee with expertise in assisted reproduction shall be present. The designated SCRO committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (a)(3) of this regulation as a condition of granting its approval. At a minimum, the SCRO committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for the need to procure or use human oocytes or create human gametes. In the case of human oocyte procurement, a justification for the number needed. If SCNT is proposed a justification for SCNT shall be provided.

(2) Demonstrate experience, expertise or training in derivation or culture of human or nonhuman stem cell lines.

(3) Provide documentation of compliance with any required review of the proposed research by an IRB, Institutional Animal Care and Use Committee (IACUC), Institutional Bioethics Committee (IBC), or other mandated review.

(b) ~~CIRM-funded r~~R~~r~~esearch involving procurement, creation or use of human blastocysts or embryos may not commence without SCRO committee review and approval in writing. The designated SCRO committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (b)(3) of this regulation as a condition

of granting its approval. At a minimum, the SCRO committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for the need to create or use blastocysts or embryos including a justification for the number needed.

(2) Demonstrate experience, expertise or training in derivation or culture of human or nonhuman stem cell lines.

(3) Provide documentation of compliance with any required review of the proposed research by an IRB, Institutional Animal Care and Use Committee (IACUC), Institutional Bioethics Committee (IBC), or other mandated review.

(c) ~~CIRM-funded h~~Human subjects research~~, as defined by Title 45, Code of Federal Regulations, Part 46 (Protection of Human Subjects), revised June 23, 2005, and California Health and Safety Code section 24173,~~ with the aim to create, from sources other than human gametes, blastocysts or embryos, ~~or use~~ a covered stem cell line may not commence without written notification of the SCRO committee. A statement from the designated institutional official (as defined in Title 17, California Code of Regulations section 100040, subdivision (b)(1)) may be provided in lieu of SCRO committee notification. The institutional official shall submit documentation of any required review of the proposed research by an IRB, IACUC, IBC or other mandated review. Research may include animal assays to evaluate pluripotency; however, subsequent introduction of derived covered stem cell lines in non-human animals shall be reviewed in accordance with subdivision (e) of this section. The designated SCRO committee may require the investigator to:

(1) Demonstrate experience, expertise or training in derivation or culture of human or nonhuman stem cell lines.

(2) Provide documentation of compliance with any required review of the proposed research by an IRB, Institutional Bioethics Committee (IBC), or other mandated review.

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

(d) ~~CIRM-funded~~ Ppurely in vitro research with the aim to create or use a covered stem cell line from non-identifiable cells may not commence with out written notification of the SCRO committee. A statement from the designated institutional official pursuant to section 100040(a~~b)(1~~) may be provided in lieu of SCRO committee notification if human somatic cells conform to the requirements of section 100080(a)(3); or the covered stem cell line(s) are recognized by an authorized authority. At a minimum the statement shall certify the:

(1) Human somatic cells conform to the requirements of section 100080(a)(3); or

(2) The covered stem cell lines are recognized by an authorized authority.

In addition, the institutional official shall submit documentation of any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.

Research may include animal assays to evaluate pluripotency; however, subsequent introduction of derived covered stem cell lines in non-human animals shall be reviewed in accordance with subdivision (e) of this section.

(e) The introduction of covered stem cells into nonhuman mammalian blastocysts or fetuses or introducing human neural progenitor cells into the brain of non-human animals at any state of embryonic, fetal, or postnatal development may not commence without SCRO committee review and approval in writing. Studies involving postnatal animals performed pursuant to a FDA Investigational New Drug

(IND) or Device application are exempt from SCRO committee review and approval. ~~CIRM-funded research introducing covered stem cell lines into non-human animals or introducing neural progenitor cells into the brain of non-human animals at any state of embryonic, fetal, or postnatal development may not commence without SCRO committee review and approval in writing.~~ The designated SCRO committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (e)(3) of this regulation as a condition of granting its approval. The SCRO committee may establish guidelines and procedures for expedited review of animal research so that review by the entire SCRO committee is not required. At a minimum, the SCRO committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for introducing stem cells into non-human animals.

(2) Provide assurance that all covered stem cell lines have been acceptably derived.

(3) Evaluate the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues.

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

(f) ~~CIRM-funded~~ Rresearch introducing cells from covered stem cell lines into a live born human may not commence without SCRO committee review and approval in writing. The designated SCRO committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (f)(4) of this regulation as a condition of granting its approval. At a minimum, the SCRO committee shall require the investigator to:

(1) Provide an acceptable scientific for rationale introducing stem cells into humans.

(2) Provide assurance that all covered stem cell lines have been acceptably derived.

(3) Evaluate the probable pattern and effects of differentiation and integration of the human cells into the human tissues.

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

(g) In cases where SCRO committee approval is required, a SCRO committee shall notify investigators in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure SCRO committee approval of the research activity. If the SCRO committee decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(h) SCRO committee approvals shall be reviewed no less frequently than once per year. The renewal review shall confirm compliance with all applicable rules and regulations. The SCRO committee may establish guidelines and procedures for expedited review of renewals so that review by the entire SCRO committee is not required.

Note: Authority cited: Article XXXV, California Constitution; and Section 125290.40(j), Health and Safety Code. Reference: Sections 125290.40 and 125290.55, Health and Safety Code.