CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

March 8, 2012

To: Scientific and Medical Accountability Standards Working Group (SWG) & Interested Parties

From: CIRM

Re: DRAFT: Proposed Revision to CIRM Medical and Ethical Standards Regulations

Background:

CIRM performs ongoing evaluation of the Medical and Ethical Standards Regulations. Based on the most recent review, CIRM is proposing amendments designed to clarify existing requirements and enhance operational efficiency.

The CIRM Medical and Ethical Standards Working Group will consider the proposed amendments on Friday April 6, 2012. In advance of this meeting, CIRM is seeking comment on the proposed amendments from interested parties. This feedback will be incorporated into the working group deliberations.

Proposal Amendment #1: Section 100060

Existing stem cell research oversight committees (SCROs) must be comprised of individuals with a variety of expertise. SCROs must also include a non-scientist outside member. Currently, the outside member(s) is the only SCRO participant who cannot receive compensation for their service to the committee. The rationale for this policy was to avoid coercion. However, in the context of IRB and IACUC reviews, where outside members are also present and provided with a meeting stipend, reviews are robust and comprehensive. In fact, committees report that outside members consistently bring thoughtful and challenging insights to the process.

CIRM is proposing to strike language prohibiting remuneration to the non-scientist public member(s).

(a) A SCRO committee shall be comprised of persons with expertise in, including but not limited to, developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical issues in stem cell research. A SCRO committee shall include at least one non-scientist member of the public who is not employed by, or appointed to, ~~or remunerated by~~ the relevant research institution and who is not part of the immediate family of a person who is affiliated with the institution. In addition, a SCRO committee shall include at least one patient advocate.

Proposed Amendment #2: Section 100070

Section 100070 addresses SCRO review and notification requirements for in vitro research. Currently, in vitro research using de-identified iPSC lines and de-identified somatic cells for iPSC derivation requires notification of the SCRO committee or a designated institutional official. The SWG recommended the notification requirement in December 2008 (see attachment 1). Since the notification standard was promulgated there has been a steady increase in the percentage of protocols performing reprogramming experiments and utilizing iPSCs. CIRM collects documentation that SCRO notification has taken place, but this procedure is proving administratively burdensome. Administrative resources are better directed towards ensuring appropriate documentation for human subjects research and mandated SCRO reviews.

For iPSC derivation and use the National Academies' state:

> ***Derivation:*** *Because non-embryo-derived hPS cells are derived from human material, their derivation may be covered by existing IRB regulations concerning review and informed consent, depending on the source of the tissue used. No ESCRO committee review is necessary, although the IRB may always seek the advice of an ESCRO committee if this seems desirable. Where appropriate, the IRB review should consider proper consent for use of the derived hPS [human pluripotent stem] cells. Some of the recommendations for informed consent that apply to hES cells also apply to hPS cells, 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.*
>
> ***USE:*** *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.*

To address consent-related considerations, CIRM requires SCRO notification when cells are identifiable – IRB regulations apply. Further, for any protocol proposing to yield gametes full SCRO review is required ((in Section 100070(a))) .The table below illustrates conditions when SCRO notification is required for iPSC research.

CIRM is proposing to eliminate the notification requirement for derivation and use of de-identified cells.

Research Activity	Current Standard	Proposed Standard	Comment
iPSC derivation with identifiable somatic cells	Notification of SCRO	Notification of SCRO	No change
iPSC derivation with de-identified somatic cell	Notification of SCRO or institutional official	No notification	Cells must meet standards for acceptable research materials § 100080
Use of iPSC to yield gametes	Full SCRO review and approval	Full SCRO review and approval	No change § 100070(a)
Use of de-identified iPSCs	Notification of SCRO or institutional official	No notification	Cells must meet standards for acceptable research materials § 100080

Proposed Amendment #3: Section 100070(f)

For research involving the transplantation of cells into humans, the existing regulation requires a SCRO to provide an acceptable scientific rationale for the intervention and to *evaluate the probable pattern and effects of differentiation and integration of the human cells into the human tissues*. A scientific and/or safety evaluation is generally performed in scientific peer review, by the FDA (in the context of a clinical trial) and/or an IRB (risk benefit analysis). Rather than replicate these evaluations, the proposed amendment is designed to make clear the SCRO may rely on the determination of a regulatory authority, such as the FDA or an IRB, with appropriate expertise in stem cell biology. Under this amendment, a SCRO could perform a safety evaluation, if deemed necessary, or defer to the findings of the regulatory authority.

(f) CIRM-funded research 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. The SCRO committee may rely on the determination made pursuant to a mandated review by a regulatory authority or IRB with appropriate expertise in stem cell biology in lieu of conducting a separate evaluation.
(4) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.

CIRM is proposing to add language to allow the SCRO committee to rely on determinations made by other regulatory authorities.

Proposed Amendment #4: Section 100080

The existing regulation 100080(a)(3) is designed to allow the use of somatic cells conforming to Federal policy (OHRP requirements) to be used to create iPSCs. The proposed amendments clarify the OHRP standard applies to cell lines derived from non-embryonic sources. The amendments also clarify the OHRP standard applies to either somatic cells used to create iPSC or existing iPSC lines that meet the Federal standard.

All covered stem cell lines used in CIRM-funded research must be "acceptably derived."
(a) To be "acceptably derived," the covered stem cell line must meet one of the following three criteria:

(3) The covered stem cell line is derived from non-embryonic sources and: is ~~non-identifiable human somatic cells under the following conditions~~:
(A) The derivation did not result from the transfer of a somatic cell nucleus into a human oocyte (SCNT) or the creation or use of a human embryo; and
(B) The original somatic cells or the resulting cell lines have no associated codes or links maintained by anyone that would identify to the investigator(s) the donor of the specimens, or, if such codes or links exist, that the identity of the donor is not readily ascertainable because, for example:
(i) The key to decipher the code or link is destroyed before the research begins;
(ii) An agreement prohibits release of the key to the investigators under any

circumstances;
(iii) IRB-approved written policies and operating procedures for a repository or data management center prohibit releasing the key under any circumstances; or
(iv) The release of the key to the investigators is forbidden by law.

CIRM is proposing to add language to clarify the scope of the existing standard for use of cells that meet Federal standards.

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Scientific and Medical Accountability Standards
Working Group Briefing Paper:
Oversight for iPS-Related Research

Background Oversight for iPS Research

The CIRM MES regulations contain provisions requiring SCRO review and approval of research intended to derive a pluripotent ("covered") stem cell line – Section 100070(c). Experiments involving somatic cell reprogramming have become common in basic- (*in vitro*) research. In many cases, such research may result in the generation of cells with pluripotent-like characteristics. SCRO committees tend to consider such experiments as *in vitro* research requiring only notification or expedited review rather than full SCRO review. Grantees have requested that CIRM clarify this position (see Section 3 of interviews summary).

iPS Experiments and the NAS Guidelines

In the 2008 amendments, the NAS hESC Research Committee indicated that ESCRO review is not necessary for non-embryo-derived iPS cell line derivations and *in vitro* experiments. The committee reasoned that since iPS cells are derived from human material, their use in research is covered by existing IRB regulations concerning review and informed consent and do not raise any special ethical concerns. One exception to the review standard is *in vitro* experiments to yield gametes. Such experiments are subject to ESCRO committee review.

Policy Considerations

CIRM has a general SCRO "notification" requirement for *in vitro* research utilizing a covered stem cell line – Section 100070(d), and SCRO committees are required to confirm documentation of compliance with any required IRB review. The notification standard could be applied to iPS experiments. Alternatively, expedited review might also be considered.

The full SCRO review and approval requirements in Section 100070(c) could be limited in scope to research intended to "create or utilize human gametes and embryos." This modification in scope would subject all gamete or embryo work to full review and *in vitro* work with somatic cells would be subject to a notification standard. Such clarification would be consistent with the NAS guidelines.

This modification in scope would be limited to *in vitro* work with human somatic cells. Experiments proposing to transplant cells with pluripotent characteristics to humans or animals would still require full review.