Summary of Major Comments & Recommendations On the CIRM MES Regulations

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Prepared by CIRM to support the Scientific and Medical Accountability Standards Working Group

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Sections:

Note: This draft document reflects comments received as of the print date. Additional comments may be received as part of the official commenting period which is open until May 1, 2006. Document may be revised without notice. An official summary will be provided to the Office of Administrative Law in the Final Statement of Reasons.

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Section 100020: Definitions

#	Ref_#	Section:	Comment from Public:
1	2-56 2-57 Note multiple comments	100020(c)	At first glance, the final sentence clearly keeps the door open to all adult stem cells. As I understand it, the argument is that this narrows the definition somewhat less than ALL adult stem cell research because the cells must be "culture-derived" and capable of "differentiation along multiple cell lineages," but this still leaves the door open to cells that we wouldn't otherwise need to consider. In one of the earlier proposed definitions, instead of "multiple cell lineages," the wording spoke of "tri-lineage," which was taken to be mesoderm, ectoderm, and endoderm (i.e., pluripotent cells). My sense is that there is no need to extend ESCRO review to include all adult stem cell research, because this is already required under section 100100 "all CIRM-funded human subjects research" to be reviewed by the IRB.
			Recommendation:
			There are at least three possible suggestions that might make things clearer and more workable for SCRO Committees: 1. Explicitly state that the only circumstance in which adult stem cells would need to be reviewed by an ESCRO Committee would be when (a) the experiments will result in de-differentiation to pluripotent cells or (b) the IRB asks for consultation from the ESCRO Committee. 2. Limit ESCRO review to any research that will result in the derivation of cells with tri-lineage (mesoderm, ectoderm, and endoderm) potential. 3. Re-word the definition (and I don't know how this might be done) by changing the focus to defining the ethical concerns to be addressed (e.g., destruction of the human blastocyst), rather than try to anticipate the nature of the products of that research (e.g., multipotent stem cells).

Original Language:	Proposed or Possible Language:
"Covered stem cell line" means a culture-derived, human stem cell population that 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.	See above recommendations

Section 100060: SCRO Membership and Function

#	Ref_#	Section:	Comment from Public:
2	2-48	100060(a)	The intent of the "public" member is still not met. The current regulations still allows an Institution to name a professional scientist as either a patient advocate or "public" member and still meet the letter of the regulation. It seems you could require what I understood as the intent of the NAS guidelines for a non-scientist by stating as much.
			Recommendation:
			SWG should clarify intent of outside member, and if necessary state "*one non-scientist member of the public*."

Original Language:	Proposed or Possible Language:
An 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. An SCRO committee shall include at least one representative of the public who is not employed by, appointed to, or remunerated by the relevant research institution. In addition, an SCRO committee shall include at least one patient advocate. No SCRO committee member may have a financial conflict of interest in the research under review.	*An 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. An SCRO committee shall include at least one <u>non-scientist member</u> of the public who is not employed by, appointed to, or remunerated by the relevant research institution. In addition, an SCRO committee shall include at least one patient advocate. No SCRO committee member may have a financial conflict of interest in the research under review.*

#	Ref_#	Section:	Comment from Public:
3	2-48	100060(a)	Why is the COI rule restricted to "financial" COI? What if the PI is the SCRO member's spouse, child, or student? What if there are non-financial conflicts? Under the rule as written may the conflicted SCRO member provide information during the SCRO meeting and not participate in the deliberations and the vote? It seems like a good use of time and resources if the question could be answered right there while avoiding undue influence or conflict. The COI rule in 45 CFR 46 seems to give enough flexibility in this area and should be considered as a starting point for this rule: 46.107(e).
			Recommendation:
			Revise to read: *No SCRO may have a member participate in the SCRO initial or continuing review of any project in which the member has a conflicting interest, except to provide information to the IRB.*

Original Language:	Proposed or Possible Language:
An 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. An SCRO committee shall include at least one representative of the public who is not employed by, appointed to, or remunerated by the relevant research institution. In addition, an SCRO committee shall include at least one patient advocate. No SCRO committee member may have a financial conflict of interest in the research under review.	*An 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. An SCRO committee shall include at least one non-scientist member of the public who is not employed by, appointed to, or remunerated by the relevant research institution. In addition, an SCRO committee shall include at least one patient advocate. <u>No SCRO may have a member participate in the SCRO initial or continuing review of any project in which the member has a conflicting interest, except to provide information to the IRB.</u>*

Section 100070: SCRO Review and Notification

#	Ref_#	Section:	Comment from Public:
4	2-51	100070	The regulations should clearly indicate whether PIs may appeal a SCRO decision to some other Institutional committee or person. Any such appeal process would surely undermine SCRO authority and the importance of PIs and SCROs negotiating the conditions for approval. Again, 45 CFR 46 may be a good beginning in which to craft such a regulation.
			Recommendation:
			Commenter suggests the following: *Appeals of ESCRO decisions must return to the ESCRO for additional review. Investigators may request to present responses to ESCRO decisions during a convened meeting. Appeals must be in writing and submitted directly to the ESCRO prior to an investigator's personal presentation to the ESCRO.* The SWG may want to consider the extent to which it regulates internal operating procedures. This level of detail may best be developed by individual institutions as internal procedures and policies.

Original Language:	Proposed or Possible Language:
None	New Section 100070(d): *Appeals of ESCRO decisions must return to the ESCRO for additional review. Investigators may request to present responses to ESCRO decisions during a convened meeting. Appeals must be in writing and submitted directly to the ESCRO prior to an investigator's personal presentation to the ESCRO.*

#	Ref_#	Section:	Comment from Staff:
5	staff	100070(a)(1)	Section (a) frames the scope of ethical covers/review in terms of research "involving derivation of covered stem cell lines or use of human oocytes or embryos." In section 100070(a)(1), the regulations focused solely on the scientific rationale for using oocytes and embryos in the context of deriving new cell lines. For consistency, these section should be parallel in structure.
			Recommendation:
			Since the overarching concern is the use of oocytes and embryos, this language should be used consistently in the regulations.

Original Language:	Proposed or Possible Language:
(1) Provide a scientific rationale for the need to derive a new human stem cell line. When such research involves the use of oocytes and embryos, 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.	*(1) Provide a scientific rationale for the need to use oocytes, embryos or derive a new human stem cell line. When such research involves the use of oocytes and embryos, 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.*

#	Ref_#	Section:	Comment from Staff:
6	staff	100070(b)	This is a technical comment. Section (b) covers the introduction of stem cell lines into human or non-human animals. One is an IRB issue and one is an IACUC issue. This dual jurisdiction can create issues when referencing this section. Also, section 100030(d) prohibits the introduction of stem cells into human embryos, the section alludes to an activity indelible for funding.
			Recommendation:
			Break up into two sections.

Original Language:	Proposed or Possible Language:
(b) CIRM-funded research introducing covered stem cell lines into human or 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 (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 assurance that all covered stem cell lines have been acceptably derived. (2) Evaluate the probable pattern and effects of differentiation and integration of the human cells into the human or nonhuman animal tissues. (3) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.	(b) CIRM-funded research introducing covered stem cell lines into humans 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 assurance that all covered stem cell lines have been acceptably derived. (2) Evaluate the probable pattern and effects of differentiation and integration of the human cells into the human tissues. (3) Provide documentation of compliance with any required review of the proposed research by an IRB, IBC, or other mandated review. (c) CIRM-funded research introducing covered stem cell lines into non-human animals 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 assurance that all covered stem cell lines have been acceptably derived. (2) Evaluate the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues. (3) Provide documentation of compliance with any required review of the proposed research by an IACUC, IBC, or other mandated review.

Section 100090: Additional Requirements for CIRM-Funded Research

#	Ref_#	Section:	Comment from Public:
7	2-9	100008(b)(1)	The meaning of "shall not compromise the optimal reproductive success" needs to be clarified. First, this statement may be interpreted to mean the researcher must not engage in any activity that poses a health risk. If this is the case, then oocyte retrieval would effectively not be allowed because it is conceivable that her fertility could be impacted by the procedure. At a minimum the language should be changed to state "shall not knowingly compromise." It appears the intent of the Working Group is that oocytes not be committed or diverted to research until the women's fertility goals or treatment is complete. The language needs state in a clear manner that oocytes intended for reproductive purposes are used for such purposes and not used in research unless the fertility treatment is complete.
			Recommendation:
			Revise to provide clarification.

Original Language:	Proposed or Possible Language:
(1) For a woman providing oocytes for research and clinical infertility treatment (either for herself or another woman), research shall not compromise the optimal reproductive success of the woman in infertility treatment.	*(1) For a woman providing oocytes for research and clinical infertility treatment (either for herself or another woman), the disposition of such oocytes shall not knowingly compromise the optimal reproductive success of the woman in infertility treatment.* *(A) A woman undergoing stimulation to produce oocytes for her own reproductive uses may not donate any eggs to research unless she has conclusively determined that she does not want or need them to optimize her own chances for reproductive success.* *(B) A woman undergoing stimulation to produce oocytes for donation to another person's reproductive efforts may not donate any of these eggs to research unless (a) the donation is permissible under her agreement with the recipient who is receiving her oocytes for reproduction and (b) her donation of oocytes for research is done without valuable consideration. (add cross-reference to use of term valuable consideration elsewhere)*

#	Ref_#	Section:	Comment from Public:
8	2-60	100090(b)(2)	The requirement that "the funded research institution has agreed to assume the cost of any medical care…" is phrased in such a way that it seems to preclude arrangements where someone other than the "funded institution" would cover such costs. For example, a commercial sponsor of research may assume such costs. The regulations should be phrased in a manner where the performance objective is clear (the research participant is not responsible for the cost of any required medical care), but does not imply sole responsibility of payment by the funded institution. Rather the funded institution must provide assurance that such costs are covered.
			Recommendation:
			Proposed revision is adapted from SB 1260 language.

Original Language:		Proposed or Possible Language:
(2) The funded institution has agreed to assume the cost of any medical care required as a direct and proximate result of oocyte donation for research.		*(2) The funded institution shall develop procedures and protocols to ensure access for any medical care required as a direct and proximate result of oocyte donation. The research protocol shall ensure that payment for coverage of resulting medical expenses be provided by the funded intuition or a designated institution.*

Section 100100: Informed Consent Requirements

#	Ref_#	Section:	Comment from Public:
9	2-58	100008(f)	Consent from each parent is difficult and not consistent with existing practice for consent for storage of cord blood.
			Recommendation:
			Because cord blood may be used to derive cell lines that might be utilized by many, principal of dual consent was applied by SWG. No specific recommendation.

Original Language:		Proposed or Possible Language:
(f) For CIRM-funded research involving the donation of the umbilical cord, cord blood or the placenta, consent shall be obtained from each known legal parent, guardian or progenitor. Informed consent shall include a statement as to whether the donated cells may be available for autologous treatment in the future.		None

#	Ref_#	Section:	Comment from Public:
10	2-59	100100 (d)(4)	The language that, "Researchers may meet this requirement by following a process by the designated IRB or SCRO Committee" implies that there is some means to meet this requirement besides such a process. It would be clearer to state, "Researchers must follow a process approved by the designated IRB and SCRO Committee." Also, this section should probably state that it does not apply retroactively to materials collected before the enactment of these regulations.
			Recommendation:
			Modify based on comment

Original Language:		Proposed or Possible Language:
(4) The researcher 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. Understanding the essential aspects of the research includes understanding at least that:		*(4) The researcher shall ascertain that the donor has understood the essential aspects of the research. Researchers must follow a process approved by the designated IRB and SCRO Committee. Understanding the essential aspects of the research includes understanding at least that:*

#	Ref_#	Section:	Comment from Public:
11	2-62	100100(d)(3)	2 Comments [1] We endorse the regulatory focus on heightened informed consent. The informed consent requirements make sense because in most cases there will be no direct benefit to the participant. The regulations overreach in this section by requiring a "deliberative" period in the consent process. Unfortunately, in the reproductive rights field, a similar approach is advocated where states require waiting periods for abortions and/or waiting periods for parental notification. Therefore, this well intended provision has the unintended consequence of undermining existing policy. Such a provision may not be necessary because you're already getting sufficient time to consider the decision to donate with the proposed evaluation of the informed consent process. [2] The requirement that donors must initiate recontact with donors seems ineffective. Researchers should have some opportunity to follow up with potential participants. Could the intent of this provision be accomplished by requiring the researchers to wait a minimum time period before recontacting potential participants?
			Recommendation:
			SWG should discuss this section in light of multiple comments.

Original Language:		Proposed or Possible Language:
(3) Steps shall be taken to enhance the informed consent process. Measures to do so shall include, but are not limited to, an adequate period of time, as determined by an IRB, to deliberate about the decision to donate. In the case of such periods of deliberation, researchers may not solicit potential donors until they have initiated recontact with the researchers.		None

Section 100120: Record Keeping

#	Ref_#	Section:	Comment from Public:
12	1-45	100100(d)(3)	Section 100120 All record keeping should be publicly available, with limited exceptions for proprietary information and patient privacy.
			Recommendation:
			The SWG made no formal decision when this comment was made at 1/31/06 meeting. The Grants Administration Policy may be a more appropriate context to discuss specific reporting of grantee information.

Original Language:	Proposed or Possible Language:
Each grantee's institution shall maintain records of all CIRM-funded research activities. At a minimum, the institution shall maintain a research registry that includes, but is not limited to, documentation of: *(a) CIRM-funded stem cell research conducted by the institution;* *(b) Any required review or notification requirements as described in 17 Cal. Code of Reg.s section 100070;* *(c) The methods utilized to characterize and screen the materials for safety;* *(d) The conditions under which the materials have been maintained and stored;* *(e) Any additional requirements set forth in any other regulations under this title;* *(f) Every gamete, somatic cell, embryo donation or product of SCNT that has been donated, created or used. This record should be sufficient to determine the provenance and disposition of such materials.*	None